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Long-acting antiretroviral therapy effectiveness and patient satisfaction using patient questionnaires: data from a real-world setting

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Abstract

Background Antiretroviral therapy (ART) for HIV infection has evolved substantially. The development of long-acting drugs, such as cabotegravir (CAB) and rilpivirine (RPV) might improve treatment satisfaction among people living with HIV (PLWH). The real-world effectiveness of long-acting ART and its effect on patient satisfaction needs to be assessed. This study investigated antiviral effectiveness and treatment satisfaction in PLWH who switched from conventional to long-acting ART (CAB + RPV).

Methods This prospective cohort study included PLWH aged 18 years and older who switched to CAB + RPV and received the injections every 8 weeks between June 2022 and May 2023, after a 4-week oral lead-in phase. The eligibility criteria included viral suppression, absence of hepatitis B virus (HBV) DNA, and no prior RPV resistance mutations. Clinical data, including renal, lipid, and glucose biomarker levels, were monitored from the baseline to 44 weeks after switching. Treatment satisfaction was assessed using the HIV Treatment Satisfaction Questionnaire. A linear mixed-effects model was used to estimate changes in clinical data from baseline.

Results Thirty-eight male participants were enrolled. Some participants had detectable levels of viral replication; however, all participants maintained viral suppression (HIV-RNA < 50 copies/mL) at 44 weeks and no cases of virological failure were detected. The creatinine level decreased by − 0.04 mg/dL (95% confidence interval [CI]: − 0.07 to − 0.01), lipid and glucose profiles remained stable, and treatment satisfaction increased by 6.6 points (95% CI: 2.4 to 10.8) after switching to CAB + RPV.

Conclusions Long-acting ART provides effective viral suppression and enhances treatment satisfaction in PLWH switching from conventional ART. Long-acting ART can improve patient well-being; however, patient selection and monitoring to prevent HBV-related complications are important.

Keywords Antiretroviral therapy, Long-acting antiretroviral therapy, Adherence, Cabotegravir, Rilpivirine, Japanese

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Background

Since the introduction of antiretroviral therapy (ART), HIV medications have continuously improved. The risk of side effects has reduced, pill sizes have shrunk, and once-daily dosing, including a single-tablet regimen, has become the norm. Furthermore, the development of long-acting antiretroviral drugs represents a significant evolution in treatment. Long-acting ART, combining the new integrase inhibitor cabotegravir (CAB) with the established non-nucleoside reverse transcriptase inhibitor, rilpivirine (RPV), achieves an adequate blood concentration to suppress HIV with injections administered every 1–2 months (intramuscularly in the buttocks). Its antiviral effectiveness is similar to that of conventional antiretroviral regimens [1–3]. Improvements in treatment satisfaction have been reported among people living with HIV (PLWH) who switched from conventional to long-acting ART [4]. However, issues have been pointed out, such as the increased frequency of clinic visits, lack of anti-hepatitis B virus (HBV) activity [5], restricted convenience for PLWH on concomitant medications [6], and the emergence of drug-resistant mutations in clinical trials [2, 3, 7].

CAB + RPV is emerging as a novel ART option in Western countries. The US Food and Drug Administration approved a monthly injectable regimen in 2021 and a bimonthly regimen in 2022. In Japan, bimonthly CAB + RPV was approved in March 2022 and made available in June 2022. Long-acting ART is not suitable for all patients with HIV, particularly untreated patients, and clinical research focuses on patients who have achieved virological suppression. The use of a long-acting injectable ART regimens eliminates the need for daily oral HIV medication and could lead to high patient satisfaction. The effect of long-acting ART on treatment satisfaction among PLWH needs to be further investigated in real-world settings.

Given this context, our study involved PLWH who switched from conventional to long-acting ART. We examined the antiviral effects of the long-acting ART and its effect on renal function, lipid metabolism, glucose metabolism, and treatment satisfaction.

Methods

This single-center, prospective, cohort study focused on PLWH aged 18 or older. Participants were those who switched from conventional to long-acting ART between June 1, 2022, and May 31, 2023. The criteria for this switch included (1) having maintained viral suppression (HIV-RNA level < 50 copies/mL) for at least 6 months before the switch, (2) being negative for HBV DNA, and (3) having no resistance mutations related to RPV and any integrase strand transfer inhibitor (INSTI) drugs in past drug resistance tests. In our facility, drug resistance testing is typically performed at the time of HIV diagnosis and virological failure. In this study, all participants underwent resistance testing at the time of diagnosis and none had RPV and INSTI resistance mutations. Patients who provided informed consent after understanding the inclusion criteria were selected. Before transitioning to long-acting ART, all patients were required to take an oral regimen of CAB and RPV for at least 4 weeks after switching from conventional ART to ensure no adverse effects. Viral load was not measured during the oral lead-in period. All participants received CAB + RPV injections every 8 weeks following the initial and second four-week loading intervals. Clinical data extracted from electronic medical records included baseline information (age [< 50, ≥ 50], sex, height), previous ART regimens, HIV-related status (CD4 positive T-lymphocyte count [CD4], HIV-RNA quantity [viral load: VL]), body weight [BW], body mass index [BMI; < 25, ≥ 25], renal function markers (serum creatinine [Cre]), and random blood lipid markers (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides [TG]), and hemoglobin A1c (HbA1c) values. For the analysis, the date of switch to long-acting ART was defined as day 0 and the start of oral CAB/RPV as week − 4. Blood tests were performed at weeks − 4, 0, 4, 12, 20, 28, 36, and 44. Confirmed virological failure (CVF) was defined as a persistent VL above 200 copies/mL. The lower limit of quantification for VL was 20 copies/mL. The clinical significance of low-level viremia below the detection limit remains unclear. Therefore, the analyses were performed using the raw VL data. Patient satisfaction with treatment was assessed using a 12-item questionnaire adapted from the original 10-item HIV Treatment Satisfaction Questionnaire (HIVTSQ), which was validated in an HIV-1 patient cohort [8]. The Japanese version of the HIVTSQ, which has previously been used in clinical trials [9], was administered in this study. This 12-item questionnaire, which was previously used in the ATLAS [1] and FLAIR [10] studies, was validated in the LATTE-2 study [11]. Two additional items were added to address the administration method of CAB + RPV LA (intramuscular injection). The items were:

(1) "How easy or difficult have you been finding your treatment to be recently?"
(2) "How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?"

The HIVTSQ status version (HIVTSQs) instructs participants to rank their answers on a 6-point Likert

scale ranging from 0 ("very dissatisfied") to 6 ("very satisfied"). Items 1–11 were summed to generate the total HIVTSQs score. Item 12 was not included in the composite HIVTSQs total score. The HIVTSQ change version (HIVTSQc) was administered exclusively at week 28. It prompts participants to evaluate their current treatment (long-acting ART) against their former treatment, rating each aspect on a scale from -3 ("much less satisfied now") to + 3 ("much more satisfied now"), with 0 denoting "no change". Contrary to the HIVTSQs, the HIVTSQc does not assess changes from a baseline score; instead, it directly gauges the perceived shifts in satisfaction compared to the previous treatment. In both versions, item scores were added together to give a total aggregate summary score, with HIVTSQs ranging from 0 ("very dissatisfied") to 66 ("very satisfied"), and HIVTSQc ranging from − 33 ("much less satisfied now") to 33 ("much more satisfied now"). The HIVTSQs was administered at weeks 0 and 28, whereas the HIVTSQc was assessed only at week 28. Patient adherence was measured as the difference between the scheduled and actual injection dates, with 7 days around the planned date considered optimal. This study determined the proportion of patients who received injections within this timeframe. Additionally, this study was conducted as a single-center study and was reviewed and approved by the Ethics Review Committee of Osaka City General Hospital (approval number: 2210072).

Statistical analysis

The baseline characteristics of the participants were presented using frequencies (percentages) and medians (interquartile range [IQR]), as appropriate. A linear mixed-effects model was used to estimate changes in clinical data and treatment satisfaction from baseline. CD4, VL, BW, Cre, HDL-C, LDL-C, TG, and HbA1c were treated as continuous outcome variables in the linear mixed model. This model incorporated both participants and weeks as random effects. Age, body mass index (BMI), progression to AIDS, and history of treatment interruptions were included as covariates in the multivariable models to adjust for potential confounders. These covariates were selected based on their potential clinical influence on the outcomes of interest. However, for the analysis of body weight, BMI was excluded from the covariates to avoid collinearity, as body weight is a component of BMI. Changes from baseline were reported with 95% confidence intervals (CIs). All statistical analyses were performed using R version 4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

This study included 38 male participants. The inclusion of only male participants was by chance and not by design. The patients' backgrounds are shown in Table 1. The median age at treatment change was 46.5 years (IQR, 38–51.5 years), and the median BMI was 24.6 kg/m^2 (IQR, 23.1–26.9 kg/m^2). Of the four participants with a history of treatment interruption, three were on INSTI-based ART. No cases of CVF were observed in these participants despite the treatment interruptions. Before the treatment change, the antiretroviral drug regimens comprised raltegravir (RAL) plus tenofovir alafenamide

Table 1 Characteristics and measurements for people living with HIV before start of oral cabotegravir plus rilpivirine in this study ($N = 38$)

Variable	Value
Age	
< 50 years	26 (68%)
≥ 50 years	12 (32%)
Height (cm), median [IQR]	168.5 [165.3–174]
Body weight (kg), median [IQR]	71.5 [65.2–79.4]
BMI	
< 25 kg/m^2	20 (53%)
≥ 25 kg/m^2	18 (47%)
Progressed to AIDS, n (%)	7 (18%)
Duration of ART (months), median [IQR]	65.5 [49–119.5]
History of treatment interruptions	4 (10.5%)
Current ART	
RAL + TAF/FTC	8 (21%)
DTG/3TC	7 (18%)
BIC/TAF/FTC	6 (16%)
DTG + TAF/FTC	6 (16%)
DRV/cobi/TAF/FTC	5 (13%)
Other regimens	6 (16%)
Clinical data, median [IQR]	
CD4 (cells/μL)	569 [455.3–889]
VL (copies/mL)	20 [20–24.8]
Cre (mg/dL)	0.91 [0.84–0.99]
HDL-C (mg/dL)	48 [41.2–54.8]
LDL-C (mg/dL)	117 [92–135]
TG (mg/dL)	138 [73–270]
BW (kg)	71.5 [65.2–79.4]
HIVTSQs score, median [IQR]	54 [45.3–60.8]

Data are presented as median [interquartile range] at the start of the oral CAB/RPV lead-in phase (week − 4)

3TC lamivudine, *ART* Antiretroviral therapy, *BIC* Bictegravir, *BMI* Body mass index, *cobi* cobicistat, *DRV* Darunavir, *DTG* Dolutegravir, *FTC* Emtricitabine, *HBcAb* hepatitis B core antibody, *HBsAb* Hepatitis B surface antibody, *HBsAg* Hepatitis B surface antigen, *IQR* Interquartile range, *RAL* Raltegravir, *TAF* Tenofovir alafenamide, *HDL-C* High-density lipoprotein cholesterol, *HIVTSQ* HIV Treatment Satisfaction Questionnaire, *LDL-C* Low-density lipoprotein cholesterol, *TG* Triglycerides, *VL* Viral load

(TAF)/emtricitabine (FTC) in eight patients (21%), dolutegravir (DTG)/lamivudine (3TC) in seven patients (18%), bictegravir (BIC)/TAF/FTC in six patients (16%), DTG + TAF/FTC in six patients (16%), and darunavir/cobicistat (DRV/cobi)/TAF/FTC in five patients (13%). Regarding hepatitis B status, 17 patients (45%) were positive for hepatitis B surface (HBs) and core (HBc) antibodies (Ab), 5 (13%) for HBsAb alone, 3 (8%) for HBs antigen (Ag) with undetectable HBV DNA, and 13 (34%) were negative for HBsAg, HBcAb, and HBsAb. At baseline, 13 participants (34%) had low-level viremia of 20–49 copies/mL; however, all met the eligibility criterion of VL < 50 copies/mL.

The changes in clinical data are shown in Fig. 1 and Supplementary Table S1. There were no cases of CVF, and the mean change in the CD4 count from − 4 to 44 weeks was − 1.6/μL (95% CI: − 62.0 to 59.4), whereas the changes in VL from − 4 to 44 weeks were − 7.3 copies/mL (95% CI: − 29.3 to 15.0). Five patients experienced treatment changes unrelated to CVF, including 3 with reactivation of HBV infection, 1 with acute hepatitis B, and 1 for personal reasons. All three patients with reactivation of hepatitis B infection were HBsAg-positive and HBV DNA-negative on blood tests prior to the change in long-acting therapy. The patient with acute hepatitis B was unvaccinated and negative for HBsAg, HBcAb, and HBsAb. Compared to -4 weeks, the creatinine levels decreased by − 0.04 mg/dL (95% CI: − 0.07 to − 0.01) at 44 weeks. There were no significant differences in mean HDL-C or TG levels across different time intervals compared to the -4 week time point; however, the LDL-C levels decreased by − 10.1 mg/dL (95% CI: − 18.7 to − 1.4) at 4 weeks and decreased by − 13.5 mg/dL (95% CI − 22.4 to − 4.5) at 12 weeks compared to -4 weeks. No significant changes were observed in HbA1c levels compared to -4 weeks; however, body weight was lower -0.87 kg (95% CI: − 1.71 to − 0.02) at 28 weeks compared to -4 weeks.

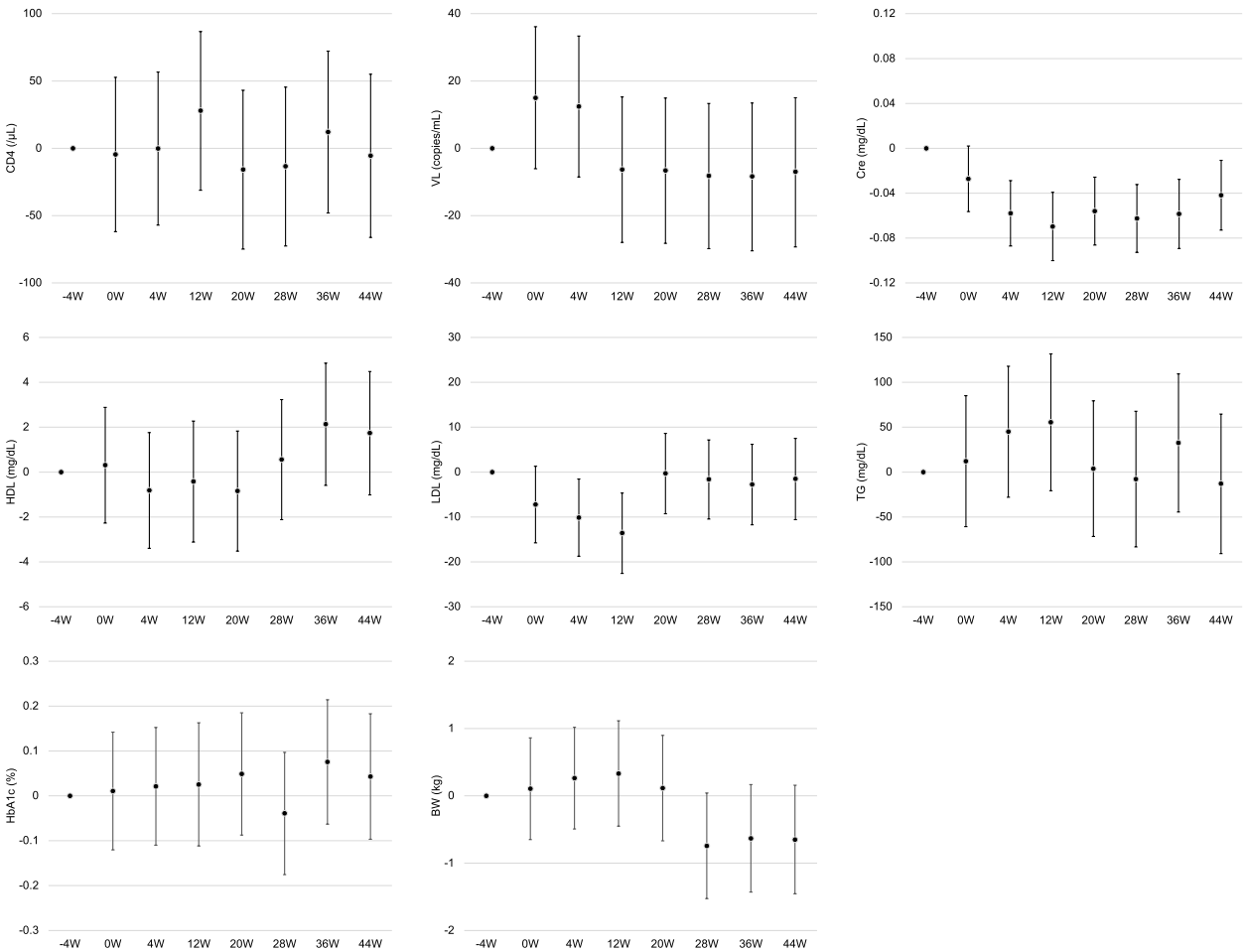

Fig. 1 Changes in clinical data after switching from conventional to long-acting antiretroviral therapy: adjusted for age, BMI, history of AIDS progression, and treatment interruptions

Changes in treatment satisfaction are shown in Fig. 2. No patients had missing HIVTSQs data. The median HIVTSQs score increased by 6.6 points (95% CI: 2.4 to 10.8) at 28 weeks. Treatment satisfaction, as assessed using the HIVTSQc, showed positive scores across all items, with a mean total score of 27.7 (standard deviation: 5.4).

Patient adherence is shown in Fig. 3. During the study period, 223 injections were administered, with 96% of the injections were administered during the dosing period, including 157 (70.4%) administered on the scheduled day, 46 (20.6%) administered 1–7 days late, and 11 (4.9%) administered 1–7 days early.

Discussion

In this study, although some participants experienced low-level viral replication; however, all participants maintained viral suppression (HIV-RNA < 50 copies/mL) at 44 weeks and no cases of CVF were observed. In the ATLAS trial, a phase 3 study, patients who switched to monthly CAB + RPV injections showed similar efficacy and safety at 48 weeks as those who continued their current treatments after initially achieving virological suppression with conventional ART [1]. The ATLAS-2 M trial, a phase 3b clinical trial comparing the efficacy and safety of the CAB + RPV bimonthly injection switch group with the CAB + RPV monthly injection switch group, also showed equivalent efficacy and safety at 48 weeks [2]. In the FLAIR trial, another phase 3 trial, patients who began with DTG/abacavir (ABC)/3TC and then switched

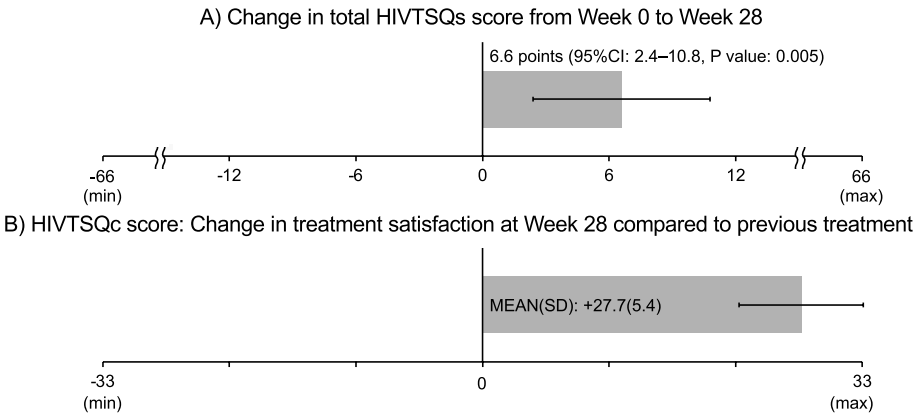

Fig. 2 Treatment satisfaction before and after switching from conventional to long-acting antiretroviral therapy. **A** HIVTSQs scores at baseline (week 0) and week 28. **B** HIVTSQc scores at week 28, representing perceived change in satisfaction relative to previous treatment (0 = no change)

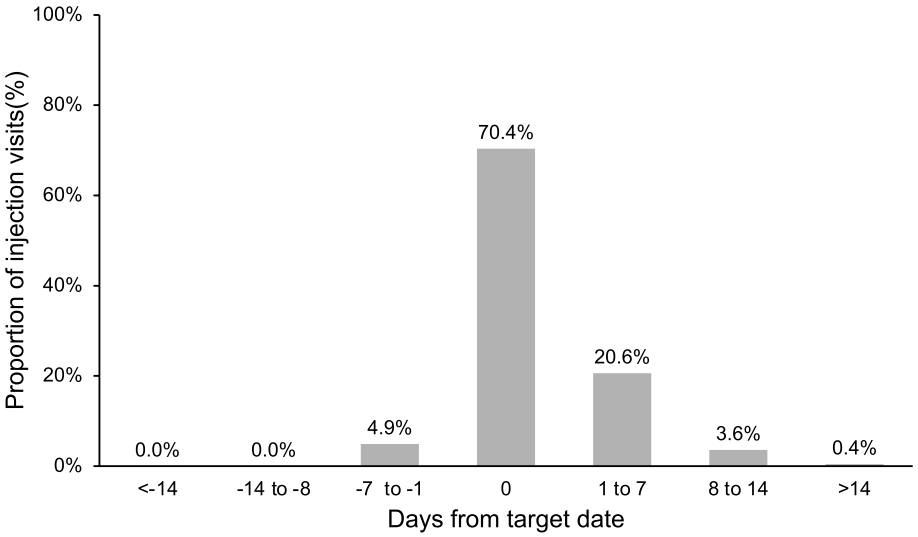

Fig. 3 Adherence to the injection schedule among patients receiving long-acting antiretroviral therapy

to monthly CAB + RPV injections were compared with those who continued DTG/ABC/3TC. Both the groups demonstrated similar efficacy and safety at 96 weeks [3].

A combined analysis of the ATLAS, ATLAS-2 M, and FLAIR trials examining factors related to CVF 48 weeks after initiating long-acting ART found that among 1,039 participants, 13 (1.3%) experienced CVF [12]. No single factor predicted CVF; however, a combination of two or more factors—pro-virus RPV resistance-related mutations, HIV-1 subtype A6/A1, and BMI ≥ 30 kg/m^2—resulted in a CVF rate of 25.7%. Although it is difficult to measure pro-virus resistance mutations and HIV-1 subtypes in clinical practice, E138A/G/K RPV resistance-related mutations were found in 8 of 1,107 (0.72%) untreated Japanese PLWH [13]. The frequency of HIV-1 subtype A in the Japanese population is 15 of 3,838 cases (0.4%) [14], and both E138A/G/K RPV resistance-related mutations and HIV-1 subtype A are relatively rare. The proportion of patients with a BMI ≥ 30 kg/m^2 among Japanese PLWH who started a tenofovir-containing regimen between 2002 and 2009 was reported as 8 among 494 cases (1.6%) [15]. However, recent reports indicate a link between ART and weight gain in PLWH, with significant weight gain observed after ART initiation, compared with non-infected individuals [16], particularly among patients treated with integrase inhibitors and TAF/FTC [16, 17]. A Swiss cohort study observed a rise in obesity among PLWH, with those having a BMI ≥ 30 kg/m^2 increasing from 4% in 2002 to 9% in 2012 and 12% in 2017 [18]. In our previous study of 543 treated PLWH, in which we used a body composition meter to assess the effect of ART, 218 patients (40.1%) were classified as obese (BMI ≥ 25 kg/m^2 and body fat percentage ≥ 20%), and 64 patients (11.8%) had a BMI ≥ 30 kg/m^2 [19]. Thus, obesity in PLWH is an important issue, and the proportion of patients with obesity and a BMI ≥ 30 kg/m^2 is expected to increase in Japan. In our study, only five participants (13%) had a BMI ≥ 30 kg/m^2, and no participants experienced CVF. Given the limited number of participants with obesity and absence of virological failure events, we cannot draw definitive conclusions about the association between obesity and virological outcomes in this population. Further studies with larger sample sizes and a higher proportion of participants with obesity are needed to better understand the potential effect of obesity on the effectiveness of long-acting ART.

A 2019 study of 2,389 HIV-positive adults from 25 countries, including 75 from Japan, assessed the factors affecting satisfaction with ART [20]. The study found that 36% of the Japanese participants viewed daily ART as a burden, 43% were reminded of their HIV status through daily intake, and 45% felt stressed by daily oral medication. Only 53% of Japanese participants reported no issues in managing their medications daily. The most sought-after improvements in HIV treatment were "reducing side effects" (53%), "minimizing long-term health impact" (48%), and "availability of long-acting treatments not requiring daily intake" (39%). This implies that a notable number of HIV-positive individuals are somewhat dissatisfied with their daily ART intake. In our hospital survey of PLWH [21], 16.2% were dissatisfied with conventional ART, whereas 54.9% preferred switching to long-acting ART. Although not all who wished to switch could do so, this indicates considerable interest among Japanese PLWH in long-acting ART. In this study, satisfaction with long-acting ART, as evaluated using the HIVTSQs/c, significantly increased. Adherence was high, with 96% of the injections administered on schedule. This suggests that long-acting ART may greatly enhance patient satisfaction, medication adherence, and overall quality of life.

In this study, an improvement in Cre levels was observed after switching to a long-acting ART. Drugs such as cobi, ritonavir (rtv), RPV, DTG, and BIC inhibit transporters, leading to decreased creatinine secretion from the renal tubules. Thus, an initial increase in serum creatinine and a decrease in creatinine clearance is observed. Cobi and DTG do not alter the true glomerular filtration rate [22, 23]. The apparent improvement in renal function due to the decrease in Cre levels can be attributed to the switch from conventional to a long-acting ART. Conversely, TAF, commonly used in conventional ART, is a prodrug of tenofovir disoproxil fumarate (TDF) and is believed to reduce the tubular toxicity associated with TDF [24, 25]. Therefore, TAF is a new treatment option for patients with reduced renal function. However, the US Department of Health and Human Services guidelines [26] recommend careful monitoring when switching from TDF to TAF, owing to the unclear long-term effects on patients with a history of renal disease, including proximal tubular injury, even though the switch is associated with improvements in proteinuria and renal biomarkers. Renal function recovery has been reported in patients with chronic kidney failure who switched to an NRTI-sparing regimen [27, 28]; however, the true improvement in renal function in this study is unclear because of the lack of measurements of urinary markers such as cystatin C and beta-2 microglobulin. Further case accumulation and evaluation of renal function using urinary markers are required to understand the effect of long-acting ART on renal function.

This study has some limitations. First, the study included a relatively small and homogeneous group of 38 male participants, potentially limiting the generalizability of the findings. A larger and more diverse sample would likely yield more comprehensive insights, applicable to a

broader population. Second, it was conducted at a single center; therefore the study may reflect specific local practices or patient demographics. Multi-center studies could provide a broader perspective and help reduce the biases associated with single-center research. Third, there is no comparative control group. Including a control group receiving standard treatment would have enhanced our ability to directly link the observed outcomes to the long-acting therapy. Fourth, the proportion of eligible participants who chose long-acting ART was not available in this study. The lack of this information may have introduced a selection bias and affected the generalizability of the results. Fifth, the linguistic validation of the Japanese version of the HIVTSQ has not been thoroughly established. The lack of a fully validated instrument may have influenced the assessment of treatment satisfaction. Additionally, the self-reported nature of the HIVTSQ may have introduced social desirability bias, potentially leading to an overestimation of treatment satisfaction. Participants might have been inclined to provide more positive responses to the questionnaire, given their awareness of being in a study evaluating a novel treatment approach.

Despite these limitations, a strength of this study is distinguished by its real-world clinical setting, providing practical insights. The extensive data collection over a significant period adds depth to our findings. Importantly, the focus on patient satisfaction introduces a valuable dimension, reflecting a holistic approach to assessing therapy effectiveness.

Conclusions

In conclusion, in patients who switched from conventional to long-acting ART, no CVF was observed, and treatment satisfaction increased. Despite limitations, such as the small and homogeneous nature of the participant group and absence of a control group, our findings underscore the potential of long-acting therapy in maintaining viral suppression and enhancing patient satisfaction and quality of life. A BMI ≥ 30 kg/m^2 has been reported as a predictor of virological treatment failure in injection regimens, and an increase in obese PLWH is expected in Japan. Further studies are needed to determine whether obesity alone can lead to treatment failure. Treatment satisfaction, as assessed using the HIVTSQs and HIVTSQc, improved, suggesting that injection regimens could contribute to patient satisfaction, medication adherence, and enhanced quality of life. Future research, involving larger and more diverse cohorts and conducted across multiple centers, is essential to corroborate these findings and broaden our understanding of the role of long-acting therapy in HIV treatment.

Abbreviations

3TC	Lamivudine
Ab	Antibody
ABC	Abacavir
Ag	Antigen
ART	Antiretroviral therapy
BMI	Body mass index
CAB	Cabotegravir
Cre	Serum creatinine
CVF	Confirmed virological failure
DTG	Dolutegravir
FTC	Emtricitabine
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HDL-C	High-density lipoprotein cholesterol
HIVTSQ	HIV Treatment Satisfaction Questionnaire
LDL-C	Low-density lipoprotein cholesterol
INSTI	Integrase strand transfer inhibitor
RPV	Rilpivirine
Rtv	Ritonavir
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TG	Triglycerides
VL	Viral load

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09904-x.

Supplementary Material 1.

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Authors' contributions

K.K. contributed to the study design, conducted the literature review, wrote the manuscript, and was responsible for the final decision to submit the manuscript. D.O. and S.K. revised the manuscript and provided valuable intellectual content. M.O., Y.K., and M.S. contributed to the data acquisition from each institution. M.S. supervised the conduct of this study. All authors reviewed the draft manuscript and critically revised it critically for intellectual content. All authors approved the final version of the submitted manuscript.

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Availability of data and materials

Raw data were generated at Osaka City General Hospital. Derived data supporting the findings of this study are available from the corresponding author K.K. on request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Review Committee of Osaka City General Medical Center (Approval Number: 2210072). The study was conducted in compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient to participate in the study.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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