Letter to the Editor

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Effects of raltegravir formulation change on medication adherence and medication errors

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SUMMARY This study was aimed at assessing the adherence and incorrect drug intake associated with changes in the dosing schedule of raltegravir, the first integrase strand transfer inhibitor, from 400 mg twice a day (BID) to 600 mg × 2 tablets once a day (QD) in human immunodeficiency virus (HIV)-infected patients. Medication adherence over 1 month was evaluated in 25 male patients using the 100-mm visual analog scale (VAS) at the 3-day recall pill count and during pharmacist counseling after the first post-change visit. VAS scores before and after the raltegravir formulation change were compared. Medication adherence increased from 96 ± 4.3 mm (BID) to 100 ± 0.3 mm (QD) ($P < 0.05$). The patients exhibited improved medication adherence; however, three patients incorrectly took the drug when the formulation changed. This discovery can be used to facilitate the treatment of HIV-infected patients to increase treatment suitability and safety.

Keywords Raltegravir, medication adherence, medication error, formulation change

Letter to the Editor,

Raltegravir, the first integrase strand transfer inhibitor, was approved in October 2007. It is a key drug in the treatment of infection with human immunodeficiency virus-1 (HIV-1) (*1*). In 2017, Cahn *et al*. reported that a change in the dosing schedule of raltegravir from 400-mg tablet taken twice a day (BID) to 1,200 mg (2 × 600 mg tablets) once a day (QD) is noninferior in efficacy (*2*). We previously reported a case in which raltegravir underdosing occurred when the formulation changed (*3*). In HIV treatment, a high level of HIV medication adherence increases the likelihood of complete control of the infection. However, the association between formulation changes and medication errors, such as incorrect use of anti-HIV agents, remains unclear. Therefore, we assessed medication adherence and incorrect drug use when the dosing schedule changed from BID to QD in raltegravir-treated patients with HIV infection. We expect that our results can shed light on how formulation changes are associated with errors and could be used by pharmacists to better treat and care for patients with HIV infection in the future.

The medical records of 25 men with HIV infection whose dosing schedules were changed from BID to QD were retrospectively reviewed at the Institute of Medical Science Hospital, the University of Tokyo, from July 2018 to September 2018. A 3-day recall was used to determine the total pill count to discover the patients who incorrectly took anti-HIV drugs. Data on medication adherence was collected from the medical and drug management instruction records. Medication adherence before and after formulation changes was evaluated using a 100-mm visual analog scale (VAS) and 3-day recall pill count. The former was self-assessed by the patients for 1 month according to pharmacist instructions. Comparisons of VAS data between BID and QD were performed using a paired *t*-test. All statistical analyses were performed using EZR (4). All *p*-values were two-sided, and values < 0.05 were considered statistically significant. The study was approved by the Institutional Review Board of our institution.

The dosing schedule for 25 patients who were prescribed raltegravir in our hospital was changed from BID to QD. The mean age of the patients was 51.9 ± 14.4 years. The drugs used by the patients included lamivudine/abacavir ($n = 11$), emtricitabine/tenofovir alafenamide ($n = 11$), and other drugs ($n = 3$), and the number of drugs used per patient was 4.5 ± 2.9. The median duration of HIV treatment was 104 months (range, 50-214 months). Medication adherence as assessed by the VAS score increased from 96 ± 4.3 mm (BID) to 100 ± 0.3 mm (QD) ($p < 0.05$, Figure 1). Three patients were found to have incorrectly taken the anti-HIV agents, including raltegravir. The incorrect drug use

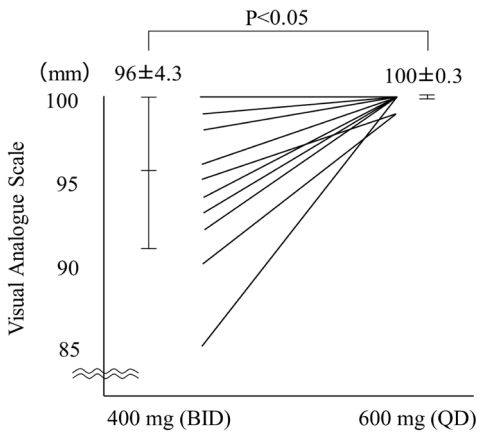

Figure 1. Patient self-assessment data using the 100-mm visual analog scale for medication adherence before and after the raltegravir dosing schedule was changed from BID to QD.

was discovered in the 3-day recall pill count. The three patients who had incorrectly taken drugs after raltegravir formulation change were elderly patients with HIV in their 50s, 60s, and 70s.

In this study, we demonstrated that changing the dosing schedule from BID to QD improved adherence in all patients. This result is similar to previous reports (*2,5-7*). However, the formulation changes caused medication errors in 3 of 25 patients. In HIV-infected patients, medication compliance of less than 95% increases treatment-resistant viral load (*8*). Therefore, our results on medication adherence and medication errors show the need for detailed instructions from pharmacists for each patient when they change dose timings. In addition, aging patients with HIV infection are more prone to medication errors as the number of medications for comorbidities increases and cognitive function declines. In particular, as anti-HIV medications are taken throughout life, the risk of medication errors is expected to increase further as daily treatment regimens, including the timing and frequency of dosing, become habitual. Thus, physicians and pharmacists must also consider polypharmacy and the complex medication treatment strategies used by patients with HIV infection. Based on our results, we can recommend that to discover any errors in dosage and medication adherence in clinical settings, strict monitoring is required using multiple methods, including subjective and objective tools, when a formulation is changed.

This study had a few imitations. First, this was a single-center study with a small number of patients. Second, our patients included many elderly patients. Interestingly, three patients who incorrectly took the anti-HIV agents were elderly. Therefore, their actions may have been influenced by and partially attributable to their age.

Our patients exhibited improved medication adherence after the dosing schedule changed from BID to QD; however, three patients incorrectly took their medications when the raltegravir formulation was changed. Although only a small proportion of patients made an error, this discovery can be used to improve the safety and suitability of HIV treatment. Pharmacists and physicians should closely monitor medication adherence and ensure that each patient takes the correct dose.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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