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# Switching to coformulated bictegravir, emtricitabine, and tenofovir alafenamide maintained viral suppression in adults with historical virological failures and K65N/R mutation ☆

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ABSTRACT

*Objectives:* Real-world experience with coformulated bictegravir, emtricitabine, and tenofovir alafenamide (BIC/FTC/TAF) is sparse as a switch regimen among people living with HIV (PLWH) having achieved viral suppression after previous virologic failures with the emergence of K65N/R.

*Methods:* In this retrospective study, PLWH aged ≥20 years who had previous virologic failures with emergent K65N/R were included for switching to BIC/FTC/TAF after having achieved plasma HIV RNA load (PVL) <200 copies/ml for ≥3 months. PLWH were excluded if integrase inhibitor resistance-associated mutations were detected. The primary end point was losing virologic control (PVL >50 copies/ml) at week 48 using a modified US Food and Drug Administration snapshot algorithm.

*Results:* A total of 72 PLWH with K65N/R who switched to BIC/FTC/TAF were identified. A total of 42 (59.7%) had concurrent M184V/I, and 9 (12.5%) had ≥1 thymidine analog mutations. The median dura-

☆ Preliminary analyses of these data were presented at the 11th IAS Conference on HIV Science, Virtual event with a local partner hub in Berlin, Germany, 18-21 July 2021 (Abstract 732).

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tion of viral suppression was 4.7 years (interquartile range 2.3-5.8), and 97.2% (n = 70) had PVL <50 copies/ml before switching. After a median observation of 98.6 weeks (interquartile range 77.9-120.3), 94.4% (n = 68) continued BIC/FTC/TAF. At week 48, the rate of losing virologic control was 2.8% (2/72). M184V/I was not associated with viral rebound.

*Conclusion:* Despite the emergence of K65N/R +/- M184V/I after virologic failures, BIC/FTC/TAF could be an option for simplification after viral suppression.



## Introduction

In people living with HIV (PLWH) who receive tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), or other nonthymidine nucleoside analogs with virological non-suppression, a single mutation at position 65 (lysine to asparagine or arginine, K65N/R) in the reverse-transcriptase (RT) gene confers high-level resistance to several nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) (Garforth *et al.*, 2014; Hawkins *et al.*, 2009; Svarovskaia *et al.*, 2007). This mutation results in a three- to four-fold decrease in the phenotypic susceptibility to tenofovir and intermediate-level resistance to cytosine nucleoside analogs, emtricitabine (FTC) and lamivudine (3TC), as well as abacavir (ABC) (Hawkins *et al.*, 2009; Margot *et al.*, 2002; Miller *et al.*, 2004; Winters *et al.*, 1997).

The emergence of K65R mutation is uncommon at virological failure (VF) on first-line tenofovir-containing antiretroviral therapy (ART): 2.7% at week 144 on a regimen with a lower genetic barrier (TDF, 3TC, and efavirenz) and 0% on regimens with a higher barrier (Margot *et al.*, 2006; Molina *et al.*, 2015; Orkin *et al.*, 2020; Paton *et al.*, 2022). In real-world settings, the database from the United States and Germany showed that the frequency of K65R mutation remained stable or declined with the increasing use of TDF and ABC (McColl *et al.*, 2008; Reinheimer *et al.*, 2016). The prevalence of transmitted K65R mutation is relatively low, at 0.1% and 0.2% in the United States and Kenya, respectively (McClung *et al.*, 2022; Silverman *et al.*, 2017). Nevertheless, the global prevalence of emergent resistance to tenofovir (K65N/R or K70E/G/Q) after first-line regimens of TDF/3TC or TDF/FTC plus non-NRTIs (NNRTIs) varies. In low-income and middle-income countries, the prevalence could be as high as 20-60% in PLWH with VF (TenoRes Study Group, 2016).

Zidovudine (AZT) is viewed as an optimal and rational NRTI backbone for sequential switch in this context for two main reasons (World Health Organization Guidelines, 2021): both K65R and M184V increase the susceptibility of HIV-1 to AZT, and bidirectional antagonism exists between the K65R and thymidine analog mutation pathways (Miller, 2004; Parikh *et al.*, 2006, 2007; Petropoulos *et al.*, 2000). Therapy with NRTI combinations that select both pathways may simultaneously delay the emergence of resistance and prolong treatment response. However, AZT is no longer recommended as first-line therapy because of its safety and tolerability issues (World Health Organization Guidelines, 2021, EACS Guidelines Version 11.0, 2021, DHHS, 2022, Saag *et al.*, 2020).

Currently, dolutegravir (DTG)-based regimens and coformulated bictegravir (BIC), FTC, and TAF are recommended in many international guidelines as the first-line regimens and stable switch regimens for suitable PLWH (EACS Guidelines Version 11.0, 2021, DHHS, 2022, Saag *et al.*, 2020). Both BIC and DTG are second-generation integrase strand-transfer inhibitors (INSTIs) and are known to possess a high genetic barrier to the emergence of resistance-associated mutations (RAMs) of HIV-1 (Deeks, 2018; Mbhele *et al.*, 2021). DTG-based ART has been shown to be efficacious after first-line VF, even in the presence of extensive NRTI resistance, which supports the use of second-generation INSTIs in PLWH with historic resistance, who are virally suppressed (Aboud *et al.*, 2019; Paton *et al.*, 2021). The 96-week data of the NADIA study showed that maintaining TDF was superior to the switch to AZT in achieving virological suppression and also suggested that the combinations could produce comparable and durable virological suppression, regardless of the presence of K65N/R (Paton *et al.*, 2022).

Some evidence from randomized stable switch studies supported BIC/FTC/TAF use in patients with K65N/R based on a mixture of RNA and DNA sequencing, although the case numbers were very small (Acosta *et al.*, 2020; Andreatta *et al.*, 2019; Molina *et al.*, 2018; Sax *et al.*, 2021). A single-center Italian prospective cohort including 290 individuals switching to BIC/FTC/TAF, among whom 54 (18.6%) presented with at least one NRTI mutation, with 48 having M184V/I mutation and six K65R mutations, showed that none had HIV RNA >20 copies/ml at the end of follow-up (Mazzitelli *et al.*, 2022). Another study from Taiwan also suggested that archived RAMs to NRTIs before the switch to second-generation INSTI-based regimens had no adverse impacts on virological suppression, regardless of the number of fully active NRTIs included in the regimens (Chen *et al.*, 2022).

In this study, we aimed to examine the clinical effectiveness of switching to BIC/FTC/TAF in maintaining the virological suppression among PLWH with archived K65N/R mutation who had achieved virological suppression with other antiretroviral regimens.

## Methods

### *Study design*

This was a multicenter, single-arm cohort study with retrospective data collection. PLWH aged 20 years or older and received HIV care at 10 designated hospitals around Taiwan between November 1, 2019 and June 30, 2022 were eligible for inclusion in this study. The study coordinator center was National Taiwan University Hospital, and the participating centers included Far Eastern Memorial Hospital, Tao-Yuan General Hospital, Chung Shan Medical University Hospital, Changhua Christian Hospital, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chi Mei Medical Center, National Cheng Kung University Hospital, Kaohsiung Medical University Hospital, and Kaohsiung Chang Gung Memorial Hospital. The 10 designated hospitals are responsible for the HIV care of approximately 40% of PLWH in Taiwan.

To be included in further analysis, PLWH had to have at least one genotypic resistance test performed with K65N/R identified by amplification of HIV RNA at their last event of VFs. Archived NRTI RAMs other than K65N/R were documented simultaneously. All included PLWH had to have remained on stable regimens with virological suppression (plasma HIV RNA load [PVL] <200 copies/ml) for 3 months or longer before the switch to BIC/FTC/TAF. Established or suspected resistance to protease inhibitors (PIs) or NNRTIs was permitted. We excluded PLWH with an archived mutation that was predicted to confer resistance to INSTIs based

on the Stanford HIV Drug Resistance Database (Pan *et al.*, 2007; Shafer, 2006). Those who did not have PVL results within the first year of switch were excluded. PLWH who received other antiretroviral medications in combination with BIC/FTC/TAF were also excluded.

*Study procedure*

In Taiwan, BIC/FTC/TAF was introduced into clinical use in October 2019. A decision to switch maintenance therapy to BIC/FTC/TAF was made at the discretion of the treating physicians after a discussion with PLWH. Among those who switched to BIC/FTC/TAF, PLWH who fulfilled the aforementioned criteria, with HIV-1 harboring the K65N/R mutation before the switch, were included. All included PLWH were followed up for at least 48 weeks after the switch to BIC/FTC/TAF. Medical records of all included PLWH were retrospectively reviewed to collect information on demographic and clinical characteristics. According to the national HIV treatment guidelines in Taiwan, all included PLWH are followed up at the hospitals every 3 months, and laboratory tests are performed every 3-6 months, which include PVL, clusters of differentiation 4 (CD4) lymphocyte count, renal function and liver function tests, lipid profile, and glucose levels. The study was approved by the Institutional Review Board or Research Ethics Committee of the participating hospitals, and written informed consent was waived due to the retrospective study design.

*Study endpoints*

The primary end point was the proportion of included PLWH experiencing viral rebound after switching to BIC/FTC/TAF at week 48, which was modified from the US Food and Drug Administration snapshot algorithm: (i) included PLWH on BIC/FTC/TAF with PVL $\geq$50 copies/ml at week 48, (ii) PLWH with PVL >200 copies/ml on BIC/FTC/TAF before week 48 of observation, and (iii) PLWH who discontinued BIC/FTC/TAF due to the lack of virological effectiveness before week 48. For missing data, we used a next-observation-carried-backward approach as a single imputation method to extend the assessment window for PLWH who missed their blood testing at week 48. In other words, PLWH who missed their blood testing at week 48 window (week 42-week 54) but remained stable on BIC/FTC/TAF would be considered as virally suppressed at week 48 if subsequent laboratory testing confirmed virological suppression. For PLWH with viral rebound (PVL $\geq$50 copies/ml but <200 copies/ml) before week 48, the decision to continue BIC/FTC/TAF or change to other salvage regimens was made by the treating physicians. Included PLWH who had the switch of ART due to adverse effects or reasons other than viral rebound, such as death, transfer of care, loss to follow-up, or remaining on BIC/FTC/TAF but without virological data, were classified as having "no virological data".

The main secondary outcome for the analysis was the time to VF (defined as having once PVL $\geq$200 copies/ml) after the switch to BIC/FTC/TAF. M184V/I was a prespecified stratification factor because this most common RT RAM not only nullified the activity of cytosine nucleoside analogs but also enhanced the susceptibility of HIV-1 to tenofovir. PLWH without a censoring event were followed up for more than 48 weeks from the day of the switch until the date of their last available PVL testing. Censoring events included discontinuation of BIC/FTC/TAF, loss to follow-up, transfer of care, death, or end of the observation on June 30, 2022, whichever occurred first. We also conducted the analysis of the time to viral rebound using a viral load threshold of 50 copies/ml in the same way. Results of genotypic resistance testing, if available, after viral rebound or VF were also recorded.

*Statistical analysis*

Baseline characteristics with descriptive statistics were summarized for all included PLWH. We performed the primary analysis after all included PLWH completed the week 48 clinic visit, with data expressed as proportions, point estimates, and 95% confidence intervals (CIs). A multivariate analysis using a logistic regression model was adapted to identify factors associated with experiencing viral rebound during the 48-week follow-up. We used a backward elimination process during the multivariate analysis, in which all possible associated factors were included in the model initially. For the secondary analyses, non-categorical variables were compared using Student's *t*-test or Mann-Whitney U-test, and categorical variables were compared using chi-squared test and Fisher's exact test. Kaplan–Meier estimates were used to estimate the incidence rate, and the log-rank test was used for comparisons between PLWH with and those without M184V/I. We investigated the associations for the time to VF and viral rebound with Cox proportional hazards model. All statistical tests were two-tailed, and *P*-values <0.05 were considered to be statistically significant. SAS version 9.4 software (SAS Institute, Cary, NC, USA) was used for all analyses.

## Results

*Study population and baseline genotypic data*

Between November 1, 2019 and June 30, 2022, we identified 72 PLWH fulfilling the inclusion criteria from the 10 participating hospitals. All the K65N/R mutations of the included PLWH were identified after their treatment failure with viral rebound to mean (SD) PVL of 4.3 (0.8) $\log_{10}$ copies/ml. The baseline characteristics and antiretroviral regimens before switching to BIC/FTC/TAF are shown in Table 1. In brief, all the included PLWH were male, with a mean age of 37.2 years (SD 7.2; range 27.7-65.7). The mode of HIV transmission was predominantly male-to-male sexual contact (91.6%). A total of 14 (19.4%) and 11 (15.3%) had hepatitis B virus and hepatitis C virus infection, respectively. Their mean CD4 counts was 602 cells/mm$^3$, and 97.2% had PVL <50 copies/ml before the switch. The median duration of virological suppression (PVL <200 copies/ml) before the switch to BIC/FTC/TAF was 4.7 years (interquartile range 2.3-5.8; range 0.3-8.9).

Before the emergence of K65N/R, most of the included PLWH were on NNRTI-based (n = 69, 95.8%), TDF-based (n = 59; 85.5%), and ABC-based (n = 10; 14.5%) ART and the remaining three used first-generation INSTIs based ART, two on elvitegravir/cobicistat/FTC/TAF, and one on TDF/FTC plus raltegravir (Table 1). Overall, 68.1% had at least one NRTI RAM other than K65N/R, and 93.1% had at least one NNRTI RAM (Table 1). Major PI RAMs were infrequent; none were expected to affect susceptibility to ritonavir-boosted PIs. There was no RAM conferring resistance to INSTIs.

The most common salvage regimens used after the emergence of K65N/R were boosted PI-based regimens (n = 57, 79.2%), AZT/3TC was used in 69.4% of the initial salvage regimens, and only three PLWH had NRTI-sparing regimens with boosted PIs plus an INSTI (Table 1). The remaining 15 (20.8%) PLWH were on first-generation INSTIs-containing regimens (elvitegravir/cobicistat/FTC/TAF: five and TDF/FTC plus raltegravir: one) or DTG- based regimens (AZT/3TC: five; ABC/3TC: two; and TDF/FTC: two; Table 1).

Before the switch to BIC/FTC/TAF, 72.2% had changed their suppressive ART more than once because of tolerability issue and adverse effects. A total of 32 (44.4%) used boosted PIs plus an INSTI, and 17 (23.6%) used AZT/3TC plus boosted PIs (Table 1).

**Table 1**
Baseline characteristics of 72 included people living with HIV-1 harboring K65N/R who switched to coformulated BIC/FTC/TAF.

| Characteristics | | | |
|---|---|---|---|
| **Age, mean (SD), years** | | 37.2 (7.2) | |
| **Male sex, n (%)** | | 72 (100) | |
| **HIV transmission risk group, n (%)** | | | |
| **M**en who have sex with men | | 66 (91.6) | |
| **Heterosexuals** | | 2 (2.8) | |
| **Injecting drug use** | | 4 (5.6) | |
| **Hepatitis B surface antigen -positive, n (%)** | | 14 (19.4) | |
| **Anti-hepatitis C virus-positive, n (%)** | | 11 (15.3) | |
| **Baseline antiretroviral therapy, n (%)** | | | |
| **Nevirapine-** | 41 (56.9) | TDF/XTC, 36 (50.0) | ABC/3TC, 5 (6.9) |
| **Efavirenz-** | 23 (31.9) | TDF/XTC, 20 (27.8) | ABC/3TC, 3 (4.2) |
| **RPV-** | 5 (6.9) | TDF/FTC, 4 (5.6) | ABC/3TC, 1 (1.4) |
| **EVG/C/FTC/TAF** | | 2 (2.8) | |
| **TDF/FTC + RAL** | | 1 (1.4) | |
| **Plasma HIV RNA load <50 copies/ml at switch, n (%)** | | 70 (97.2) | |
| CD**4 count at switch, mean (SD), cells/mm$^3$** | | 602 (251) | |
| **Duration of viral suppression <200 copies/ml before switch, median (IQR), years** | | 4.7 (2.3-5.8) | |
| **Archived NRTI RAMs, n (%)** | | | |
| **M184V/I** | | 43 (59.7) | |
| **≥1 TAM** | | 9 (12.5) | |
| **≥3 TAMs** | | 1 (1.4) | |
| **Archived NNRTI RAMs, n (%)** | | 67 (93.1) | |
| **Archived PI RAMs, n (%)** | | 3 (4.2) | |
| **Antiretroviral therapy used before switch to BIC/FTC/TAF, n (%)** | | | |
| **DTG + DRV/r** | | 29 (40.2) | |
| **DTG + ATV/r** | | 1 (1.4) | |
| **RAL + DRV/r** | | 1 (1.4) | |
| **RAL + LPV/r** | | 1 (1.4) | |
| **AZT/3TC + PI/r** | | 17 (23.6) | |
| **AZT/3TC + DTG** | | 5 (6.9) | |
| **AZT + RAL + DRV/r** | | 1 (1.4) | |
| **TDF/FTC + DRV/r** | | 1 (1.4) | |
| **TDF + RPV + LPV/r** | | 1 (1.4) | |
| **TDF/FTC + DTG** | | 2 (2.8) | |
| **TDF/FTC + RAL** | | 1 (1.4) | |
| **ABC/3TC + ATV/r** | | 1 (1.4) | |
| **ABC/3TC + DTG** | | 2 (2.8) | |
| **EVG/C/FTC/TAF** | | 5 (6.9) | |
| **EVG/C/FTC/TAF + DRV** | | 3 (4.2) | |
| **DTG + etravirine + DRV/r** | | 1 (1.4) | |

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; AZT, zidovudine; BIC, bictegravir; C, cobicistat; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; RAL, raltegravir; RAMs, resistance-associated mutations; RPV, rilpivirine; TAF, tenofovir alafenamide; TAM, thymidine analog mutation; TDF, tenofovir disoproxil fumarate.
[a]All people living with HIV in the cohort received coformulated BIC/FTC/TAF.

*Virological effectiveness*

For the primary end point at week 48, the rate of experiencing viral rebound was 2.8% (2/72; 95% CI: 0.5-8.9; Figure 1): one individual had PVL of 69 copies/ml at week 51, and the other one had PVL of 95,300 copies/ml at week 38 (Table 2, case 4 and 68**)**. Seven (9.7%) missed their blood testing at week 48 window (week 42 to week 54), and all were receiving BIC/FTC/TAF for more than 60 weeks (Figure 1). No PLWH discontinued BIC/FTC/TAF before week 48. A total of 63 (87.5%) maintained virological suppression at week 48, and one had PVL of 68 copies/ml at week 25 (Table 2, case 11). No factors associated with experiencing viral rebound were identified.

*Secondary end points*

Our cohort had a median follow-up duration of 98.6 weeks (interquartile range 77.9-120.3; range 38-131.7). Three (4.2%) PLWH had VF (once PVL ≥200 copies/ml) after switching to BIC/FTC/TAF, with an estimated incidence of 2.2 per 100 person-years (95% CI: 0.6-6.1). The Kaplan–Meier survival plots estimating PLWH with archived K65N/R plus M184V/I versus those with K65N/R only for time to VF are shown in Figure 2. All the 43 PLWH with K65N/R plus M184V/I maintained PVL <200 copies/ml, which was significantly higher than those without M184V/I (log-rank test *P*-value = 0.0449). However, we could not estimate the influence of M184V/I in the Cox proportional hazards model because of the low frequency of virological nonsuppression.

Throughout the study period, eight (11.1%) of the included PLWH had viral rebound (PVL ≥50 copies/ml), and their characteristics are shown in Table 2. The estimated incidence of viral rebound was 6.1 per 100 person-years (95% CI: 2.8-11.6). The Kaplan–Meier survival plots estimating PLWH with archived K65N/R plus M184V/I versus those with K65N/R for time to viral rebound (log-rank test *P*-value = 0.24) are shown in Figure 3.

Of the three PLWH with VF (Table 2), one (case 54) had plasma HIV RNA of 216 copies/ml at week 61, probably because of co-administration of dietary supplements containing divalent cations with BIC/FTC/TAF, who subsequently re-achieved virological suppression after counseling; the second one (case 56) had PVL of 239 copies/ml at week 87; and the third one (case 68) fulfilled our primary end point, with a PVL of 95,300 copies/ml at week 38. He reported poor adherence and was lost to follow-up for about half a year. After resuming BIC/FTC/TAF for 4 weeks, the PVL was

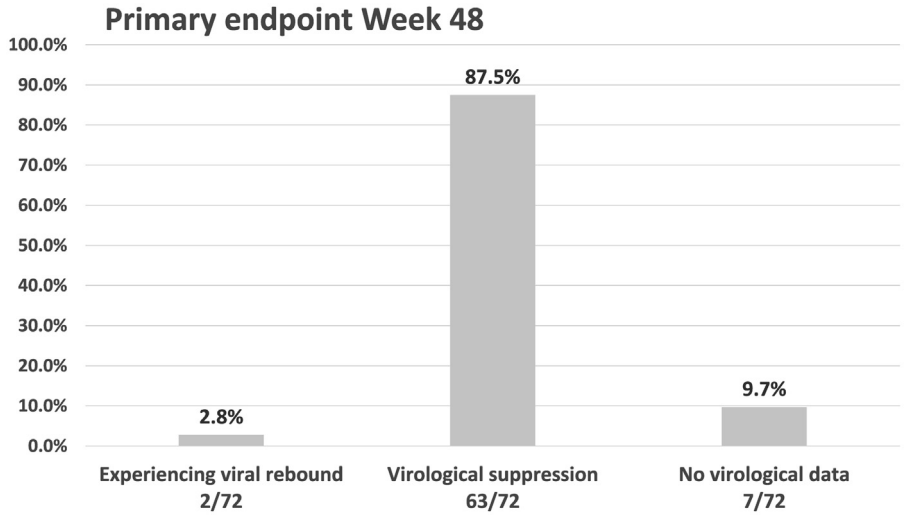


**Figure 1.** Virological effectiveness of switch to coformulated bictegravir, emtricitabine, and tenofovir alafenamide at Week 48 using a modified US Food and Drug Administration snapshot algorithm.

**Table 2**
Patients with plasma HIV RNA >50 copies/ml during the 2.5-year follow-up.

| No. | Archived nucleos(t)ide reverse-transcriptase inhibitor-resistance-associated mutation before switching | Before switching | PVL <200 copies/ml before switch (years) | PVL, copies/ml | Off BIC/FTC/TAF | Other comments |
|---|---|---|---|---|---|---|
| **a. Plasma HIV RNA ≥200 copies/ml** | | | | | | |
| 54 | K65R | Atazanavir/ritonavir + DTG | 4.8 | Wk 0-49: PVL, <50; Wk 61: PVL, 216; Wk 75-119: PVL, <50 | No | Viral rebound due to co-administration of dietary supplements containing divalent cations; PVL <50 copies/ml for four consecutive tests from Wk 75 to Wk 119 |
| 56 | K65KR | AZT/3TC + DRV/r | 4.7 | Wk 0-74: PVL, <50; Wk 87: PVL, 239; Wk 99: PVL, 121 | No | |
| 68 | K65R | AZT/3TC + DTG | 3.3 | Wk 0-26: PVL, <50; Wk 38: PVL, 95,300; Wk 72: PVL, 47 | Wk 38 to Wk 68: loss to follow-up | Experiencing viral rebound at Wk 38; resuming BIC/FTC/TAF at Wk 68, with PVL 47 copies/ml at Wk 72 |
| **b. Plasma HIV RNA 50-200 copies/ml** | | | | | | |
| 4 | K65R and M184I | TDF + rilpivirine + ritonavir-boosted lopinavir | 2.7 | Wk 0-92: PVL, <50; Wk 115: PVL, 54 | No | |
| 11 | A62V, K65R and M184V | TDF/FTC + raltegravir | 1.6 | Wk 0-12 PVL, <50; Wk 25: PVL, 68; Wk 30-76: PVL, <50; Wk 89: PVL, 129 | No | PVL <50 for three consecutive tests from Wk 30 to Wk 89 |
| 55 | K65R | AZT/3TC + DRV/r | 5.8 | Wk 0-36: PVL, <50; Wk 51: PVL, 69 | No | Experiencing viral rebound at Wk 51 |
| 66 | A62V, K65R, and M184IV | AZT/3TC + DRV/r | 0.5 | Wk 0-45: PVL, <50; Wk 67: PVL, 109; Wk 78-119: PVL, <50 | No | PVL <50 for three consecutive tests from Wk 78 to Wk 119 |
| 51 | K65R | DRV/r + DTG | 3.7 | Wk 0-74: PVL, <50; Wk 99: PVL, 176; Wk 108-122: PVL, <50 | No | PVL <50 for two consecutive tests from Wk 108 to Wk 122 |

Abbreviations: 3TC, lamivudine; AZT, zidovudine; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; FTC, emtricitabine; PVL, plasma HIV RNA load; TDF, tenofovir disoproxil fumarate; Wk, week

47 copies/ml at week 72 of his study entry. There were four censoring events: two transfers of care, one death due to pulmonary hemorrhage from pre-existent bronchiectasis and *Mycobacterium avium* complex infection, and one discontinuation of BIC/FTC/TAF for the initiation of rifapentine and isoniazid for tuberculosis infection treatment.

## Discussion

To the best of our knowledge, we present the first data from a multicenter retrospective cohort study evaluating the impact of archived K65N/R mutation on the effectiveness of the switch to BIC/FTC/TAF as the maintenance therapy in PLWH who had

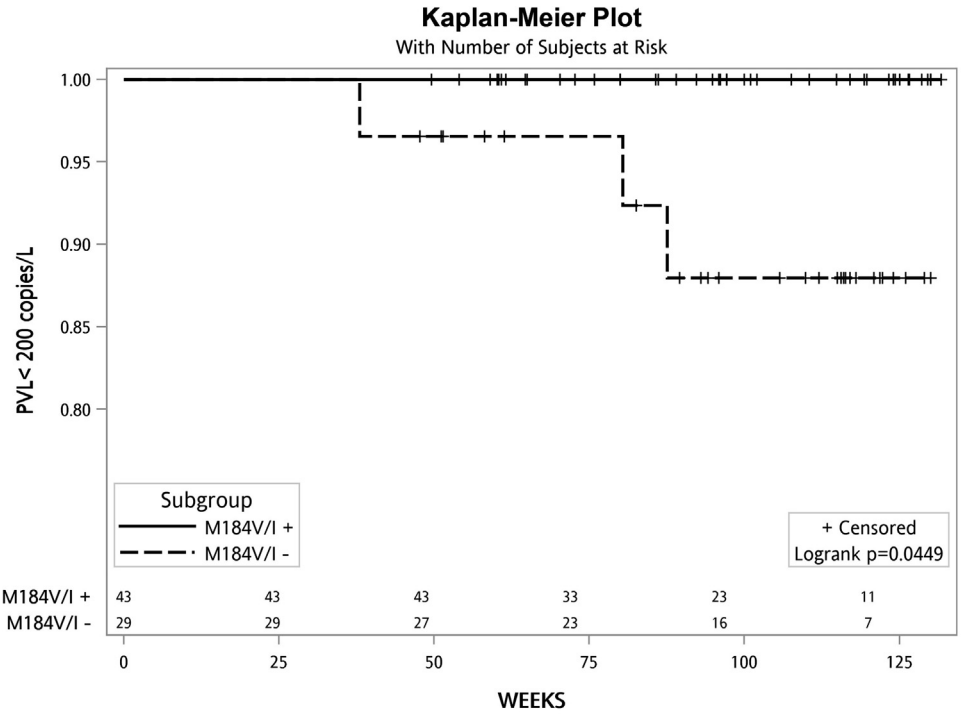


**Figure 2.** Kaplan-Meier plots showing time to virologic failure to 200 copies/ml or more in the included people living with HIV (K65N/R plus M184V/I vs K65N/R) were switched to coformulated bictegravir, emtricitabine, and tenofovir alafenamide.
Abbreviation: PVL, plasma HIV RNA load.

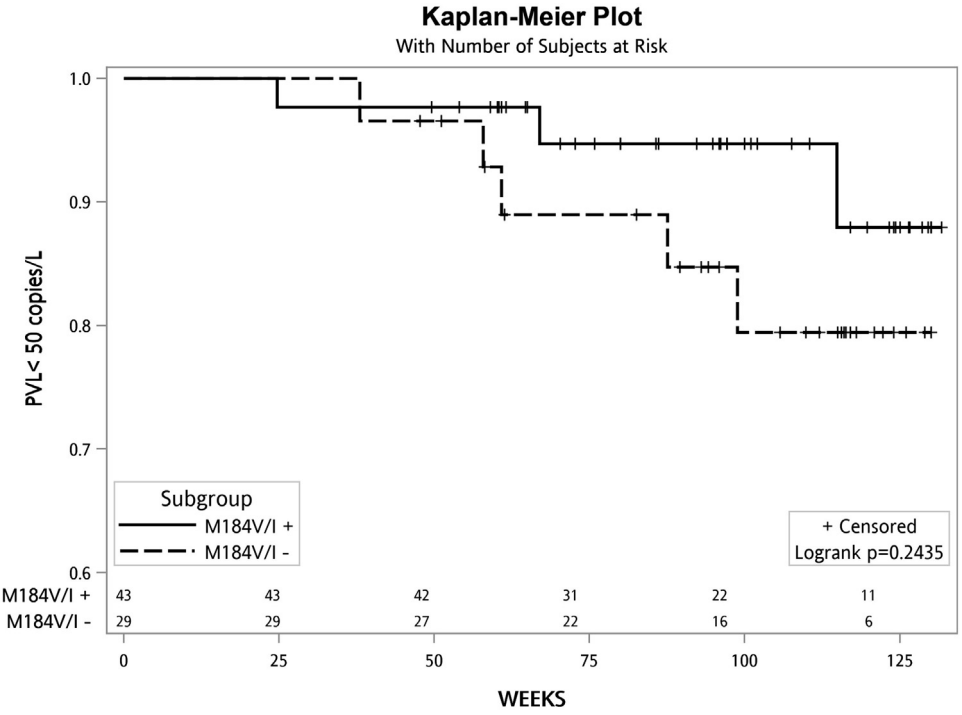


**Figure 3.** Kaplan-Meier plots showing time to the first event of viral rebound (PVL >50 copies/ml) in people living with HIV (K65N/R plus M184V/I vs K65N/R) who were switched to coformulated bictegravir, emtricitabine, and tenofovir alafenamide.
Abbreviation: PVL, plasma HIV RNA load.

previously experienced VFs. A high proportion (87.5%) of the included PLWH maintained virological suppression at week 48, and the incidence of viral rebound to >200 copies/ml was low (2.2 per 100 person-years) during the study period. The findings of our study are consistent with several trials that supported the use of tenofovir plus 3TC or FTC and a second-generation INSTI in PLWH with VF while receiving an NNRTI-based regimen or in a stable switch among PLWH with historic RAMs to NRTIs (Aboud *et al.*, 2019; Mulenga *et al.*, 2022; Paton *et al.*, 2022).

The recently published VISEND study in Zambia and NADIA study in Kenya, Uganda, and Zimbabwe confirmed TDF/3TC/DTG as a second-line treatment after failures with NNRTI-based regimens (Mulenga *et al.*, 2022; Paton *et al.*, 2022). Our results of maintaining virological control with BIC/FTC/TAF are consistent with these findings and suggest that BIC/FTC/TAF could be a switching option for PLWH who are virally suppressed and are on second-line regimens. The fixed-dose combination containing second-generation INSTIs continue to provide benefits, such as favorable tolerability and toxicity profile, reduced pill burden, durable efficacy, the minimal potential for drug interactions due to the absence of a pharmacokinetic booster, and a high barrier to resistance to PLWH as a first-line ART and second-line antiretroviral regimens at VF while receiving NNRTI-based regimens (Chen *et al.*, 2021, 2022).

Once VF is ascertained, second-line ART should avoid suboptimal therapy and ideally display a higher genetic barrier. Choosing optimal second-line regimens is informed by drug resistance testing in resource-rich countries and should include at least two new active drugs (one with a high genetic barrier to resistance) (DHHS, 2022). In resource-limited areas, the World Health Organization (2021) provides an algorithm for choosing the second-line regimen based on considerations of drug resistance. Our data showed that nearly two-thirds of our included PLWH who adapted AZT/3TC plus boosted PIs (n = 47) as the initial salvage regimens, but 70% of them subsequently changed the regimens due to tolerability and safety issues. The regimen of DTG plus boosted PIs (mostly boosted darunavir) was the most common regimen before the switch to BIC/FTC/TAF. The two-drug regimen of DTG plus boosted PIs consists of two antiretrovirals with a high genetic barrier and is recommended as a salvage therapy for highly experienced PLWH to maximize the likelihood of regaining viral suppression (DHHS, 2022). However, the drug-drug interactions and metabolic derangement are the main concerns with this regimen (Lee *et al.*, 2021).

Recycling tenofovir may raise concerns about a potential suboptimal therapy. However, the findings of inverse correlation between virological suppression and the number of active NRTIs in DAWNING study were in line with those of SECOND-LINE, SELECT, and EARNEST trials (Aboud *et al.*, 2019; Boyd *et al.*, 2015; La Rosa *et al.*, 2016; Paton *et al.*, 2017; Stockdale *et al.*, 2018). Furthermore, the NADIA study showed similar treatment responses (TDF-based vs AZT-based) in the participants with K65R mutation, despite the presence of a high prevalence of M184V/I (Paton *et al.*, 2021, 2022). All PLWH in our study had archived K65N/R, and the time to viral rebound (>50 or 200 copies/ml) were not affected by the presence of M184V/I during a 2.5-year follow-up. The findings of the current and previous studies suggest that the genotypic resistance testing does not precisely predict NRTI activity in second-generation INSTI-based regimens. However, high-level resistance to DTG can still occur, and monitoring the emergence of resistance to second-generation INSTIs in cases of longer-term VF is critical (Paton *et al.*, 2022).

In France, an international cohort study tried to analyze the antiviral activities of AZT and TDF in the presence of the K65R mutation. The bootstrap analyses constructed using 1000 replicates showed similar magnitudes in the reduction of PVL with AZT versus TDF in the setting of PLWH with HIV-1 harboring K65R (Grant *et al.*, 2010). The reduction in viral replicative fitness associated with the K65R mutation may explain the retained activity of tenofovir, despite the reduced phenotypic susceptibility (Weber *et al.*, 2005).

Our study has several limitations. First, this was a single-arm retrospective observational study. We did not have HIV RNA assessments at uniform time points for the included PLWH after the switch to BIC/FTC/TAF. The primary analysis showed that around 10% of the included PLWH missed the viral load testing at week 48 due to the COVID-19 pandemic; however, the rate of discontinuation of BIC/FTC/TAF was low (2.7%) during the 2.5 years of follow-up. Second, although the decision to switch to BIC/FTC/TAF was made by the treating physicians and the median duration of virological suppression before the switch was 4.7 years, we had no data on how many patients might have been eligible but did not switch to BIC/FTC/TAF, nor do we know what were the reasons or concerns of the physicians. It is likely that the PLWH who were adherent were considered suitable for this regimen. The results may not be generalizable to those who are not adherent to ART. Third, we did not have the resistance testing of those experiencing viral rebound, especially the individual with PVL >1000 copies/ml (Table 2, case 68). Finally, given the retrospective study design and case number of the study, residual confounding cannot be excluded.

## Conclusion

In conclusion, we demonstrate that BIC/FTC/TAF was effective in maintaining viral suppression for PLWH with HIV-1 harboring K65R RAM. Given the good tolerability, low toxicity, reduced pill burden, and high genetic barrier to resistance, BIC/FTC/TAF could be a therapeutic option for second-line treatment simplification.

## Declaration of competing interest

C.-C.H. received research support from Gilead Sciences, Merck, and ViiV; received speaker honoraria from Gilead Sciences; and served on the advisory boards for Gilead Sciences. H.-Y.S. has received research support from Gilead Sciences. The other authors have no competing interests to declare.

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## Ethical approval

The study was approved by the institutional review board or research ethics committee of the participating hospitals and written informed consent was waived due to the retrospective study design.

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## Author contributions

M.-S.T, C.-J.Y., and C.-C.H.: conception and design of the study; M.-S.T., H.-Y.S., C.-P.C., C.-H.L., C.-Y.L., C.-E.L., H.-J.T., T.-C.H., C.-W.L., Y.-T.L., and B.-H.L.: acquisition of data; M.-S.T.: data analysis and data interpretation; M.-S.T., H.-Y.S., C.-P.C., C.-H.L., C.-Y.L., C.-E.L., H.-J.T., T.-C.H., C.-W.L., Y.-T.L., and B.-H.L.: revising the manuscript critically for important intellectual content; M.-S.T., C.-J.Y., and C.-C.H.: drafting and revision of the manuscript. All authors read and approved the final version to be submitted.

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