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Original Article

Effectiveness of second-generation integrase strand-transfer inhibitor-based regimens for antiretroviral-experienced people with HIV who had viral rebound

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KEYWORDS
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Dolutegravir;

Abstract *Background:* Antiretroviral regimens containing a second-generation integrase strand-transfer inhibitor (INSTI) plus 2 nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) are the recommended therapy for people with HIV (PWH) who are antiretroviral-naïve or on stable antiretroviral therapy (ART) with viral suppression. Real-world data on the virologic effectiveness of co-formulated bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) among PWH with virologic failure while receiving other ART remain sparse.
Methods: We retrospectively reviewed the medical records of PWH who had viral rebound with plasma HIV RNA >1000 copies/mL and were switched to either dolutegravir combined with 2

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Resistance-associated mutation;
Genetic barrier

NRTIs or BIC/FTC/TAF. The primary end point was re-achieving viral suppression within the first 48 weeks of switch. The association between NRTI-related resistance-associated mutations (RAMs) and virologic effectiveness was examined.
Results: Seventy-nine PWH with viral rebound while receiving other antiretroviral regimens were included. Within the first 48 weeks of switch, the overall probability of re-achieving viral suppression was 79.7% (82.5% [33/40] and 76.9% [30/39] for BIC/FTC/TAF and dolutegravir-based regimens, respectively, p = 0.78). PWH with a higher CD4 lymphocyte count (adjusted odds ratio, per 100-cell/mm^3 increase, 1.41; 95% confidence interval, 1.02–1.95) were more likely to re-achieve viral suppression. Among PWH switching to BIC/FTC/TAF who had pre-existing RAMs to NRTIs before switch, 14 of 15 (93.3%) successfully achieved viral suppression.
Conclusions: Switching to BIC/FTC/TAF and dolutegravir-based regimens could re-achieve viral suppression in four-fifth of the PWH who experienced viral rebound during treatment with other antiretroviral regimens. Pre-existing NRTI-related RAMs did not have adverse impact on the effectiveness of dolutegravir combined with 2 NRTIs or BIC/FTC/TAF.

Introduction

Choosing a suitable salvage antiretroviral therapy (ART) is important for people with HIV (PWH) who experience virologic failure. An optimal second-line regimen could re-establish viral suppression, prevent further accumulation of resistance-associated mutations (RAMs), mitigate the risk of onward HIV transmission, and reduce HIV-related morbidities and mortalities.[1–4] Before the era of integrase strand-transfer inhibitors (INSTIs), boosted protease inhibitor (PI)-based regimens had been recommended as salvage ART in most international guidelines due to their high genetic barrier to emergence of antiretroviral resistance.[1–3]

After the introduction of dolutegravir (DTG), a second-generation INSTI with high genetic barrier, its efficacy as salvage therapy has been demonstrated when compared with PIs in randomized clinical trials.[5–7] In the DAWNING study, DTG combined with 2 nucleoside reverse-transcriptase inhibitors (NRTIs) was superior to boosted lopinavir-based ART in re-achieving viral suppression among PWH who experienced virologic failure while receiving first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy.[5] The study was terminated early due to the superiority with DTG-based therapy. In the NADIA study, DTG combined with 2 designated NRTIs was non-inferior to boosted darunavir with 2 NRTIs in terms of viral suppression at week 48 (90.2% vs. 91.7%, respectively) among PWH with virologic failure while receiving an NNRTI plus tenofovir disoproxil fumarate (TDF) and lamivudine or emtricitabine.[6,7] With the findings of these two clinical trials, DTG plus 2 NRTIs are currently recommended for PWH who experience virologic failure with their first-line NNRTI-based ART in different HIV treatment guidelines.[1,2]

Bictegravir (BIC), another second-generation INSTI, also has a high genetic barrier similar to DTG, and, when co-formulated with emtricitabine and tenofovir alafenamide (BIC/FTC/TAF), has been shown to have similar clinical efficacy as DTG plus FTC/TAF or lamivudine/abacavir in antiretroviral-naïve PWH.[8,9] Real-world data also suggested similar risks of lower-level viremia and virologic failure between PWH who were stably switched to DTG plus 2 NRTIs and those who were switched to BIC/FTC/TAF, regardless of the presence of NRTI-related RAMs.[10] However, studies on the effectiveness of switch to BIC/FTC/TAF in the cases of virologic failure are limited. In the retrospective study, we aimed to assess the virologic effectiveness of second-generation INSTI (either co-formulated BIC/FTC/TAF or DTG-based regimens) for PWH who had experienced viral rebound while receiving other antiretroviral regimens.

Material and methods

Study design and patients

This was a single-center, retrospective cohort study conducted in the National Taiwan University Hospital (NTUH). PWH who were aged ≥20 years and received HIV care with at least 3 months of ART prescription between 1 January 2016 and 30 March 2022 were eligible for the study. For eligible PWH, available results of plasma HIV RNA load (PVL) were retrieved from the electronic medical record database (National Taiwan University Hospital-Integrated Medical Database; NTUH-IMD). We then screened these PWH to identify those who were receiving ART and had ever achieved viral suppression (defined as PVL <50 copies/mL) before developing viral rebound (defined as PVL >1000 copies/mL). PWH who did not have clinic visits or drug refills within the 6 months prior to their viral rebound were excluded. PWH who experienced viral rebound but remained on the same background antiretroviral regimens were also excluded. Among those eligible PWH, we included those who switched from their original background ART to a second-generation INSTI-based ART (either BIC/FTC/TAF or DTG plus 2 NRTIs). All included PWH were followed since the day of switch (to either BIC/FTC/TAF or DTG-based regimens) until the date of their last available PVL testing before a censoring event occurred. Censoring events in this analysis included changes made to the core agents (BIC or DTG) of ART, death, loss to follow-up (no

clinics visits or drug refills for >6 months) or the end of observation (30 March 2022), whichever occurred first.

According to the national HIV treatment guidelines in Taiwan, PWH are advised to receive determinations of PVL and CD4 cell count at least every 3–6 months for those on stable ART, with additional testing in the presence of virologic rebound or ART switch. During the observation period, quantification of PVL was performed using the Cobas® Amplicor HIV-1 Monitor Test (Cobas® Amplicor v.1.5; Roche Diagnostics, Indianapolis, IN, USA) with a lower detection limit of 20 (1.3 $\log_{10}$) copies/mL. The demographic and clinical variables, including age, sex, date of HIV diagnosis, date of outpatient clinics and ART prescriptions, PVL, CD4 lymphocyte counts and other laboratory results were also retrieved from the NTUH-IMD.

We also collected the available reports of HIV genotypic resistance testing of included PWH. In Taiwan, genotypic resistance testing is performed before initiation of first-line therapy for the purpose of surveillance or at the time of virologic failure on an as-needed basis at several designated hospitals and Taiwan Centers for Disease Control. For PWH who had available genotypic resistance reports, their archived RAMs to NRTIs or INSTIs before the switch was reviewed and the genotypic resistance scores (GSSs) were determined using the Stanford HIV Drug Resistance Database.[11–13] Each antiretroviral agent would be assigned with a score of 0 (high-level resistance), 0.25 (intermediate-level resistance), 0.50 (low-level resistance), 0.75 (potential low-level resistance) or 1 (susceptible). The study was approved by the Research Ethics Committee of the hospital (registration number, 202205040RINB) and informed consent was waived due to the retrospective study design and decoding of the personal identifiers.

Study end points

The primary end point was the proportion of PWH who re-achieved and maintained viral suppression, defined as PVL <50 copies/mL, within the first 48 weeks of switch to either BIC/FTC/TAF or DTG-based regimens. PWH who had a censoring event before week 48 would be considered to have re-achieved viral suppression if they could achieve viral suppression and maintain PVL <50 copies/mL until the censoring event. Secondary end points included the probabilities of re-achieving viral suppression within the first 48 weeks for the two subgroups receiving BIC/FTC/TAF or DTG-based regimens. Furthermore, the proportions of re-achieving viral suppression beyond 48 weeks were also estimated, with two different definitions by either a strict (PVL <50 copies/mL) or more lenient PVL threshold (PVL <200 copies/mL). For the included PWH with available archived data of RAMs before switch, the association between GSS and viral suppression was also analyzed.

Statistical analysis

Demographic and clinical characteristics were reported for the included PWH, with additional comparisons between those who were switched to the BIC/FTC/TAF and those who were switched to DTG-based ART. Non-categorical variables were compared using Student's t-test or Mann–Whitney U-test, and categorical variables were compared using $\chi 2$ test or Fisher's exact test. Kaplan–Meier plots were used to compare the durations needed to re-achieve viral suppression between the two regimens. Univariate and multivariate logistic regression models were created to adjust for confounders and to identify potential factors associated with re-achieving viral suppression after switch to INSTI-based second-line therapy. In the multivariate analysis, we constructed the logistic regression model using a backward stepwise elimination process, in which all possible relevant variables were included in the model initially. The variable with the largest P-value was then removed from the model. The process was repeated until all factors in the model had a P-value of <0.2. Statistical analyses were performed using STATA software version 14.0 S/E (Stata Corp., College Station, TX, USA). All P-values were two-sided.

Results

Study population

During the study period, we identified 79 PWH who met the criteria of viral rebound and switched to second-generation INSTI-containing regimens (Fig. 1). Of them, 40 PWH switched to BIC/FTC/TAF (BIC group) and 39 PWH to DTG-based ART (DTG group). The median observation duration was 89 weeks (interquartile range [IQR], 39–118 weeks), which was not significantly different between the two groups of included PWH (95 weeks [IQR, 63–114] for BIC group and 70 weeks [IQR, 30–123] for DTG group; $p = 0.39$). The comparisons of baseline characteristics between the two groups of included PWH are shown in Table 1.

Compared with PWH in the DTG group, those in the BIC group had a significantly lower median CD4 lymphocyte count before switch (390 vs 232 cells/mm^3, $p = 0.049$) and longer duration of HIV diagnosis (median, 4 vs 8 years, $p = 0.007$). Most PWH (82.1%) in the DTG group switched from NNRTI-based ART to DTG-based regimens, while 75% of the PWH in the BIC group were receiving a first-generation INSTI-based ART before switch. The proportions of PWH having available genotypic resistance profiles and the distributions of NRTI-related RAMs were similar for both groups, though PWH in the BIC group were more likely to have INSTI-related RAMs.

Virologic response

According to our definition, the overall probability of re-achieving viral suppression within the first 48 weeks after ART switch was 79.7% (63/79) of the included PWH. There was no statistically significant difference in re-achieving viral suppression between the two groups within 48 weeks (82.5% [33/40] for PWH in the BIC group and 76.9% [30/39] for those in the DTG group; $p = 0.78$). The intervals between ART switch and viral re-suppression are compared in Fig. 2, which did not significantly differ between the two groups.

When extending the observation beyond 48 weeks, 71 (89.9%) of the included PWH had re-achieved and

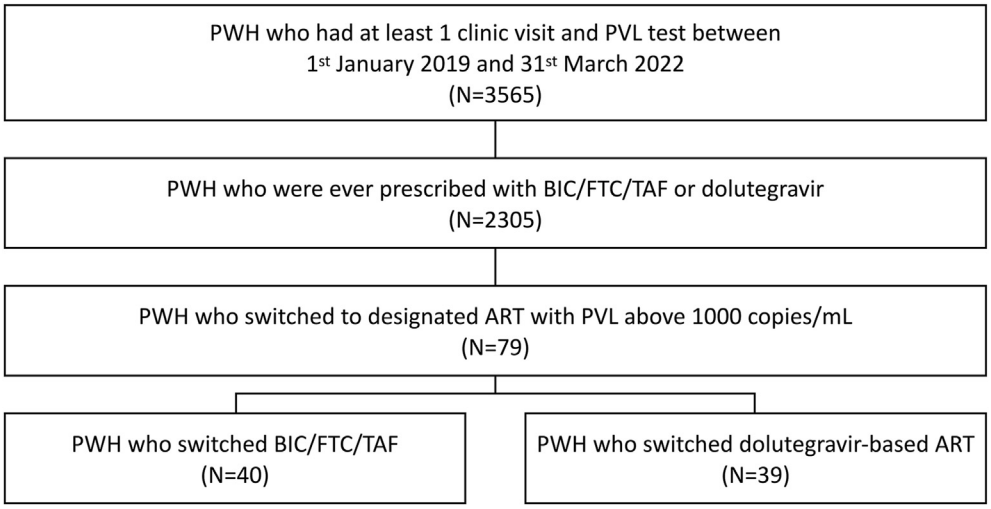

Figure 1. The study flow. **Abbreviations**: PWH, people with HIV; PVL, plasma HIV viral load; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ART, antiretroviral therapy.

maintained viral suppression below 50 copies/mL during the entire observation period (95.0% [38/40] for PWH in the BIC group and 84.6% [33/39] for those in the DTG group, $p = 0.15$) before any censoring events occurred. If we used a more lenient threshold of viral suppression (PVL <200 copies/mL), the proportion of viral re-suppression during the entire observation period was 92.4% (95.0% [38/40] for PWH in the BIC group and 89.7% [35/39] for those in the DTG group, $p = 0.43$). The detailed sequential changes of PVL after switching to either regimen are demonstrated in Fig. S1.

Overall, seven (17.5%) PWH in the BIC group and nine (23.1%) in the DTG group did not achieve virologic suppression within the first 48 weeks of switching. In the BIC group, two out of the seven PWH who failed to achieve virologic suppression were lost to follow-up before week 48, while the remaining five continued bictegravir-based ART and eventually achieved virologic suppression.

Table 1 Baseline characteristics of the included PWH who switched to co-formulated bictegravir/emtricitabine/tenofovir alafenamide or DTG-based regimens.

Characteristic	All PWH (N = 79)	BIC/FTC/TAF (N = 40)	DTG-based ART (N = 39)
Age, median (IQR), years	36.4 (32.6–43.1)	38.1 (33.8–46.0)	36.3 (29.7–40.9)
Male sex, n (%)	75 (94.9)	38 (95)	37 (94.9)
PVL at switch, median (IQR), log_{10} copies/ml	4.4 (3.7–4.9)	4.4 (3.6–4.7)	4.4 (3.7–5.0)
CD4 count at switch, median (IQR), cells/mm^3	323 (180–538)	232 (146–418)	390 (244–624)
Duration of HIV diagnosis before switch, median (IQR), years	4 (2–8)	8 (3–11)	4 (2–5)
Duration of follow-up after antiretroviral switch, median (IQR), weeks	89 (39–118)	95 (63–114)	70 (30–123)
Antiretroviral-regimens used before switch, n (%)			
PI-based regimens	5 (6.3)	5 (12.5)	0 (0)
NNRTI-based regimens	37 (46.8)	5 (12.5)	32 (82.1)
INSTI-based regimens	37 (46.8)	30 (75)	7 (17.9)
PWH with available genotypic resistance results, n (%)	70 (88.6)	36 (90)	34 (87.2)
PWH with any NRTI-related RAMs	30/70 (42.9)	15/36 (41.7)	15/34 (44.1)
PWH with M184I/V mutation	25/70 (35.7)	12/36 (33.3)	13/34 (38.2)
PWH with INSTI-related RAMs	8/70 (11.4)	6/36 (16.7)	2/34 (5.9)
NRTI choices at switch, n (%)			
tenofovir disoproxil fumarate plus emtricitabine	–	–	10 (25.6)
abacavir plus lamivudine	–	–	28 (71.8)
tenofovir alafenamide plus emtricitabine	40 (100)	40 (100)	–

Abbreviations: BIC/FTC/TAF, co-formulated bictegravir/emtricitabine/tenofovir alafenamide; INSTI, integrase strand-transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV; PVL, plasma HIV viral load; RAM, resistance-associated mutation.

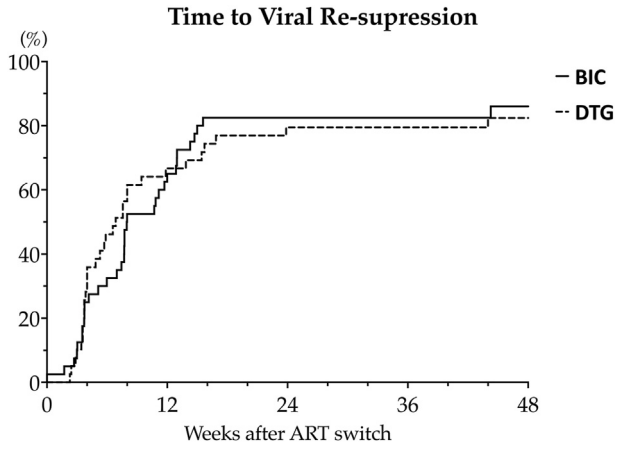

Figure 2. Time to viral re-suppression within the first 48 weeks after switching to co-formulated bictegravir/emtricitabine/tenofovir alafenamide and dolutegravir-based regimens. **Abbreviations**: ART, antiretroviral therapy; BIC, bictegravir; DTG, dolutegravir.

Similarly, four PWH who failed to achieve virologic suppression in the DTG group were lost to follow-up before week 48, and the remaining four were continued on dolutegravir-based ART and eventually achieved virologic suppression; and only one PWH remained HIV viremic after week 48 and was switched to boosted darunavir-based ART at week 70. Out of these 16 PWH, five underwent genotypic resistance testing, and no emerging RAMs to NRTIs or INSTIs were detected.

In multivariate logistic regression model, the only factor associated with re-achieving viral suppression within 48 weeks was baseline CD4 lymphocyte counts before switch (adjusted odds ratio, per 100-cell/mm^3 increase, 1.41; 95% CI, 1.02—1.95). Choice of core agents of ART (BIC vs DTG) was not associated with the probability of re-achieving viral suppression in both univariate and multivariate analysis.

Archived RAM and the effectiveness of BIC/FTC/TAF

In our cohort, 70 of 79 (88.6%) included PWH had available genotypic resistance data prior to the switch to BIC/FTC/TAF or DTG-based antiretroviral regimens; and 32 of them (45.7%) had documented archived RAMs to NRTIs or INSTIs. Of these 32 PWH, 93.8% had NRTI-related RAMs and 78.1% were known to have HIV-1 harboring M184V/I mutation before switch. Only two PWH in the DTG group had RAMs conferring high-level resistance to tenofovir, such as K65R. In terms of RAMs to INSTIs, two PWH had HIV-1 harboring RAMs that are predicted to confer potential low-level resistance to BIC (one with S147G and one with E92Q mutation) and one PWH had HIV-1 harboring RAMs that were predicted to confer intermediate-level resistance (with a combination of Q148R and N155H) (13). However, despite the presence of RAMs to NRTIs or INSTIs, only 4 PWH with archived RAMs (1 with BIC/FTC/TAF and 3 with DTG-based regimens) failed to re-achieve viral suppression after switch. The overall virologic responses after switch for those with archived RAM are listed in Table 2. Both regimens demonstrated a high probability of re-achieving viral suppression (15/16 [93.8%] for PWH in the BIC group and 13/16 [81.3%] for those in the DTG group, $p = 0.6$). Furthermore, the predicted GSS was not associated with virologic success after switch for both groups.

Discussion

In this retrospective cohort study, we examined the virologic effectiveness of second-generation INSTI-based ART for PWH who had experienced viral rebound with a PVL >1000 copies/mL while receiving previous antiretroviral regimens. In our cohort, 79.7% (63/79) of included PWH re-achieved viral suppression within the first 48 weeks of ART switch. The proportions of re-achieving viral suppression within 48 weeks after ART switch were not statistically significantly different between the two groups (82.5% [33/40] for those switching to BIC/FTC/TAF vs. 76.9% [30/39] for those switching to DTG-based regimens).

Our finding demonstrating the virologic effectiveness of second-generation INSTI-based regimens for PWH who required salvage therapy is consistent with the findings in the DAWNING and NADIA trials. Both trials demonstrated that DTG-based ART was at least non-inferior to boosted PI among PWH with virologic failure to NNRTI-based regimens.[5,6] However, unlike DTG-based regimens, the clinical evidence supporting the use of BIC/FTC/TAF as salvage therapy remains scarce. In a case series with 50 PWH with pre-existing NRTI-related RAMs, Shafran et al. reported a high proportion of treatment success after switching to BIC/FTC/TAF, with 49 of 50 (98.0%) included PWH remaining virally suppressed after a median follow-up of 18.6 months.[14] However, only 8% of the PWH included in the study was HIV viremic before switch. In another retrospective cohort study from Spain, the virologic effectiveness among 506 treatment-experienced PWH was examined. In this cohort, 66 (13.4%) PWH were switched to BIC/FTC/TAF with a PVL above 50 copies/mL (15). The authors also demonstrated a high rate of virologic suppression, with 83% PWH achieving virologic suppression at week 48. However, the specific results regarding viremic PWH before switch were not reported in the study.

In our study, 30 PWH had archived NRTI-related RAMs before switching to second-generation INSTI-based ART, with 25 with HIV-1 harboring M184V mutation, and 22 (73.3%) PWH were able to successfully re-achieve viral suppression (Table 2). No significant difference was observed between BIC group and DTG group in terms of viral suppression. This finding was in line with that of NADIA trial, in which the inclusion of NRTIs with no predicted activity in the regimens was not associated with virologic failure in participants receiving DTG-based ART as salvage therapy.[6] Previous studies focusing on DTG-based ART also demonstrated that pre-existing NRTI-related RAMs did not have adverse impact on virologic suppression after stable switch.[16] The discrepancies between the predicted activities and real-life effectiveness could probably be explained by the impairment of viral fitness or replicative capacity of HIV-1 in the presence of NRTI-related RAMs.[17—19] Aside from adding to the evidence supporting the effectiveness of DTG in the presence of NRTI-related RAM, this study and our previous study also demonstrated BIC/FTC/TAF might also possess similarly high antiviral

Table 2 Detailed clinical information of 32 PWH who had previously archived resistance-associated mutations to nucleoside reverse-transcriptase inhibitors or integrase strand-transfer inhibitors.

No.	Previous ART history	NRTI-related RAMs	INSTI-related RAMs	ART before switch	INSTI used	PVL before switch	Results
1	XTC, ABC, AZT, TAF, DRV/r, DTG, EVG/c	A62V, M184V	ND	TAF/FTC/EVG/c	BIC	2060	Lost to follow-up after 6 months
2	XTC, ABC, AZT, LPV/r, DTG	D67DN, M184MV	ND	ABC/3TC/DTG	BIC	1200	virally re-suppressed
3	XTC, TAF, EVG/c	D67DG	ND	TAF/FTC/EVG/c	BIC	72100	virally re-suppressed
4	XTC, TDF, EFV, RPV	A62AV, T69NT	ND	TDF/FTC/RPV	BIC	272000	virally re-suppressed
5	XTC, AZT, TDF, TAF, DRV/r, RAL, DTG, EVG/c	M184MV, T69Deletion	ND	TAF/FTC/EVG/c	BIC	10900	virally re-suppressed
6	XTC, TDF, TAF, DRV/r, DTG, EVG/c	K70R, M184V, K219E	S147SG	TAF/FTC/EVG/c	BIC	19600	virally re-suppressed
7	XTC, ABC, AZT, TDF, NPV, RPV, ATV, RAL	V75IV, M184V	Y143R	TDF/FTC/RAL	BIC	4320	virally re-suppressed
8	XTC, ABC, AZT, TDF, ATV/r, RPV, DRV/r, DRV/c, RAL	M184MV	Q148QR, N155HN	TDF/FTC/DRV/c	BIC	1460	virally re-suppressed
9	XTC, ABC, TDF, TAF, EFV, EVG/c	L74LS	ND	TAF/FTC/EVG/c	BIC	4930	virally re-suppressed
10	XTC, TDF, RTV, DRV/r	L74V, M184V	ND	TDF/FTC/DRV/r	BIC	4720	virally re-suppressed
11	XTC, ABC, AZT, TDF, TAF, NVP, LPV/r, DTG, EVG/c	M184V	ND	TAF/FTC/EVG/c	BIC	1188	virally re-suppressed
12	XTC, ABC, AZT, TDF, TAF, RPV, RAL, DTG, EVG/c	ND	T66I, T97A	TAF/FTC/EVG/c	BIC	1650	virally re-suppressed
13	XTC, ABC, TDF, ATV, DTG	Y115F, M184V, V75AV	A128T	ABC/3TC/DTG	BIC	1740	virally re-suppressed
14	XTC, TDF, RPV, RTV, ATV/r, DRV/r, DRV/c	M184V	ND	TDF/FTC/DRV/c	BIC	2860	virally re-suppressed
15	XTC, ABC, AZT, TDF, LPV/r, DRV/r, DTG	M184I	E92Q	TDF/FTC/DRV/r	BIC	2440	virally re-suppressed
16	XTC, ABC, TAF, ATV/r, DTG, EVG/c	A62V, M184V	ND	ABC/3TC/DTG	BIC	9290	virally re-suppressed
17	XTC, AZT, RPV, LPV/r,	D67DNG, M184V	ND	AZT/3TC/LPV/r	DTG	1090	virally re-suppressed
18	XTC, AZT, RPV	M184V	ND	AZC/3TC/RPV	DTG	32000	virally re-suppressed
19	XTC, ABC, AZT, RPV, LPV/r, DRV/r	M184IMV	L74IM	AZC/3TC/DRV/r	DTG	74300	virally re-suppressed
20	XTC, ABC, TDF, EFV, NVP, LPV/r	L74V, M184V	ND	TDF/FTC/EFV	DTG	790000	virally re-suppressed
21	XTC, TDF, EFV	M184V	ND	TDF/FTC/EFV	DTG	5910	Not suppressed
22	XTC, TDF, EFV, DRV/r	M41ML, K65R, M184V	ND	TDF/FTC/DRV/r	DTG	14400	virally re-suppressed
23	XTC, AZT, TDF, NPV, EFV, LPV/r, RAL	M184V	ND	TDF/FTC/EFV	DTG	39000	virally re-suppressed
24	XTC, TDF, EFV, NVP	L74F	ND	TDF/FTC/EFV	DTG	85600	virally re-suppressed
25	XTC, ABC, TDF, EFV, LPV/r	M184V	ND	TDF/FTC/EFV	DTG	25500	virally re-suppressed
26	XTC, TDF, NVP, EFV	M184V	ND	TDF/FTC/EFV	DTG	2450	virally re-suppressed
27	XTC, TDF, RPV	M184V	ND	TDF/FTC/RPV	DTG	4400	virally re-suppressed
28	XTC, ABC, LVP/r, DRV/r, RAL	M184V	ND	TDF/FTC/DRV/r	DTG	1650	virally re-suppressed
29	XTC, ABC, TDF, EFV, LPV/r	ND	A128T	TDF/FTC/EFV	DTG	5490	Not suppressed
30	XTC, ABC, TDF, NVP, LPV/r	M184V	ND	TDF/FTC/LPV/r	DTG	16500	virally re-suppressed
31	XTC, AZT, RPV	M41ML, K65R, M184V	ND	TDF/FTC/EFV	DTG	1470	virally re-suppressed
32	XTC, ABC, AZT, TDF, NVP, LPV/r	T69NT	ND	AZT/3TC/LPV/r	DTG	544000	Not suppressed

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; DRV/c, cobicistat-boosted darunavir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; INSTI, integrase strand-transfer inhibitor; LPV/r, ritonavir-boosted lopinavir; ND, not detected; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PVL, plasma HIV RNA load; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; XTC, lamivudine or emtricitabine.

activities in PWH with HIV-1 harboring NRTI-related RAMs.[20] Another Spanish cohort study including 69 PWH with pre-existing NRTI-related RAMs before switching to BIC/FTC/TAF also demonstrated that 88.4% of them achieved virologic suppression at week 48; however, only 8 PWH (11.6%) in the cohort had PVL above 50 copies/mL before switch.[15] It is noteworthy that one of our PWH successfully re-achieved viral suppression despite presence of RAMs to INSTI that might confer intermediate-level resistance to BIC prior to switch. The preexisting RAMs to INSTIs before switch likely arose from previous exposure to first-generation INSTIs such as raltegravir and cobicistat-boosted elvitegravir. The explanation to this finding is unclear, but it might be related to the high genetic barrier and higher BIC concentration achieved during daily dosing.[21] It is important to note that, in the NADIA trial, more PWH who failed to achieve viral suppression with DTG-based regimen had emergence of RAMs to INSTIs compared with boosted darunavir-based regimens. However, no genotypic resistance testing was performed for PWH included in our study after ART switch. Therefore, it was not clear whether similar risk of emergence of INSTI resistance would occur in PWH switching to BIC/FTC/TAF as salvage therapy. More studies of larger sample sizes and longer durations of follow-up are warranted to better understand the role of BIC/FTC/TAF as salvage therapy in PWH harboring RAMs to INSTIs that confer low-to intermediate-level resistance.

Our study had several limitations and our findings should be interpreted with necessary caution. The study was based on data retrospectively extracted from electronic medical database of a university hospital and, therefore, the timing and reason of virologic failure could not be confirmed for all included PWH and the indication and timing of ART switch might vary with different healthcare providers. Therefore, we attempted to reduce the risks of confounding by clearly defining the inclusion criteria and primary end point using PVL criteria. Furthermore, due to the retrospective study design and impact of COVID-19 epidemics in Taiwan during the observation period,[22,23] clinic visits and PVL testing had become very irregular for some PWH in our cohort and we were unable to perform a standard FDA snapshot analysis due to the irregular timing of PVL testing during the observation period. Finally, limited by the small sample size, the comparisons between BIC and DTG groups were very likely underpowered and subgroup analyses with PWH harboring different combinations of archived RAMs were not performed. Moreover, our study included only treatment-experienced PWH with virologic failure and our findings might not be generalizable to treatment-naïve PWH or virally-suppressed PWH in consideration of choosing an alternative antiretroviral regimen.

In conclusion, we have demonstrated in this retrospective study including PWH with viral rebound during antiretroviral treatment that the virologic effectiveness with BIC/FTC/TAF was similar to that with DTG-based therapy, when prescribed as salvage regimens. Moreover, a high proportion of PWH with archived NRTI-related RAMs could re-achieve viral suppression with either BIC/FTC/TAF or DTG-based ART.

Ethical approval

The study was approved by the Research Ethics Committee of National Taiwan University Hospital (Taipei, Taiwan) [registration no. 202205040RINB]. Informed consent was waived due to the retrospective study design.

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Declaration of Competing Interests

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Appendix A. Supplementary data

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