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# A case of under-dosing after raltegravir formulation change in an elderly patient treated for HIV

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Our case was a 70-year-old male (height: 168 cm, weight: 74.3 kg) with polypharmacy (total 15 drugs including 10 tablets) who was treated for HIV infection. His dosing schedule of raltegravir was changed from BID (a 400 mg tablet, twice) to QD (2x600 mg tablet, once). After a month, we found that he miss-took raltegravir for 1x600 mg tablet at once. His HIV-1 RNA increased from undetectable levels to < 20 copies per mL. Pharmaceutical companies should therefore carefully consider swallowing difficulties in old patients, such as by reformulating medications so that only one dosing is required per day and decreasing the size of tablets to 7–8 mm in diameter or orally distinguish tablet.

## 1. Introduction

Raltegravir, a first integrase strand transfer inhibitor approved in October 2007, is a key pharmacological treatment for human immunodeficiency virus-1 (HIV-1) infections. The standard approved dose of raltegravir is a 400 mg tablet taken twice a day (BID). Recently, Cahn et al. (2017, 2018) reported findings from the ONCEMRK trial that revealed the efficacy and safety of 1200 mg raltegravir (2 × 600 mg tablets) once a day (QD) to be noninferior to that of 400 mg BID, over a study period of at least 96 weeks, in 797 participants with a mean age of 35.9 (85%, males). Consequently, in May 2018, the Ministry of Health, Labour and Welfare approved 1200 mg raltegravir (2 × 600 mg tablets) QD in Japan. We report on a case who miss-took raltegravir according to the formulation change from 400 mg BID to 1200 mg (2 × 600 mg tablets) QD, who subsequently exhibited a slight increase in virus copies. This patient was treated at the Institute of Medical Science Hospital, the University of Tokyo.

## 2. Case report

Our case was a 70-year-old male (height: 168 cm, weight: 74.3 kg) with polypharmacy (total 15 drugs including 10 tablets) who was treated for HIV infection (raltegravir, darunavir, ritonavir, tenofovir alate namide/emtricitabine), hypertension (candesartan), diabetes mellitus (ipragliflozin), dyslipidemia (rosuvastatin), hyperuricemia (febuxostat), insomnia (brotizolam), prostate cancer (follow-up without medication), and others. He was diagnosed with HIV in 2010 and received medication as an outpatient for 8 years. In August 2018, the raltegravir dosing schedule changed from 400 mg BID to 1200 mg (2 × 600 mg tablets) QD, which was communicated to the patients by pharmacists. At his next visit to our hospital in September, the pharmacist discovered that the patient had been underdosed (600 mg QD). He had misunderstood that the changed formulation similarly changed the dosing frequency from BID to QD, and he could not take one tablets for a month. His HIV-1 RNA increased from undetectable levels to <20 copies per mL. He did not experience any adverse effect.

## 3. Discussion

Cahn et al. study's hypothesis was based on other research and suggested that changing the dosing schedule from BID to QD would improve the quality of life and adherence in HIV patients (Parienti et al. 2009; Cooper et al. 2010, 2011; Jayaweera et al. 2009). We agree with changing the dosing schedule from BID to QD, but the tablet sizes for most HIV drugs, including raltegravir, are very large compared with a suitable tablet size of 7–8 mm in diameter (Oshima et al. 2006). Thus, pharmaceutical companies should consider medication formulations as pharmaceutical technology continues to advance. In addition, 600 mg raltegravir requires two tablets at once. This is concerning because HIV patients have extended lifespans as a result of novel HIV drug development. Several elderly patients in our hospital have multiple chronic conditions and frequently exhibit hyper-polypharmacy (taking >10 drugs), including HIV drugs, insulin self-injection, and multiple other drugs. Our patients reflect the global trend of HIV patients reaching an advanced age. Pharmaceutical companies should therefore carefully consider swallowing difficulties in these patients, such as by reformulating medications so that only one dosing is required per day and decreasing the size of tablets to 7–8 mm in diameter or orally distinguish tablet.

Conflicts of interest: None declared.

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