A 27-year-old HIV-infected pregnant Japanese woman was admitted to our hospital at gestational week 14. The patient’s HIV viral load was 71,000 copies/mL, and her CD4 cell count was 147 cells/mm³. Zidovudine, lamivudine, and lopinavir/ritonavir were administered at gestational week 18. Because the viral load increased to 222,000 copies/mL at the initiation of antiretroviral therapy, we added raltegravir. The decrease in the viral load was satisfactory, and a caesarean delivery was performed. Although the plasma concentration of raltegravir in the neonate was significantly high (2,482 ng/mL), no adverse event was confirmed. There was no evidence of the mother-to-child transmission of HIV.

Key words: raltegravir, integrase strand transfer inhibitor, plasma concentration, HIV, pregnancy

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measured by a physician in another clinic and the value was 71,000 copies/mL in gestational week 12). No major mutation associated with drug resistance was detected. There was no evidence of an opportunistic infection or liver/renal functional disorder. During the initial evaluation, there were no special events with the exception of an allergy (a rash and fever) to sulfamethoxazole-trimethoprim (ST), thus we changed ST to atovaquone for the prophylaxis of pneumocystis pneumonia. At gestational week 18, the standard ART during pregnancy recommended by the Japanese manual for the prevention of the mother-to-child transmission of HIV (LPV/rtv 400/100 mg twice daily, AZT 300 mg twice daily and 3TC 150 mg twice daily) (1) was administered; however, the VL and CD4 cell counts at the initiation of ART were 222,000 copies/mL and 111 cells/mm$^3$, respectively. One week after the start of ART, RAL (400 mg twice daily) was added to the initial regimen. Because there was only 20 weeks until the expected date of confinement, and due to the possibility of premature birth, we expected the efficacy of RAL to provide a more rapid virological suppression than that of LPV/rtv (3, 6). The VL was decreased to 860 copies/mL at gestational week 21. We additionally changed AZT/3TC to abacavir (ABC)/3TC (600/300 mg once daily), which is marketed as EPZICOM® (EPZ), due to decreases in her hemoglobin level from 9.2 g/dL to 8.2 g/dL at gestational week 23. However, because an adverse event of vomiting occurred 5 hours after the first dose, we immediately stopped EPZ. After 5 days of stopping EPZ, we increased the dose of LPV/rtv to 600/150 mg twice daily due to the possibility of insufficient plasma concentrations of LPV in late pregnancy (7) and added 3TC again. Her ART regimen finally settled at 3TC/LPV/rtv/RAL. In order to confirm the efficacy of ART during pregnancy, we evaluated the trough plasma concentrations of the drugs, LPV at gestational week 25 and RAL at gestational week 26, and the results were 5.06 μg/mL and 72 ng/mL, respectively. According to these results, we reduced the dose of LPV/rtv to 800/200 mg at gestational week 34. At this point, the VL was suppressed to less than 20 copies/mL.

A caesarean delivery was performed at gestational week 38, with the administration of AZT infusion during delivery without complications. Because a small number of cases are reported in Japan, the Japanese manual recommends AZT infusion for all patients to insure that the mother-to-child transmission of HIV is prevented (1). The body weight of the infant was 2,662 g, with Apgar scores of 8/9. The infant was prescribed AZT syrup for four weeks. Breastfeeding was avoided. There was no evidence of the mother-to-child transmission of HIV at 1 and 4 months. In addition, the infant’s plasma concentration of RAL was evaluated 1.5 hours after delivery (6 hours after the mother’s last dose of RAL), and the result was 2,482 ng/mL. The plasma concentration of RAL decreased to less than 10 ng/mL at 53 days after birth. The mother’s clinical course, including the plasma concentrations of the drugs, is detailed in Figure.

**Discussion**

RAL is the first INSTI (approved in the U.S. by 2007 and in Japan by 2008) to demonstrate a strong efficacy for a rapid reduction of the VL (3). Recently, new INSTIs such as elvitegravir and dolutegravir have come onto the market; however, RAL remains among the first-line regimens in the guideline for ART (8).

RAL is a relatively venerable INSTI, although the experience of using INSTIs for pregnant women is limited. We searched the PubMed, Google Scholar and Ichushi (the Japanese database for medical literature and conference proceedings) databases for RAL-prescribed pregnancy case reports and clinical studies written in the English and Japanese languages, and identified 138 cases, including two non-Japanese case reports from Japan (4, 5, 9-28). In the litera-
ture review, the VL before the start of RAL varied from a non-detectable level to 17,400,000 copies/mL, and most of the patients (at least 100 patients, 72%) were administered RAL in the third trimester (late pregnancy). The duration of RAL use also varied from just 14 hours to the entire maternal period. Confirmed adverse events caused by RAL were definitive in the case of one mother with elevated liver enzymes (9, 10) and were suspected in two other cases with elevated liver enzymes and vomiting, respectively (11). In the infants, no adverse events and two HIV infections (1.4%) were documented. Because these data demonstrated the safety and efficacy of RAL, RAL was finally included as a preferred drug in the last updated (Aug. 6, 2015) version of the U.S. guideline (7). Moreover, our patient’s plasma concentration of RAL was not significantly different in the second trimester (72 ng/mL) from that measured post-partum concentration (79.2 ng/mL), and both values were compatible with the median trough concentrations described in the U.S. guideline (72 ng/mL, range: 29-118) (8).

RAL is also known to have a high placental transfer. In the present infant, the plasma concentration of RAL was significantly higher (2,482 ng/mL) than that of the mother. Despite the detection of a high plasma concentration of RAL in her infant, no adverse events occurred. This case is the first Japanese case report to describe the plasma concentration of RAL in a mother and her infant. According to the facts of this case and a literature review, we confirmed the safety and efficacy of RAL, even in relatively early gestation. However, the efficacy of RAL for the rapid reduction of the VL was not concluded in our case because the effect of the initial regimen was not determined. The lack of data concerning Japanese mothers and infants suggests the need for further study regarding the efficacy and safety of prescribing RAL during pregnancy. In addition, the observational periods in previous studies and in our case have been short, and long-term data of children’s growth are required in further research.

The Kurume University Research Ethics Committee (http://www.med.kurume-u.ac.jp/med/joint/rimri/) approved this study and written informed consent was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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References


| Table. The Relationship of Plasma Concentration of RAL between Mothers and Infants. |
|---------------------------------|-----------|-----------------|-----------|-----------------|-----------|-----------------|-----------------|-----------------|-----------------|
| Reference Case No. | (12) | (12) | (12) | (13) | (13) | (13) | Our case |
| Race | Rwandan | Ghanian | Ugandan | Ugandan | Ghanian | Zimbabwean | Japanese |
| Collection time of mother's samples | | | | | | | |
| after delivery (hours) | 0 | 1 | 0 | 3 | 1 | 9 | - |
| after maternal dose of RAL (hours) | 6 | 3 | 10.5 | 7 | 13 | 12 | - |
| Plasma concentration of RAL in mother (ng/mL) | 2,318 | 64 | 300 | 493 | 22 | 50 | 72* |
| Collection time of infant's samples | | | | | | | |
| after delivery (hours) | 1 | 2 | 0.5 | 3 | 1 | 2.5 | 1.5 |
| after maternal dose of RAL (hours) | 7 | 4 | 11 | 7 | 13 | 5.5 | 6 |
| Plasma concentration of RAL in infant (ng/mL) | 3,781 | 120 | 602 | 3,634 | 209 | 776 | 2,482 |
| Infant/mother plasma concentration ratio of RAL | 1.63 | 1.88 | 2 | 7.37 | 9.5 | 15.52 | 34.5 |

RAL: raltegravir
* Our case's trough plasma concentration of RAL was checked in second trimester.


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