Effectiveness of switching to bictegravir/emtricitabine/tenofovir alafenamide in virologically suppressed people with HIV with historical drug resistance mutations

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To the Editor: China provides free antiretroviral therapy (ART) for people with human immunodeficiency virus (HIV), typically using two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). This regimen has significantly reduced mortality and slowed HIV spread over the past 20 years.[1,2] However, it has a low barrier to resistance, making drug resistance mutations (DRMs) a significant challenge. Following virological failure with a regimen of tenofovir (TFV), lamivudine or emtricitabine (3TC or FTC), and an NNRTI (efavirenz or nevirapine), DRMs to 3TC/FTC or TFV are common.[3] Despite this, 3TC/FTC and TFV are still included in many single-tablet regimens (STRs), raising concerns about their effectiveness following first-line ART failure. Bictegravir, a second-generation integrase strand transfer inhibitors (INSTIs) co-formulated with FTC and TFV alafenamide (B/F/TAF), offers effective viral suppression, minimal drug interactions, high resistance barriers, and excellent tolerability.[4] B/F/TAF is recommended as a preferred regimen for both initial treatment and switching in people with HIV (PWH).[2,5] While data suggest B/F/TAF is effective in virologically suppressed patients with historical DRMs, the available data are limited and retrospective.[6–8]

To evaluate the effectiveness of switching to B/F/TAF in virologically suppressed PWH with historical DRMs, we conducted a prospective, multicenter, single-arm cohort study at specialized tertiary hospitals in Nanjing, Suzhou, and Nantong (detailed protocol in Supplementary Data, http://links.lww.com/CM9/C163). PWH aged 18 years or older with a history of HIV DRMs, a viral load (VL) below 200 copies/mL for at least 3 months, and no contraindications to B/F/TAF were included in the study. The primary outcome was the proportion of patients with virological response, defined by the US Food and Drug Administration snapshot algorithm as (1) plasma VL (PVL) <50 copies/mL at week 48; or (2) two consecutive PVL ≥200 copies/mL or PVL >1000 copies/mL before week 48. The second outcome was the 48-week treatment retention rate, which included rates of discontinuation due to treatment failure and adverse events. Ethical approval (No. 2022-LS-ky019) and informed consent were obtained. The study was registered with the Chinese Clinical Trial Registry (ChiCTR2200063461).

From August 2022 to July 2023, the study enrolled 62 patients. Clinical and laboratory features, along with outcomes, are summarized in Table 1 and Supplementary Tables 1 and 2, http://links.lww.com/CM9/C163. Of these, 56 underwent plasma HIV RNA genotypic resistance testing, and the remaining six were tested for HIV DNA genotypic resistance. The cohort was predominantly male (60/62, 96.8%), with a median age of 37 years (interquartile range [IQR]: 33–47 years). One patient was managing active tuberculosis with a treatment regimen that did not include rifamycin-based drugs. At baseline, the median CD4 cell count was 426 cells/μL (IQR: 305–584 cells/μL),

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Table 1: Clinical and Laboratory Features, and Outcomes of the 62 people with HIV Switching to B/F/TAF.

Variables	Total
Age (years)	37 (33–47)
Gender	
Male	60 (96.8)
Female	2 (3.2)
HIV risk factor	
Homosexual	44 (72.1)
Heterosexual	14 (23.0)
Transfusion	2 (3.2)
Others	2 (3.2)
Time on virological suppression before switch (months)	40 (29–63)
Initial ART regimens	
3TC/TDF	47 (75.8)
3TC/AZT	13 (21.0)
NVP	14 (22.6)
EFV	45 (72.6)
Last antiretroviral regimens before switch	
3TC/ (TDF or TAF)	26 (41.9)
3TC/AZT	25 (40.3)
DTG	21 (33.9)
LPV/r	50 (80.6)
CD4 cell count at switch (cells/μL)	426 (305–584)
<200 cells/μL	7 (11.3)
≥200 to <500 cells/μL	28 (45.2)
≥500 cells/μL	27 (43.5)
PVL <50 copies/mL at switch	59 (95.2)
Archived NRTIs DRMs	56 (90.3)
M184V/I	42 (67.7)
K65R/N	21 (33.9)
Any TAMs	20 (32.3)
1–2 TAMs	18 (29.0)
≥3 TAMs	2 (3.2)
M184V/I+ K65R/N	11 (17.7)
M184V/I+ ≥3 TAMs	2 (3.2)
PVL <50 copies/mL at Week 48	59/59 (100)
Discontinuation of B/F/TAF for any reason	2 (3.2)
Discontinuation due to treatment failure	0
Discontinuation due to safety concerns	0

Data were summarized as median (interquartile range), *n* (%) or *n*/N (%). ART: Antiretroviral therapy; AZT: Zidovudine; B/F/TAF: Bictegravir/emtricitabine/tenofovir alafenamide; DRMs: Drug resistance mutations; DTG: Dolutegravir; EFV: Efavirenz; HIV: Human immunodeficiency virus; LPV/r: Lopinavir/ritonavir; NRTIs: Nucleoside reverse transcriptase inhibitors; NVP: Nevirapine; PVL: Plasma viral load; TAF: Tenofovir alafenamide; TAMs: Thymidine analogue mutations; TDF: Tenofovir disoproxil fumarate; 3TC: Lamivudine.

with a median duration of maintaining a PVL below 200 copies/mL for 40 months (IQR: 29–63 months) [Supplementary Table 1, http://links.lww.com/CM9/C163].

The initial ART regimens for all studied participants included 3TC, with 47 patients (75.8%) receiving TFV disoproxil fumarate (TDF). Upon the failure of the initial ART, second-line treatments were administered accordingly: 50 patients (80.6%) received lopinavir/ritonavir (LPV/r)-based regimens, and 25 patients (40.3%) were treated with zidovudine (AZT). Additionally, nine patients (14.5%) received a second-line regimen that included both dolutegravir (DTG) and LPV/r. For two patients with concurrent hepatitis B virus (HBV) infection, their second-line ART regimens were specifically customized to include 3TC + AZT + TDF + LPV/r and 3TC + AZT + TDF + DTG, respectively.

Preexisting NRTI DRMs were documented in 56 patients (90.3%). M184V/I, observed in 67.7% of these patients, was the most prevalent NRTI DRM, followed by K65R/N in 33.9%. A co-occurrence of M184V/I and K65R/N was identified in 11 patients (17.7%). Among those with preexisting NRTI DRMs, only 10 (16.1%) were considered potentially susceptible to FTC, and 26 (41.9%) to TAF. Archived NNRTI DRMs were found in 60 patients (96.8%). The most frequent NNRTI DRM was V106M/A (38.7%), followed by V179D/E (33.9%), Y181C/I/V (32.3%), and K103N/S (27.4%). Additionally, PI DRMs were detected in three patients [Supplementary Table 2, http://links.lww.com/CM9/C163].

From week 12 to week 48 of the B/F/TAF treatment, the percentage of PWH who maintained PVL below 50 copies/mL varied from 93.3% to 100%, while those with levels below 200 copies/mL ranged from 97.8% to 100% [Supplementary Figure 1A, http://links.lww.com/CM9/C163]. By week 48, 60 patients (96.8%) remained on B/F/TAF, and PVL results were available for 59 of them. All these patients exhibited PVL below 50 copies/mL, irrespective of preexisting DRMs, as detailed in Supplementary Figure 1B, http://links.lww.com/CM9/C163. For the patient missing a week 48 PVL result, the VL at week 36 was below 50 copies/mL. During the 48-week B/F/TAF treatment period, viral rebound was observed in 7 patients (11.3%) [Supplementary Figure 2 and Supplementary Table 3, http://links.lww.com/CM9/C163]. The peak PVLs ranged from 65.5 copies/mL to 220 copies/mL, with two patients exceeding 200 copies/mL. Among these seven patients with viral rebound, three had both M184V and K65R DRMs. At the time of the regimen switch, four patients were receiving a combination treatment that included both DTG and LPV/r. Follow-up PVL tests were conducted on 6 of the 7 patients, all of whom demonstrated a PVL below 50 copies/mL at the next visit.

From week 12 to week 48 after switching to B/F/TAF therapy, the median CD4 cell counts fluctuated between 451 (IQR: 353–581) cells/μL and 506 (IQR: 337–700) cells/μL. Concurrently, the median CD4/CD8 ratios varied from 0.49 (IQR: 0.32, 0.68) to 0.58 (IQR: 0.41, 0.85) [Supplementary Figure 3A,B, http://links.lww.com/CM9/C163]. Paired T cell count data before and 48 weeks post-switch to B/F/TAF therapy were available for 52 patients. Compared to baseline, there was a significant increase in both CD4 cell counts and CD4/CD8 ratios at week 48 (median [IQR] CD4 count: 426 [IQR: 294–585] *vs.* 493 [IQR: 405–576], $P = 0.003$; median [IQR] CD4/CD8 ratio: 0.56 [IQR: 0.34–0.67] *vs.* 0.58 [IQR: 0.41–0.85], $P = 0.001$) [Supplementary Figure 3C,D, http://links.lww.com/CM9/C163].

Of the 2 discontinuations within 48 weeks, one patient relocated and stopped treatment at week 12, and the other switched regimens for cost reasons at week 36. During 48 weeks, three patients (4.8%) had mild diarrhea, one (1.6%) had mild dizziness, and one (1.6%) had mild nausea and vomiting, all resolving within a week. No grade 3–4 bone marrow suppression or renal impairment occurred, and no patients discontinued B/F/TAF due to safety concerns.

In 2022, B/F/TAF became more affordable in China through national insurance negotiations. Although data on B/F/TAF for HIV resistance is still emerging, it shows promise. The DAWNING trial found DTG with two NRTIs superior to LPV/r in PWH with NNRTI-based therapy failure.[9] The NADIA study showed DTG plus two NRTIs was as effective as darunavir/ritonavir-based therapy.[10] Notably, 3TC + TDF + DTG was effective despite K65R and M184V/I mutations, supporting its use when NNRTI-based therapy fails.[10] Due to similarities between B/F/TAF and the 3TC + TDF + DTG regimen, B/F/TAF is expected to have comparable efficacy. Recent small-scale studies support its feasibility for PWH with preexisting drug resistance.[6–8]

In our study, despite many patients having M184V/I or K65R/N DRMs, no patient lost virologic control at week 48. The regimen was well tolerated, with no discontinuations due to side effects, and showed gradual improvement in immunological parameters. Our study confirms B/F/TAF is a viable option for PWH with preexisting NRTI resistance mutations after viral suppression. It should be noted that, in our study, seven patients experienced viral blips. The precise causes of these blips remain unclear.

Our study has several limitations. First, it was conducted as a single-arm observational study with a relatively small sample size. The findings need verification in larger populations, particularly among PWH who have coexisting M184V/I and K65R/N mutations. Second, the high cost of PVL testing led to many patients not undergoing PVL tests at weeks 12, 24, and 36, potentially leading to an underestimation of the prevalence of viral blips.

In summary, the use of B/F/TAF in practical settings has demonstrated strong effectiveness in sustaining viral suppression among PWH who have preexisting DRMs. Owing to its favorable tolerability, minimal toxicity, lower pill burden, and substantial resistance barrier, B/F/TAF presents a viable option for simplifying second-line treatments in individuals who have experienced failure with NNRTI-based first-line therapies after achieving viral suppression.

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Conflicts of interest

None.

References

1. Cao W, Hsieh E, Li T. Optimizing treatment for adults with HIV/AIDS in China: Successes over two decades and remaining challenges. Curr HIV/AIDS Rep 2020;17:26–34. doi: 10.1007/s11904-019-00478-x.
2. AIDS and Hepatitis C Professional Group, Society of Infectious Diseases, Chinese Medical Association; Chinese Center for Disease Control and Prevention. Chinese guidelines for the diagnosis and treatment of HIV/AIDS (2021 edition). Infect Dis Immun 2022;2:145–167. doi: 10.1097/ID9.0000000000000044.
3. TenoRes Study Group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: A multicentre retrospective cohort study. Lancet Infect Dis 2016;16:565–575. doi: 10.1016/s1473-3099(15)00536-8.
4. Pham HT, Mesplède T. Bictegravir in a fixed-dose tablet with emtricitabine and tenofovir alafenamide for the treatment of HIV infection: Pharmacology and clinical implications. Expert Opin Pharmacother 2019;20:385–397. doi: 10.1080/14656566.2018.1560423.
5. Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF, *et al*. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society–USA panel. JAMA 2023;329:63–84. doi: 10.1001/jama.2022.22246.
6. Sax PE, Andreatta K, Molina JM, Daar ES, Hagins D, Acosta R, *et al*. High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I. AIDS 2022;36:1511–1520. doi: 10.1097/QAD.0000000000003244.
7. Micán R, de Gea Grela A, Cadiñanos J, de Miguel R, Busca C, Bernardino JI, *et al*. Impact of preexisting nucleos (t) ide reverse transcriptase inhibitor resistance on the effectiveness of bictegravir/emtricitabine/tenofovir alafenamide in treatment experience patients. AIDS 2022;36:1941–1947. doi: 10.1097/QAD.0000000000003311.
8. Tsai MS, Sun HY, Chen CP, Lee CH, Lee CY, Liu CE, *et al*. Switching to coformulated bictegravir, emtricitabine, and tenofovir alafenamide maintained viral suppression in adults with historical virological failures and K65N/R mutation. Int J Infect Dis 2023;126:39–47. doi: 10.1016/j.ijid.2022.11.012.
9. Aboud M, Kaplan R, Lombaard J, Zhang F, Hidalgo JA, Mamedova E, *et al*. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): An open-label, non-inferiority, phase 3b trial. Lancet Infect Dis 2019;19:253–264. doi: 10.1016/S1473-3099(19)30036-2.
10. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, *et al*. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): Week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV 2022;9:e381–e393. doi: 10.1016/S2352-3018(22)00092-3.

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