scientific reports

Check for updates

OPEN

Relationship between adherence to bictegravir/emtricitabine/tenofovir alafenamide fumarate and clinical outcomes in people with HIV in Japan: a claims database analysis

Nao Taguchi[1], Yi Piao[1], Annalisa Rubino[2], KuanYeh Lee[3], Megan Chen[4], Keisuke Harada[1], Tetsuya Tanikawa[1] & Toshio Naito[5]✉

A lack of adherence to long-term antiretroviral therapy may impact viral suppression. The current study examined the relationship between medication adherence and clinical outcomes in people with human immunodeficiency virus infection (PWH) receiving bictegravir, emtricitabine, and tenofovir alafenamide fumarate (B/F/TAF). A retrospective cohort study using two Japanese claims databases was conducted. Adherence was measured by the proportion of days covered (PDC). Patients were grouped into 3 PDC category and persistence was estimated by Kaplan-Meier method. Cox regression analysis was performed to investigate whether the PDC was associated with treatment discontinuation. Among 952 patients, 820 (86.1%), 95 (10.0%), and 37 (3.9%) patients were grouped into the PDC ≥ 90%, 80– < 90%, and < 80% groups, respectively. Across all PDC groups, more than 90% of patients who received B/F/TAF were receiving treatment at 1 year. There was no significant difference in the risk of discontinuation between the lower PDC groups (80– < 90% and < 80%) and the PDC ≥ 90% group (0.400 [0.096, 1.661]; 2.244 [0.663, 7.594], hazard ratio [95% confidence interval], respectively). A drug resistance test was implemented for 15 patients, none of whom discontinued B/F/TAF after the test. The results suggest that events that could cause discontinuation, such as virologic failure, were not associated with PDC.

The development of combination antiretroviral therapy (ART) has significantly increased the life expectancy of people with human immunodeficiency virus (HIV) infection (PWH). Until an HIV eradication strategy is discovered, PWH require lifelong ART to maintain viral suppression. Long-term medication use is associated with a number of issues, such as worsening quality of life, financial burden, and drug resistance[1]. Hence, treatment adherence is important for maintaining viral suppression to achieve long-term treatment success[2–4].

While some studies have indicated that 95% adherence is necessary to maintain viral suppression[2], others have suggested that this level of adherence is not necessary with more recent regimens and that the level of adherence required may vary between treatments[3,4]. Factors such as the ease of administration, including the number of pills and frequency of doses, and the motivation of patients are reported to be important factors in maintaining treatment adherence[5]. Regarding ART regimens, several real-world studies have reported that single-tablet regimens (STRs) have better adherence and long-term persistence than multiple-tablet regimens (MTRs)[5–7].

One STR—a combination tablet containing bictegravir, emtricitabine, and tenofovir alafenamide fumarate (B/F/TAF)—was launched in 2019 and recommended as a first-line treatment in Japanese clinical guidelines. B/F/TAF is a fixed-dose triple combination therapy that is taken as a single tablet once daily with or without food, low drug-drug-interaction and has a high resistance barrier. These features are also highlighted in the Japanese guidelines as a principal factor for treatment optimization in the setting of viral suppression, including improvement

[1]Gilead Sciences, K.K., Tokyo, Japan. [2]Gilead Sciences Europe Ltd, Uxbridge, UK. [3]Gilead Sciences, Taipei, Taiwan. [4]Gilead Sciences, Foster City, USA. [5]Department of General Medicine, Faculty of Medicine, Juntendo University, Tokyo, Japan. ✉email: naito@juntendo.ac.jp

of patient quality of life (QOL)[8]. In a cohort study, Maggiolo et al. examined the association between adherence (measured by the proportion of days covered [PDC]) and treatment outcomes in PWH treated with B/F/TAF. Although this was a single-center study and the number of patients was limited, they reported that PWH with > 70% of PDCs by B/F/TAF achieved HIV RNA < 200 copies/mL and maintained viral suppression[9]. Pooled analysis of 5 clinical trials revealed that virologic suppression by B/F/TAF was similar between participants with high and intermediate adherence (≥ 95% and ≥ 85% – < 95%) and those with low adherence (< 85%)[10]. Regarding intermittent B/F/TAF treatment (administered 4 or 5 days per week), virologic failure was observed in only 2 patients with low adherence, and resistance did not occur in an observational study[11]. In addition, in all clinical trials, few participants met the criteria for drug resistance testing, and the development of resistance associated with mutations to a component of B/F/TAF was not observed[12–15]. However, the data are available from clinical studies in non-Japanese populations, and there is a lack of large real-world evidence for the relationship between adherence to B/F/TAF therapy and clinical outcomes in a Japanese clinical setting.

Therefore, this study investigated the relationship between medication adherence measured by the PDC and treatment outcomes in PWH prescribed B/F/TAF using Japanese claims databases.

Methods

Study design and data source

A retrospective cohort study using data extracted from two databases, Medical Data Vision (MDV) and JMDC, was performed. The MDV database includes more than 40 million patients and covers approximately 27% of acute hospitals in Japan[16]. The JMDC database consists of data from health insurance societies covering approximately 15 million individuals[17]. Records of diagnoses (ICD-10 codes), treatments (e.g., medication, surgery, and examinations), and health care costs may be collected from both databases.

Since the MDV database is hospital-based, it was not possible to track patients who were transferred to other hospitals. However, the MDV database covers large hospitals, such as acquired immune deficiency syndrome (AIDS) core (base) hospitals, where most HIV treatment is provided in Japan[18] and where the number of enrolled individuals is greater than that in the JMDC database. The MDV database was treated as the primary data source for this study.

To identify the study population and collect data on patient characteristics, the study period was defined as between October 2018 and the latest cutoff time in each database (MDV, September 2022; JMDC, June 2022).

An ethics review was unnecessary for this study because it was a secondary analysis of anonymized processed databases.

Study population

Since B/F/TAF was introduced in Japan in April 2019, patients were identified between April 2019 and September 2021 (MDV) or June 2021 (JMDC) (defined as the identification period). The inclusion criteria were as follows: (i) received a diagnosis of HIV/AIDS (ICD 10 code: B20-B24) during the identification period; (ii) received a prescription of B/F/TAF during the identification period; (iii) received at least two prescriptions of B/F/TAF throughout the study period; and (iv) were at least 18 years old at the first prescription of B/F/TAF (defined as the index date). Patients with no claims data for at least three months prior to the index month (defined as the lookback period) were excluded. The study population was followed up from the index date to a maximum of 365 days.

Variables and outcomes

Adherence

As a measure of medication adherence, the PDC of B/F/TAF was calculated. The PDC was defined as the proportion of days covered in the follow-up period. Adjustments were made for overlapping days of supply due to early refills. The subsequent prescription date was shifted forward to the day after the end of the supply of the previous prescription (i.e., each day has a single opportunity to be "covered" or "not covered", removing the risk of overlap)[9,19]. A threshold PDC ≥ 90% indicated good adherence, reflecting current clinical practices.

Clinical outcomes

Regarding clinical outcomes, the following three endpoints were evaluated as time to event data.

(i) Time to discontinuation: Treatment discontinuation was defined as an interval between the end of supply and the next prescription date of 90 days or more. Patients without discontinuation were defined as "persistent".

(ii) Time to a drug resistance test: A drug resistance test is considered for the case of viremia of 500–1000 copies/mL and is recommended for the case of more than 1000 copies/mL in the Japanese clinical guideline for HIV drug resistance testing[20]. The records were considered surrogate markers of viremia. The implementation of a drug resistance test was defined by the receipt of a genotypic test for drug resistance. Patients who discontinued treatment were classified as censored.

(iii) Time to the combined endpoint: The combined endpoint was defined as the discontinuation of treatment (definition (i)) after the implementation of a drug resistance test (definition (ii)). This endpoint implies drug discontinuation after viremia, a possible surrogate marker of virologic failure, as Japanese guidelines highly recommend resistance testing before changing the ART for virologic failure[8]. Hence, in this study, this combined endpoint was considered a surrogate endpoint for virological failure.

Patients who dropped out or died were censored. The follow-up started from the index date to the event, censored, or 1 year, whichever came first.

Patient characteristics

Age at the index date, comorbidities (renal disease, mental disease, metabolic disease, cardiovascular disease, and hepatitis B virus infection) within the lookback period or in the index month, pill number burden (the number of unique co-medications (any formulation) prescribed on the index date other than ART), ART experience (ART prescription within the previous 105 days), and an AIDS-defining condition within the lookback period or in the index month were collected as patient characteristics. Operational definitions, such as the ICD-10 codes in the claims databases, are shown in Supplementary Tables S1, S2.

Statistical analysis

In the primary analysis, a Kaplan−Meier curve for each outcome was generated. The persistence rate at 1 year (discontinuation-free survival estimated by the Kaplan−Meier method) was also estimated. The relationships between PDC and clinical outcomes were examined using multivariable Cox regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the PDC < 80% and PDC 80–< 90% groups relative to the PDC ≥ 90% group (reference case) were estimated. Patient characteristics were included in a Cox regression analysis as covariables to adjust for confounding factors. Among patient characteristics, renal disease was rare in all PDC groups; therefore, it was excluded as a covariable from the analysis.

In the secondary analysis, the relationships between patient characteristics and clinical outcomes (discontinuation and a drug resistance test) were evaluated by univariate Cox regression analysis, which included each characteristic as an exploratory variable.

Furthermore, to examine the relationships between PDC and clinical outcomes over a longer period, the same analysis as the primary analysis was conducted for the two-year follow-up period. To investigate the association of ART experience in the primary analysis, a subgroup analysis of ART experience (naïve/experienced) was also performed.

All the statistical analyses were performed using SAS ver. 9.4. $P < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

A total of 952 patients were included in the MDV database analysis (Fig. 1). There were 820 (86.1%), 95 (10.0%), and 37 (3.9%) patients in the PDC ≥ 90%, 80 – < 90%, and < 80% groups, respectively. The distribution of patient characteristics across the three PDC groups is shown in Table 1.

The average age of all patients was 43.6 years, and the patients in the lower PDC group (< 80%) were slightly older (45.7 (13.2) years, mean (SD)) than those in the PDC ≥ 90% and PDC 80– < 90% groups (43.5 (12.0) and 43.5 (12.1) years, respectively). The lower PDC group (< 80%) included a greater percentage of patients with mental disease (27.0%) than the PDC ≥ 90% and PDC 80 – < 90% groups (12.3 and 20.0%, respectively). Metabolic disease was the most frequent comorbidity in all PDC groups (31.6% in total). Few patients had renal disease (2.6%). The average number of co-medications being taken in PDC ≥ 90%, PDC 80 – < 90% and PDC < 80% groups were 1.9 (2.9), 2.1 (2.5) and 2.4 (3.7), respectively. Approximately 70% of patients in the study population were ART-experienced.

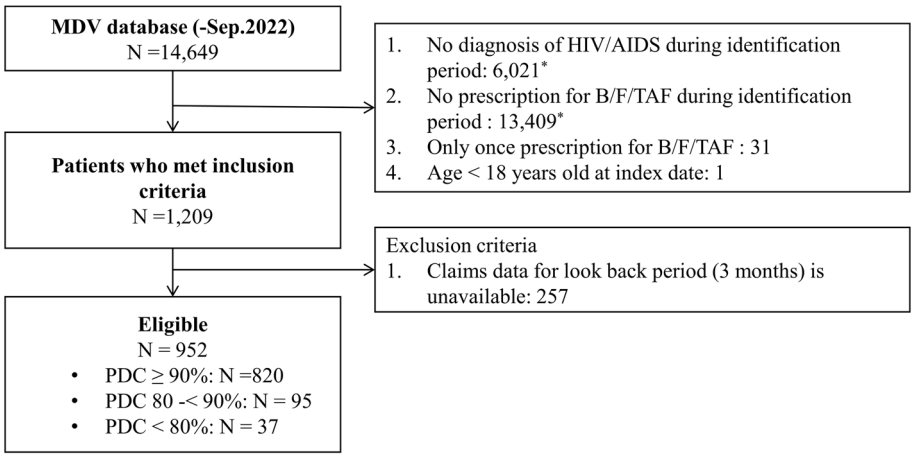

Figure 1. Flowchart of patient selection. * Patients who met both criteria were double counted. *AIDS* acquired immunodeficiency syndrome, *HIV* human immunodeficiency virus, *MDV* medical data vision, *PDC* proportion of days covered.

	PDC			Total
	≥ 90%	80–< 90%	< 80%	
N	820	95	37	952
Age				
Mean ± SD	43.5 ± 12.0	43.5 ± 12.1	45.7 ± 13.2	43.6 ± 12.1
18–29	104 (12.7%)	11 (11.6%)	3 (8.1%)	118 (12.4%)
30–39	213 (26.0%)	23 (24.2%)	10 (27.0%)	246 (25.8%)
40–49	270 (32.9%)	37 (38.9%)	11 (29.7%)	318 (33.4%)
50–59	154 (18.8%)	16 (16.8%)	7 (18.9%)	177 (18.6%)
60–69	61 (7.4%)	4 (4.2%)	3 (8.1%)	68 (7.1%)
70-	18 (2.2%)	4 (4.2%)	3 (8.1%)	25 (2.6%)
Comorbidity				
Renal disease (Yes)	25 (3.0%)	0 (0.0%)	0 (0.0%)	25 (2.6%)
Mental disease (Yes)	101 (12.3%)	19 (20.0%)	10 (27.0%)	130 (13.7%)
Metabolic disease (Yes)	256 (31.2%)	33 (34.7%)	12 (32.4%)	301 (31.6%)
Cardiovascular disease (Yes)	138 (16.8%)	17 (17.9%)	6 (16.2%)	161 (16.9%)
Hepatitis B virus (Yes)	97 (11.8%)	11 (11.6%)	7 (18.9%)	115 (12.1%)
Pill number burden				
Mean ± SD	1.9 ± 2.9	2.1 ± 2.5	2.4 ± 3.7	1.9 ± 2.9
0	382 (46.6%)	40 (42.1%)	17 (45.9%)	439 (46.1%)
1–2	225 (27.4%)	25 (26.3%)	9 (24.3%)	259 (27.2%)
3-	213 (26.0%)	30 (31.6%)	11 (29.7%)	254 (26.7%)
ART experience				
Naïve	253 (30.9%)	17 (17.9%)	11 (29.7%)	281 (29.5%)
Experienced	567 (69.1%)	78 (82.1%)	26 (70.3%)	671 (70.5%)
AIDS-defining condition (Yes)	318 (38.8%)	35 (36.8%)	12 (32.4%)	365 (38.3%)

Table 1. Patient characteristics. The data are presented as the number (%) of patients unless otherwise noted. *AIDS* acquired immunodeficiency syndrome, *ART* antiretroviral therapy, *PDC* proportion of days covered, *SD* standard deviation.

Relationships between PDC and clinical outcomes

According to the MDV data, during the 1 year follow-up period, 46 out of 952 patients (4.8%) discontinued B/F/TAF. More than 90% of patients who received B/F/TAF were receiving treatment at 1 year, regardless of the PDC group (94.9% in the PDC ≥ 90% group, 97.9% in the PDC 80 – < 90% group and 90.3% in the PDC < 80% group) (Table 2, Fig. 2). The risk of discontinuation did not significantly differ between the PDC groups (PDC 80– < 90% vs. PDC ≥ 90%, 0.400 [0.096, 1.661], p = 0.207; PDC < 80% vs. PDC ≥ 90%, 2.244 [0.663, 7.594], p = 0.194, HR [95% CI]).

The frequency of drug resistance tests was low (15 events/952 patients, Fig. 3). The risk of the implementation of a drug resistance test did not significantly differ between the PDC 80– < 90% group and PDC ≥ 90% group (0.872 [0.109, 7.003], p = 0.898, HR [95% CI]); however, it was significantly greater in the PDC < 80% group than in the PDC ≥ 90% group (10.323 [2.549, 41.798], p = 0.001).

No combined events were observed during the 1 year follow-up period in the three groups.

Although the statistical detection power was insufficient, similar trends were observed in the JMDC database analysis. All results obtained using the JMDC database are shown in the supplementary materials (Supplementary Figs. S3–S9, Supplementary Tables S3, S4).

Relationships between patient characteristics and clinical outcomes

Pill number burden was defined as the number of pills other than ART prescribed on the index date. Patients categorized as having a pill number burden greater than 3 had a significantly greater risk of treatment discontinuation

PDC	N	Events	Persistence rate at 1 year (%)
≥ 90%	820	41	94.9
80–< 90%	95	2	97.9
< 80%	37	3	90.3
Total	952	46	95.1

Table 2. Persistence rate at 1 year. *PDC* proportion of days covered.

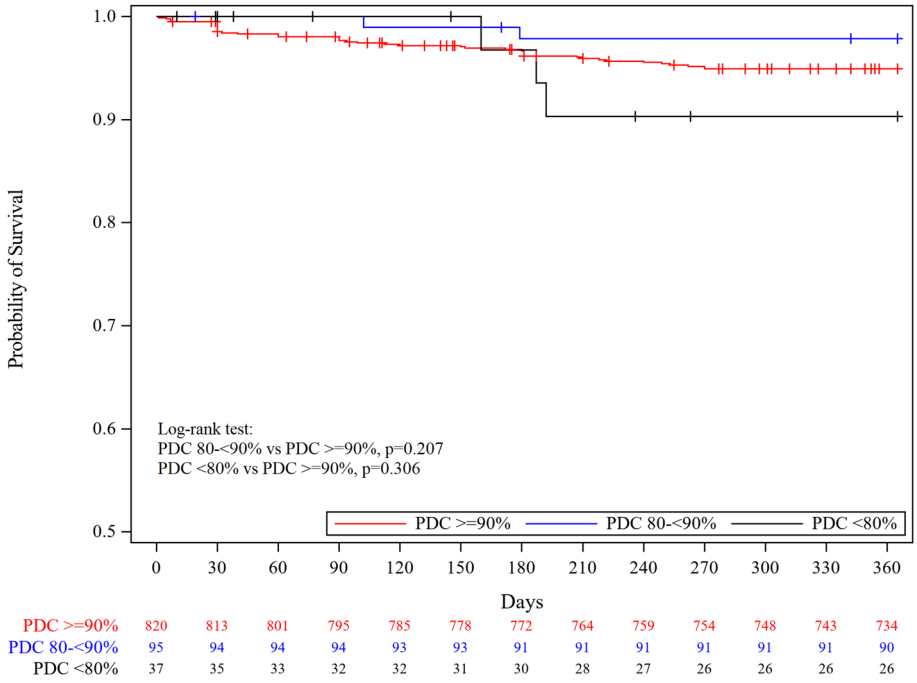

Figure 2. Time to discontinuation. Kaplan-Meier curves of the time to discontinuation in each PDC group. *PDC* proportion of days covered.

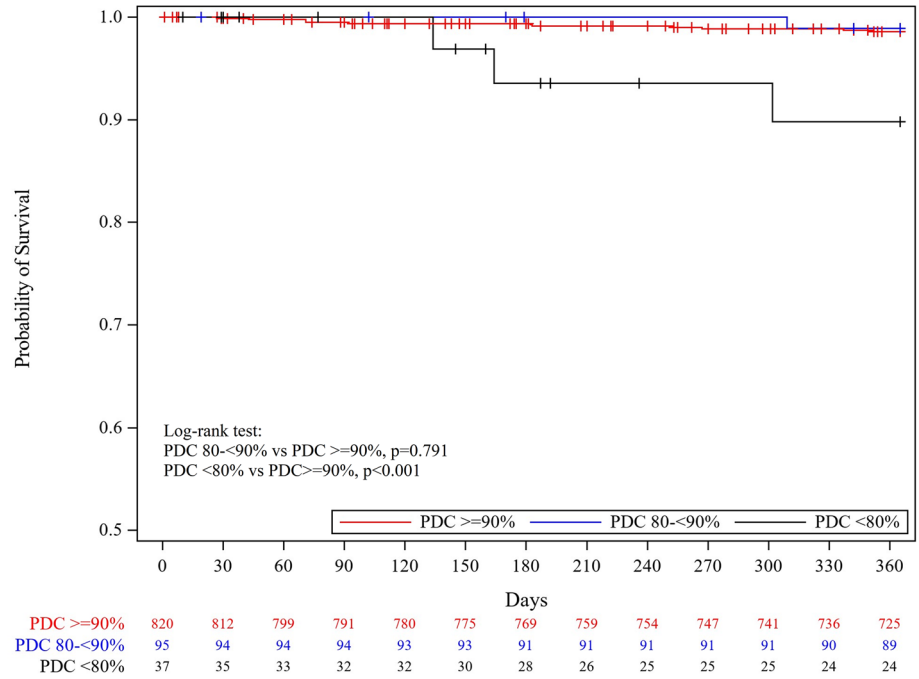

Figure 3. Time to a drug resistance test. Kaplan-Meier curves of the time to a drug resistance testin each PDC group. *PDC* proportion of days covered.

than those categorized as having no pill number burden (2.486 [1.246, 4.957], p = 0.010, hazard ratio [95% CI]) (Fig. 4a,b). Similar result was observed in the result of JMDC database (Fig. S6). ART experience showed significantly lower risk of treatment discontinuation and implementation of resistance test (0.486 [0.272, 0.868], p = 0.015, 0.350 [0.127–0.964], p = 0.042, hazard ratio [95% CI])). No statistically significant difference was found in other characteristics such as age, comorbidities, and experience of AIDS.

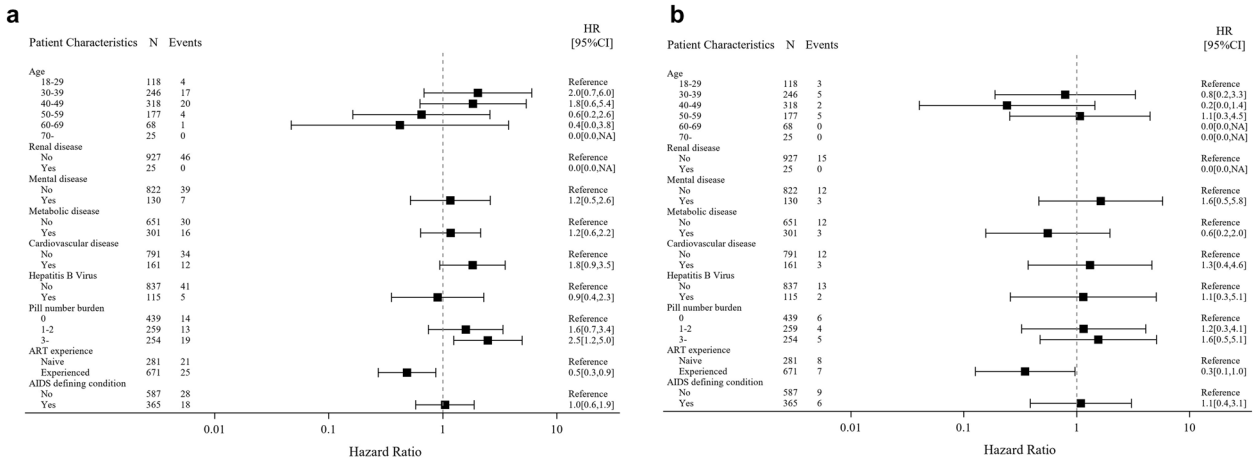

Figure 4. Relationships between patient characteristics and clinical outcomes. (**a**) Time to discontinuation. (**b**) Time to a drug resistance test. The HR and 95% CI of each patient characteristic for clinical outcomes ((**a**) time to discontinuation, (**b**) time to a drug resistance test) are shown. Since the hazard ratio (HR) for renal disease was extremely small (< 0.01), the plot was not presented. *AIDS* acquired immunodeficiency syndrome, *ART* antiretroviral therapy, *CI* confidence interval, *HR* hazard ratio.

Relationships between PDC and clinical outcomes at 2 years

At 2 years, there were 878 (92.2%), 54 (5.7%), and 20 (2.1%) patients in the PDC ≥ 90%, 80– < 90%, and < 80% groups, respectively. The proportion of patients with a low PDC (80– < 90% and < 80%) was lower than that at the 1 year follow-up (Fig. 5).

During the 2 year follow-up period, 81 patients discontinued B/F/TAF, and the persistence rate at 2 years was 90.9%. The PDC < 80% group had a significantly greater risk of both treatment discontinuation and the implementation of a drug resistance test (discontinuation, 2.959 [1.021, 8.573], p = 0.046; drug resistance test, 14.026 [3.486, 56.439], p < 0.001, hazard ratio [HR] [95% CI]) but not of the combined endpoint (no event in the PDC < 80% group, 1 event in the PDC ≥ 90% group).

The PDC 80 – < 90% group had a significantly greater risk of the implementation of a drug resistance test (discontinuation, 1.943 [0.926, 4.076], p = 0.079; drug resistance test, 5.702 [2.039, 15.946], p = 0.001; combined endpoint, 52.914 [0.982, 2851.418], p = 0.051, HR [95% CI]) (Fig. 5a,b).

Subgroup analysis of treatment-naïve and treatment-experienced patients

Among treatment-naïve patients, the persistence rates at 1 year were 92.3, 100.0, and 71.4% in the ≥ 90%, 80– < 90%, and < 80% PDC groups (n = 253, 17, and 11), respectively. Among treatment-experienced patients, the persistence rates at 1 year were 96.1, 97.4, and 95.8% in the ≥ 90%, 80 – < 90%, and < 80% PDC groups, respectively (n = 567, 78, and 26) (Supplementary Figs. S1, S2).

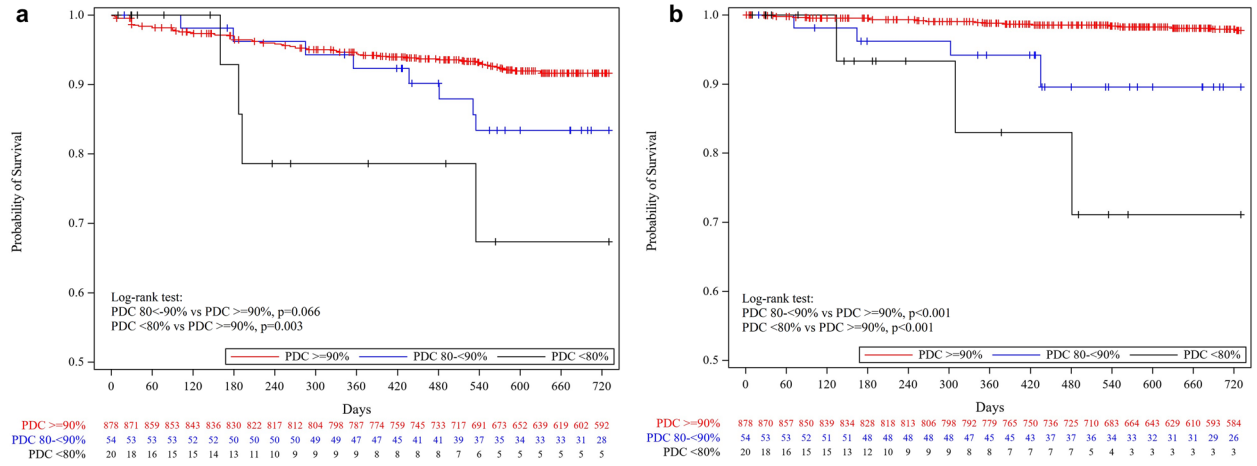

Figure 5. The PDC and clinical outcomes at 2 years. (**a**) Time to discontinuation (**b**) Time to drug resistance test. Kaplan-Meier curves of each PDC group during the 2 year follow-up for (**a**) time to discontinuation and (**b**) time to a drug resistance test. *PDC* proportion of days covered.

In the low PDC group (< 80%), treatment discontinuation and the implementation of a drug resistance test were more frequent for treatment-naïve patients than for treatment-experienced patients (percentage of patients with a drug resistance test; naïve, 2/11 (18.2%); experienced, 1/26 (3.8%)).

Discussion

This is the first analysis to investigate the association between adherence measured by the PDC and the persistence of B/F/TAF in a Japanese clinical setting. The analysis revealed that 86.1% of Japanese PWH had high adherence (PDC ≥ 90%). The discontinuation risk did not differ among the PDC groups, and resistance tests were rarely implemented. Furthermore, pill number burden was associated with discontinuation risk.

In the present study, no statistically significant difference was observed in the risk of discontinuation among the 3 PDC groups during the 1 year follow-up. Even PDC ≥ 90% is considered as a threshold as an optimal adherence for ART[21,22], Maggiolo et al. demonstrated that a PDC as low as 70% was sufficient to obtain the desired virologic outcome (viral load < 200 copies/mL and < 50 copies/mL) in a B/F/TAF cohort study[9], and similar results were observed in clinical trials[10]. We did not examine the PDC < 70% group in the present study due to the small number of patients with a PDC < 70%; however, we confirmed that the risk of discontinuation in the PDC < 80% group did not significantly differ from that in the PDC ≥ 90% group in real-world settings in Japan. The appropriate threshold of optimal adherence to reduce the PWH burden might be needed to reconsider in the future. The overall persistence rate of B/F/TAF at 1 year (95.1%) was also consistent with past observational studies and clinical trials[11,12,23]. Since the number of patients in the PDC < 80% group decreased during the 2 year follow-up, this relationship remains unclear. Therefore, further studies with larger sample sizes are needed to examine the long-term effects of PDC therapy.

Nevertheless, the present results suggest that regardless of the PDC, the effectiveness and tolerability of B/F/TAF contribute to the high persistence rate in Japan. Although the difference between other ART regimens was not analyzed in this study, Wang et al. reported that the persistence rate at one year of other ART regimens was less than 90% in an MDV database study[6]. As this past study suggested a difference in the persistence rate between ART regimens in the Japanese real world, further investigation is needed.

The results obtained on the time to the implementation of a drug resistance test showed that the number of suspected cases of resistance was significantly greater in the PDC < 80% group than in the PDC ≥ 90% group. However, since the number of events was very small, the 95% CI of the HR was very wide. Although the criteria for a drug resistance test differed, the frequency of its implementation was also low (0.7–1.3%) according to other studies[24–26]. Armenia et al. reported that previous resistance and virologic failure under INSTI before switching to B/F/TAF significantly increased virologic rebound[27]. These patient characteristics could also affect the time to resistance test in this study, especially for patients in the low PDC group. However, further studies are needed to take these factors into consideration.

Regarding the combined endpoint, discontinuation after a drug resistance test was not observed in any PDC group during the 1 year follow-up. Although 3 patients experienced the combined endpoint at the 2 year follow-up, 2 patients restarted B/F/TAF after the defined time of discontinuation (90 days), and only 1 patient switched from B/F/TAF to other ARTs. In two clinical trials on B/F/TAF (study 1489 and study 1490), the rate of early discontinuation after conducting a drug resistance test at 48 weeks was low (0.8%)[24]. A previous intermittent B/F/TAF treatment study reported no case of treatment discontinuation due to virologic failure for 96 weeks[11]. Our results using real-world data from Japan were consistent with these findings.

A large pill number burden was associated with the discontinuation of B/F/TAF in this study. Previous studies have reported the characteristics of PWH in Japan using Japanese claims databases. They showed that the number of elderly PWH increased and that the percentage of patients with multiple comorbidities as well as multiple comedications was greater than that in those without HIV in Japan[28–30]. Another study using the MDV database demonstrated that persistence was longer with STR than with MTR[6]. Based on these findings and the present results, a reduction in the pill number or the use of STR to improve adherence may be effective methods for preventing discontinuation. Previous studies using Japanese claims databases reported that persistence was better in patients receiving INSTI[31,32]. Therefore, STR, including INSTI, has potential as a treatment option in clinical practice in Japan. Additionally, reduction of pill burden by using fixed-dose combination therapy for comorbidities such as antihypertensive/antihyperlipidemic agent may help improve adherence and persistence of ART. However, further research is needed.

Treatment experience with ART was associated with the discontinuation of B/F/TAF and the implementation of a drug resistance test. Among a small proportion of treatment-naïve PWH who had a low PDC, a higher discontinuation rate and implementation of drug resistance tests were found. Because of the lack of data on the baseline viral load, it is difficult to interpret the results. However, further studies are needed to investigate the associations between patient characteristics, including viral load, and persistence. Understanding their clinical characteristics and more careful management should be provided.

There were several limitations that need to be addressed. Since this study was based on claims databases, the results of laboratory tests, such as the viral load of HIV and the results of drug resistance tests, were not available. Therefore, treatment discontinuation and the implementation of a drug resistance test were defined as clinical outcomes in the present study. These events do not always indicate virologic failure. Evaluation of cause of discontinuation by medical records is required for more robust data. Although the baseline data of these tests could be a patient characteristic that affects the study results, it was not considered for analysis because it was not available. Furthermore, although the PDC is generally the recommended measure of medication adherence, it does not reflect the actual intake of medications by the patient. Adherence to B/F/TAF may be overestimated. Moreover, the MDV database is hospital-based and does not include previsit data. Therefore, patients who started treatment at their first hospital visit may have been excluded from the study population due to the lack

of a lookback period. As mentioned above, the study population from the MDV database included more patients who switched from treatment to B/F/TAF and fewer treatment-naïve patients. This might cause selection bias. On the other hand, since the JMDC database allows data to be traced back in time, even before a clinic/hospital visit, it is possible to cover treatment-naïve patients. Therefore, the same analysis as that for the MDV database using the JMDC database was performed; however, the small sample size was another limitation for the JMDC database. Although there are limitations in each database, the MDV database covers 27% of acute hospitals across Japan, and we conducted the analysis using two types of databases, which improves the generalizability of the findings. Finally, because this was an observational study, care needs to be taken when interpreting the results. The associations found in this study cannot be directly considered causal relationships.

Conclusion

Among PWH treated with B/F/TAF, no statistically significant differences were observed in treatment discontinuation or the implementation of a drug resistance test among the PDC groups (≥ 90%, 80– < 90%, and < 80%). Furthermore, treatment discontinuation was not observed after the implementation of a drug resistance test (the combined endpoint). These findings suggest that events caused drug discontinuation (e.g., virologic failure) rarely occur, regardless of the PDC.

The relationships between adherence measured by the PDC and clinical outcomes among PWH treated with B/F/TAF in Japan were examined using real-world data. The present results on B/F/TAF will contribute to the development of new treatment strategies for PWH, such as those with co-medications.

Data availability

The datasets generated and/or analyzed during the present study are not publicly available because they were purchased from commercial providers (Medical Data Vision Co., Ltd. and JMDC Inc.) but are available from the corresponding author upon reasonable request.

Received: 22 December 2023; Accepted: 16 July 2024
Published online: 22 July 2024

References

1. Taiwo, B. O. *et al.* Treatment and comorbidity burden among people living with HIV: A review of systematic literature reviews. *J. Drug Assess.* **12**, 1–11 (2023).
2. Paterson, D. L. *et al.* Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann. Intern. Med.* **133**, 21–30 (2000).
3. Gordon, L. L., Gharibian, D., Chong, K. & Chun, H. Comparison of HIV virologic failure rates between patients with variable adherence to three antiretroviral regimen types. *AIDS Patient Care STDs* **29**, 384–388 (2015).
4. Byrd, K. K. *et al.* Antiretroviral adherence level necessary for HIV viral suppression using real-world data. *JAIDS J. Acquir. Immune Defic. Syndr.* **82**, 245–251 (2019).
5. Priest, J. *et al.* Retrospective analysis of adherence to HIV treatment and healthcare utilization in a commercially insured population. *J. Med. Econ.* **24**, 1204–1211 (2021).
6. Wang, X., Schmerold, L. & Naito, T. Real-world medication persistence among HIV-1 patients initiating integrase inhibitor-based antiretroviral therapy in Japan. *J. Infect. Chemother.* **28**, 1464–1470 (2022).
7. Cohen, J. *et al.* Real-world adherence and persistence for newly-prescribed HIV treatment: Single versus multiple tablet regimen comparison among US medicaid beneficiaries. *AIDS Res. Ther.* **17**, 12 (2020).
8. Research Group for Establishment of Team Medical Care and Improvement of Medical Standard in HIV Infection and Hemophilia. *Guidelines for Anti-HIV Treatment.*, https://hiv-guidelines.jp/index.htm (2023).
9. Maggiolo, F. M. D. *et al.* Real world data on forgiveness to uncomplete adherence to bictegravir/ emtricitabine/tenofovir alafenamide. *J. Int. Assoc. Provid. AIDS Care* **21**, 23259582221140210 (2022).
10. Andreatta, K. *et al.* Efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus dolutegravir (DTG)-based 3-drug regimens in adults with HIV who have suboptimal antiretroviral adherence. *Open Forum Infect. Dis.* https://doi.org/10.1093/ofid/ofad500.1396 (2023).
11. Sellem, B. *et al.* Intermittent bictegravir/emtricitabine/tenofovir alafenamide treatment maintains high level of viral suppression in virally suppressed people living with HIV. *J. Pers. Med.* **13**, 583 (2023).
12. Sax, P. E. *et al.* Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: Five-year follow-up from two randomized trials. *EClinicalMedicine* **59**, 101991 (2023).
13. Maggiolo, F. *et al.* Bictegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: Results of a 96-week, phase 3b, open-label, switch trial in virologically suppressed people >/=65 years of age. *HIV Med.* **24**, 27–36 (2023).
14. Sax, P. E. *et al.* Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with human immunodeficiency virus. *Clin. Infect. Dis.* **73**, e485–e493 (2021).
15. Gaur, A. H. *et al.* Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: Week 48 results of a single-arm, open-label, multicentre, phase 2/3 trial. *Lancet Child Adolesc. Health* **5**, 642–651 (2021).
16. Medical Data Vision Co., L. *MDV EBM insight*, https://www.mdv.co.jp/ebm/ (2023).
17. JMDC Inc. *JMDC Claims Database*, https://www.jmdc.co.jp/jmdc-claims-database/ (2023).
18. Yokomaku, Y. Toward the establishment of a sustainable system for collecting and analysing information of HIV/AIDS treatment in Japan. *Infect. Agents Surveill. Rep.* **44**, 163–164 (2023).
19. Nau D. *Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence*, http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf (2011).
20. Japan Agency for Medical Research and Development, Research Project for Practical AIDS Control. *Guideline for HIV Drug Resistance Test. version 10*, https://www.hiv-resistance.jp/pdf/hiv_resistance_guideline_v10.pdf (2017).
21. Pharmacy Quality Alliance. *Adherence Measures.*, https://www.pqaalliance.org/index.php?option=com_content&view=article&id=610:adherence-measures&catid=32:measures (2022).
22. McComsey, G. A., Lingohr-Smith, M., Rogers, R., Lin, J. & Donga, P. Real-world adherence to antiretroviral therapy among HIV-1 patients across the United States. *Adv. Ther.* **38**, 4961–4974 (2021).
23. Watanabe, D. *et al.* Efficacy, safety and tolerability of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in clinical practice: Results of a 12-month analysis of BICSTaR Japan (2nd). *J. AIDS Res.* **24**, 294 (2022).

24. Acosta, R. K. *et al.* Resistance analysis of bictegravir-emtricitabine-tenofovir alafenamide in HIV-1 treatment-naive patients through 48 weeks. *Antimicrob. Agents Chemother.* **63**, 10–1128 (2019).
25. Daar, E. S. *et al.* Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV* **5**, e347–e356 (2018).
26. Molina, J. M. *et al.* Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV* **5**, e357–e365 (2018).
27. Armenia, D. *et al.* Bictegravir/emtricitabine/tenofovir alafenamide ensures high rates of virological suppression maintenance despite previous resistance in PLWH who optimize treatment in clinical practice. *J. Glob. Antimicrob. Resist.* **30**, 326–334 (2022).
28. Ruzicka, D. J., Imai, K., Takahashi, K. & Naito, T. Comorbidities and the use of comedications in people living with HIV on antiretroviral therapy in Japan: A cross-sectional study using a hospital claims database. *BMJ Open* **8**, e019985 (2018).
29. Ruzicka, D. J., Imai, K., Takahashi, K. & Naito, T. Greater burden of chronic comorbidities and co-medications among people living with HIV versus people without HIV in Japan: A hospital claims database study. *J. Infect. Chemother.* **25**, 89–95 (2019).
30. Naito, T. *et al.* Comorbidities and co-medications among 28 089 people living with HIV: A nationwide cohort study from 2009 to 2019 in Japan. *HIV Med.* **23**, 485–493 (2022).
31. Ruzicka, D. J., Kuroishi, N., Oshima, N., Sakuma, R. & Naito, T. Switch rates, time-to-switch, and switch patterns of antiretroviral therapy in people living with human immunodeficiency virus in Japan, in a hospital-claim database. *BMC Infect. Dis.* **19**, 505 (2019).
32. Naito, T. *et al.* Analysis of antiretroviral therapy switch rate and switching pattern for people living with HIV from a national database in Japan. *Sci. Rep.* **12**, 1732 (2022).

Acknowledgements

This study was sponsored by Gilead Sciences, K.K. The authors acknowledge the contributions of Masahisa Jinushi, James Jarrett, and Megan Dunbar to this study. Medical writing and editorial assistance were provided by Sachie Inoue and Yuriko Masuda of CRECON Medical Assessment, Inc., and were funded by Gilead Sciences, K.K.

Author contributions

All the authors contributed to the study design and interpretation of the results. All authors critically revised the draft manuscript and approved the final manuscript.

Competing interests

NT, YP, AR, KL, MC, KH and TT are Gilead employees and stockholders. TN has received research grants from Gilead Sciences, consulting fees from Nobelpharma Co., Ltd., and TSUMURA & CO., and he has received lecture fees from MSD K.K., ViiV Healthcare and Gilead Sciences.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-67837-6.

Correspondence and requests for materials should be addressed to T.N.