# An open-label evaluation of safety and tolerability of coformulated bictegravir/emtricitabine/tenofovir alafenamide for post-exposure prophylaxis following potential exposure to human immunodeficiency virus-1

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## Abstract

**Background:** Single-tablet regimen (STR) provides a convenient once-daily regimen for the prevention of human immunodeficiency virus (HIV) infection. Here, we investigated the safety and tolerability of coformulated bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as a three-drug, STR for post-exposure prophylaxis (PEP) in Chinese individuals.

**Methods:** This was a prospective, open-label, single-arm trial conducted in a sexually transmitted diseases and acquired immunodeficiency syndrome clinic of a tertiary hospital in Beijing, China. Adults requiring PEP were prescribed BIC/FTC/TAF one pill once a day for 28 days. Clinical and laboratory data were collected and analyzed at baseline, weeks 2, 4, 8, 12, and 24.

**Results:** Of 112 participants enrolled in the study, 109 (97.3%) were male and the mean age was 30 ± 8 years. PEP completion was 96.4% (95% confidence interval: 91.1–99.0%). Two participants stopped PEP after 2 days because the source partner was identified as HIV uninfected. One participant was excluded due to hepatitis B virus infection according to the exclusion criteria. One discontinued due to the participant's decision. No participant acquired HIV through week 24. Adherence was 98.9% (standard deviation [SD]: 3.3%) by self-reporting and 98.5% (SD: 3.5%) by pill count. Only five participants experienced mild clinical adverse events attributed to the study drug (including headache, diarrhea, and nausea) and four participants had elevated serum creatinine (grade 1).

**Conclusions:** A once daily, STR of BIC/FTC/TAF used as PEP was safe and well-tolerated with a high rate of completion and adherence in Chinese. BIC/FTC/TAF may be a good option for PEP.

**Trial Registration:** ChiCTR.org.cn, ChiCTR2100048080

**Keywords:** Post-exposure prophylaxis; Human immunodeficiency virus; Bictegravir/emtricitabine/tenofovir alafenamide; Adverse event

## Introduction

Antiretroviral therapy is widely used in the treatment of human immunodeficiency virus (HIV) infection and is commonly recommended to prevent HIV infection following blood, sexual, or percutaneous exposure.[1-3] Evidence for efficacy, timing of initiation, and duration of post-exposure prophylaxis (PEP) have been extrapolated from animal[4,5] and human studies.[6,7] Non-occupational post-exposure prophylactic treatment (nPEP) has been clinically recommended since 2005.[8] Most guidelines[9,10] recommend using a three-drug combination for PEP.

PEP may cause adverse effects, including cutaneous allergy, gastrointestinal disorders, and hepatorenal toxicity. Although these adverse effects are generally not severe, a meta-analysis[11] demonstrates that only 56.6% of PEP users completed the full standard 28-day course of therapy. Recent studies suggested that a single-tablet regimen (STR) may improve PEP completion.[12,13] The combinations of either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) with either emtricitabine (FTC) or lamivudine are recommended as the preferred nucleoside reverse transcriptase inhibitor (NRTI) in many PEP guidelines.[1,14,15]

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In August 2019, BIC/FTC/TAF, a STR, was approved in China for treatment of HIV-1 infection in adults. The drug contains 50 mg of bictegravir, 200 mg of FTC, and 25 mg of TAF. TAF has a more favorable safety profile than TDF.[16] BIC/FTC/TAF can be taken once daily with or without food. All components of the STR are readily absorbed after administration. In studies in people living with HIV (PLWH), BIC/FTC/TAF was effective, well-tolerated, and convenient.[17,18] These characteristics make it a potential candidate for PEP. However, there is little literature about BIC/FTC/TAF as a PEP regimen in Chinese. The primary objective of this study was to evaluate the safety, tolerability, and adherence of BIC/FTC/TAF when used as a 28-day PEP regimen in Chinese.

## Methods

### Ethical approval

This study was approved by the Ethics Committee of Beijing Youan Hospital, Capital Medical University (No. [2021]078). All participants signed an informed consent.

### Study design

This study was a prospective, open-label, single-arm trial conducted in the sexually transmitted diseases and acquired immunodeficiency syndrome (STD/AIDS) clinic of Beijing Youan Hospital, Capital Medical University, a tertiary care hospital in Beijing, from May 2021 to February 2022. Individuals who met the inclusion criteria for PEP treatment were offered the option of participating in the study. All participants received coformulated BIC/FTC/TAF as a single tablet once a day for 28 days.

### Eligibility criteria

Participants were eligible for the study if they met the following criteria: (1) age ≥18 years, (2) HIV uninfected, and (3) potential sexual exposure to HIV-1 within 72 h, including anal, vaginal, oral, or other mucosal route exposure to ejaculate, cervicovaginal secretion, or rectal secretion from an HIV infected partner or high-risk partner of unknown HIV status. Participants were ineligible if they were taking any medication contra-indicated with study medication. Participants were subsequently withdrawn from the study if baseline screening showed serological evidence of HIV infection, chronic/active hepatitis B, serum alanine aminotransaminase (ALT) of >5 times the normal upper limit, or serum estimated glomerular filtration rate (eGFR) of <30 $mL{\cdot}min^{-1}{\cdot}1.73{\cdot}m^{-2}$ (Cockcroft–Gault equation, actual weight).

### Study procedure

Potential participants presenting at the STD/AIDS clinic for PEP during the investigation period were evaluated. If the patient met the criteria, he/she would be informed about the study. After providing informed consent, participants completed a survey about their specific demographic variables, risk behaviors at the time of exposure, and the source of their exposure. Blood was sampled and tested at baseline, weeks 2, 4, 12, and 24. The laboratory tests included serologies (for HIV, hepatitis B, hepatitis C, and syphilis), biochemistry (urea, sodium, potassium, calcium, phosphate, creatinine, and eGFR), liver function tests (total protein, albumin, ALT, alkaline phosphatase, γ-glutamyl transferase, and bilirubin), blood glucose, and lipids. HIV ribonucleic acid (RNA) testing was also performed at baseline to exclude acute HIV infection. HIV antigen-antibody (Ag/Ab) combination testing was performed at each visit using Vidas HIV DUO Ultra (bioMerieux, Marcy l'Etoile, France).

The primary outcome of the study is to evaluate the safety and tolerability of BIC/FTC/TAF in preventing HIV transmission after a high-risk sexual contact exposure in HIV uninfected adults. The secondary outcome of the study is to evaluate the adherence to the drug used in PEP. Drug adherence was measured by self-report and pill count.

### Data analysis

Descriptive statistics were performed. Continuous data were presented as the mean ± standard deviation (SD) if not otherwise specified. All statistical analyses were performed using SPSS version 17.0 (IBM Corp., Chicago, IL, USA). The changes from baseline in laboratory parameters were tested for significance using the *t*-test. A *P* value of <0.05 was considered statistically significant.

## Results

### Baseline characteristics

A total of 112 participants were enrolled in the study between May 2021 and February 2022, and received at least one dose of BIC/FTC/TAF; these patients comprised the primary analysis set [Figure 1]. The participants were mostly male (109, 97.3%), with a mean age (SD) of 30 (8) years. Exposures consisted of heterosexual intercourse, homosexual intercourse, and oral intercourse. The mean exposure time was 27.5 ± 18.8 h. Nearly half of the participants started PEP within 24 h of exposure [Table 1].

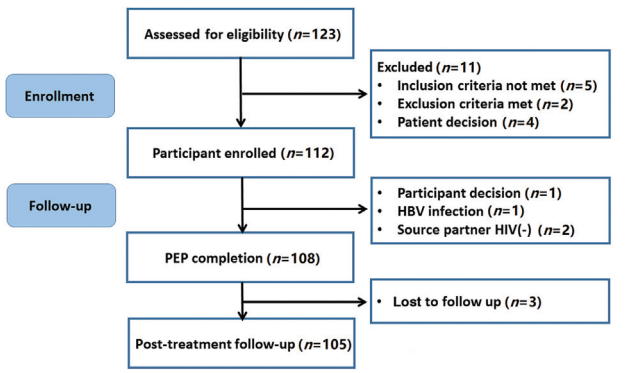


**Figure 1:** Flowchart showing the disposition of patients during the research. HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; PEP: Post-exposure prophylaxis.

**Table 1: Baseline characteristics of the 112 participants who received at least one dose of BIC/FTC/TAF for PEP of HIV.**

| Variables | Values |
|---|---|
| Age (years) | 30 ± 8 |
| Male | 109 (97.3) |
| Type of exposure | |
| Anal sex | 58 (51.8) |
| Vaginal intercourse | 43 (38.4) |
| Oral sex | 29 (25.9) |
| Time from exposure (h) | 27.5 ± 18.8 |
| ≤ 24 | 54 (48.2) |
| 25–48 | 45 (40.2) |
| 49–72 | 13 (11.6) |

Data are presented as mean ± standard deviation or *n* (%). BIC/FTC/TAF: Bictegravir/emtricitabine/tenofovir alafenamide; PEP: Post-exposure prophylaxis; HIV: Human immunodeficiency virus.

**Table 2: Serum creatinine of each patient who received BIC/FTC/TAF for PEP of HIV and compared with baseline.**

| Visit time | Creatinine (μmol/L) | *t* values | *P* values |
|---|---|---|---|
| Baseline (*n* = 112) | 76.69 ± 11.99 | | |
| Week 2 (*n* = 110) | 83.85 ± 11.66 | 4.510 | <0.0001 |
| Week 4 (*n* = 108) | 82.64 ± 11.35 | 3.777 | 0.0002 |
| Week 8 (*n* = 106) | 78.31 ± 12.07 | 0.994 | 0.3214 |
| Week 12 (*n* = 106) | 74.67 ± 11.43 | 1.272 | 0.2048 |
| Week 24 (*n* = 105) | 74.23 ± 11.59 | 1.535 | 0.1263 |

BIC/FTC/TAF: Bictegravir/emtricitabine/tenofovir alafenamide; PEP: Post-exposure prophylaxis; HIV: Human immunodeficiency virus.

### Treatment outcomes

Of the 112 participants, PEP completion was 96.4% (95% confidence interval: 91.1–99.0%). Completion failures (*n* = 4 [3.6%]) occurred at a median time of 5 days (range, 2–14 days). Two participants stopped PEP because the source partner was found to be HIV uninfected. One participant was excluded due to hepatitis B virus (HBV) infection. One discontinued due to the participant's decision (serum creatinine elevation, grade 1). In the 108 participants who completed PEP, self-reported medication adherence to all expected doses was 98.9% (SD: 3.3%). Of the 95 participants with pill count data, adherence was 98.5% (SD: 3.5%). The number of participants who responded to follow-up at 2, 4, 8, 12, and 24 weeks were 110, 108, 106, 106, and 105, respectively. No participant was found to acquire HIV through week 24.

### Safety

Two participants reported mild headache, two experienced mild diarrhea, and one reported mild nausea. These events resolved spontaneously without stopping PEP. There was one serious adverse event not related to the study drug: the participant died as a result of a traffic accident.

Regarding laboratory tests, four participants had elevated serum creatinine (grade 1) at week 2, among whom one participant decided to withdraw from the study. The others continued on study with creatinine remaining stable at week 4 and returning to normal at week 8. The mean serum creatinine of the participants with available data at baseline, weeks 2, 4, 8, 12, and 24 is shown in Table 2.

## Discussion

Our hospital is one of the accredited HIV/AIDS hospitals, caring for >10,000 people PLWH, accounting for nearly half of the PLWH in Beijing, and providing counseling on prevention of occupational and non-occupational exposure to HIV. Most of the participants were male, with a mean age of 30 years. This finding was similar to the results of the studies from the United States[17] and Europe[18,19] where nPEP was mostly sought by young men. In Africa,[20,21] however, participants were predominantly young women, and the most frequent reason for seeking nPEP was sexual assault.

Completion of a 28-day course of therapy is important for PEP. A randomized clinical trial[22] showed that PEP completion rate was higher in the STR arm than that in the multiple tablet regimen (MTR) arm. The completion rates were 67% and 71% in two PEP trials using elvitegravir/cobicistat/emtricitabine/tenofovir DF (E/C/F/TDF),[22,23] and 82% for taking E/C/F/TAF.[13] In two PEP studies using TDF/FTC/rilpivirine (RPV),[12,24] the completion rates were 86.1% and 92.0%. In our study, 96.4% of the participants completed PEP, which was numerically higher than the completion rates from the above studies using STR regimens for PEP. The adherence to BIC/FTC/TAF was high by both self-report (98.9%) and pill count (98.5%). These results are similar to those observed with TDF/FTC/RPV,[12] but higher than with E/C/F/TDF.[13] Though this study, like other PEP studies, was not powered to assess efficacy for HIV prevention, the lack of any HIV infections was promising.

Our study showed that BIC/FTC/TAF was well tolerated as a PEP regimen. Fewer than 5% of the participants experienced mild clinical adverse events attributed to the study drug. Only four (3.6%) participants had mild elevation of serum creatinine, consistent with the well-described inhibition of tubular secretion of creatinine, without affecting renal glomerular function, by integrase inhibitors. The increases in serum creatinine returned to baseline levels 1 month after the completion of the course of PEP. The adverse event rates were lower in PEP users than those observed in PLWH,[25,26] which may be due to the shorter duration of drug intake and the difference in demographics.

Besides the efficiency and safety mentioned above, BIC/FTC/TAF has a high genetic barrier to resistance[27,28] and all three antiretroviral components are fully active against HIV-2 *in vitro*, properties that make it an attractive regimen for PEP.

The current study had several limitations. The sample size was relatively small. The study was uncontrolled and open-labeled. The participants experienced non-occupational exposures and some of them might have undergone PEP before and taken antiretroviral drugs such as TDF, FTC, dolutegravir, or lopinavir/ritonavir. Repeated exposure to a drug may lead to adaption in the digestive tract. Selection bias may have occurred as the exposed individuals seen in the emergency room of our hospital could not be included in this study. Further larger prospective randomized controlled clinical trials using this particular combination of drugs for PEP are required for definitive evidence of benefit for this drug combination to be gleaned in patients potentially exposed to HIV-1 via sexual, percutaneous, and serosanguinous routes.

In conclusion, a once-daily, STR of BIC/FTC/TAF used as PEP for 28 days was well tolerated, with high levels of adherence and high completion rates. Using BIC/FTC/TAF as PEP may be a good option.

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### Conflicts of interest

None.

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