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Nucleos(t)ide reverse transcriptase inhibitor-sparing regimens in the era of standard 3-drug combination therapies for HIV-1 infection

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Abstract: Nucleos(t)ide reverse transcriptase inhibitor (NRTI)-sparing regimens have often been selected as antiretroviral therapy (ART) for HIV-1 infection recently, but data for characteristics have been lacking. This study aimed to document the current status of NRTI-sparing regimens in the era of standard 3-drug combination therapies. We cross-sectionally compared characteristics of patients treated with NRTI-sparing regimens (NRTI-sparing group) with dolutegravir plus tenofovir alafenamide fumarate/emtricitabine as a standard ART group in 2018. The NRTI-sparing and the standard ART groups included 61 and 469 patients, respectively. The mean (± standard deviation) age and serum creatinine of the NRTI-sparing group were significantly higher than those of the standard ART group (57.6 ± 12.8 years vs 42.8 ± 10.4 years ($p < 0.05$) and 2.09 ± 3.10 mg/dL *vs.* 0.93 ± 0.19 mg/dL ($p < 0.05$), respectively. The percentage of patients with NRTI-sparing regimens increased with age; with less than 5% in their 50s or younger, 8.4% in their 60s, and 14.1% aged ≥ 70 years. The primary reason for switching to the NRTI-sparing regimen was due to reduced renal function. According to the limited data, viral suppression was achieved at week 48 in all patients in the NRTI-sparing group. No patient had treatment failure nor developed drug resistance. The use of NRTI-sparing regimens increased with age. They were more frequently used in patients aged ≥ 60 years and those with decreased renal function.

***Keywords*:** antiretroviral therapy, renal function, aging

Introduction

An antiretroviral regimen for HIV-1 infection generally comprises two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), namely backbone, plus a third drug from the integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI) drug classes (*1*), namely key drug. However, in some cases, NRTIs cannot be used because of medication-related adverse effects, accumulated toxicity, or drug resistance. In such situations, NRTI-sparing regimens can be selected. NRTI-sparing regimens are usually composed of two drugs, one each from two of the following three drug classes: INSTI, PI, or NNRTI. Several studies have shown the effectiveness and safety of NRTI-sparing regimens (*2-4*). The U.S. Department of Health and Human Services guidelines recommend darunavir/ritonavir (DRV/r) + raltegravir (RAL) for antiretroviral treatment-naïve patients who cannot use NRTIs (*1*). Although Japanese guidelines stipulate that NRTI-sparing regimens can be used for maintenance treatment in cases with well-controlled viral load, this recommendation is not based on evidence from Japanese patients. Therefore, this study aimed to figure out the status of NRTI-sparing regimens and reasons for regimen change in patients with HIV-1 infection. Efficacy of the NRTI-sparing regimens were also examined in the limited data.

Patients and Methods

There were 2,317 Japanese HIV-1-infected patients who had been treated with any antiretroviral treatment (ART) at AIDS Clinical Center, National Center for Global Health and Medicine as of the date of March 31, 2018. Among them, patients treated with tenofovir alafenamide fumarate/emtricitabine (TAF/FTC) + dolutegravir (DTG) and with NRTI-sparing regimens were included as the standard ART group and the NRTI-sparing group, respectively, and the characteristics why they were selected were analyzed cross-sectionally. The regimen of the standard ART group was chosen because it was the most frequently used one for ART naïve patients in 2018. Comparisons of the two groups were performed using Welch's *t* test and a $p < 0$ .05 was considered statistically significant. EZR (Saitama Medical Center, Jichi Medical

University, Saitama, Japan) was used for analyses.

As to efficacy of the NRTI-sparing group, the plasma HIV-RNA viral load (pVL) at 48 weeks after initiating the NRTI-sparing regimens was evaluated. Treatment success was defined if pVL was suppressed below 50 copies/ml. Patients whose initial pVL were less than 200 copies/ml and those who were lost to follow-up at the 48th week were excluded from the efficacy analysis.

This study was approved by the institutional review board of National Center for Global Health and Medicine (approval number: 3080).

Results

The NRTI-sparing group and the standard ART group included 61 (2.6%) and 469 (20.2%) patients, respectively, among 2,317 patients on ART. All patients of the NRTI-sparing group were switched from standard ART (a key drug + 2 NRTI backbone) except for 3 ART naïve patients. As for the 3 patients, NRTIs needed to be avoided due to renal function: two undergoing dialysis and one low creatinine clearance (CrCl) (< 30 mL/min).

Table 1 shows the patient characteristics. The NRTI-sparing group was significantly older than the standard treatment group (mean age ± standard deviation; 57.6 ± 12.8 years *vs.* 42.8 ± 10.4 years, $p < 0.05$, respectively). The mean serum creatinine (SCr) of the NRTI-sparing group was significantly higher than that of the standard ART group (2.09 ± 3.10 mg/dL *vs.* 0.93 ± 0.19 mg/dL, $p < 0.05$, respectively) and lower estimated glomerular filtration rate (eGFR) (60.7 ± 30.4 mL/min *vs.* 76.2 ± 32.5 mL/min, $p < 0.05$, respectively). The NRTI-sparing group also had a higher mean triglyceride (TG) than the standard ART group (201 ± 143 mg/dL *vs.* 135 ± 113 mg/dL, $p < 0.05$, respectively).

Figure 1 shows details of NRTI-sparing regimens. The most frequently used NRTI-sparing regimen was DTG + rilpivirine (RPV) (n = 28, 45.9%). If regimens were integrated into classes, the combinations were summarized with INSTI + NNRTI in 59% and INSTI + PI in 29.5%, namely almost all regimens included INSTI.

The primary reasons for changing to NRTI-sparing regimens were due to decreased renal function (n = 21, 34.4%), followed by avoidance of side effects (n = 15, 25.9%) or of drug-drug interactions (n = 7, 12.1%), drug resistance (n = 4, 6.9%), and desire to decrease daily pill number (n = 4, 6.9%). Then, we further analyzed status of the NRTI-sparing and the standard groups dividing by SCr levels (Figure 2). As presented, if SCr was elevated over 1.2 mg/dL, the NRTI-sparing regimen was preferentially selected.

Next, we showed connection between age and the NRTI-sparing regimens in Figure 3. As clearly stated, elderly patients were preferably treated with the NRTI-sparing regimens especially over their 60s. In detail, the usage rate was less than 5% among those in their 50s or younger, whereas it increased to 8.4% (19/225) and 14.1% (12/85) among those in their 60s and over 70 years, respectively.

None of the NRTI-sparing group had treatment

Table 1. Patients' demographics

Group *n* (%)	NRTI-sparing 61 (2.6)	Standard ART 469 (20.2)	*p*
Age, mean ± SD years	57.6 ± 12.8	42.8 ± 10.4	< 0.05
Male sex, *n* (%)	58 (95.1%)	445 (94.9%)	-
Infection route, *n*			
MSM	30	397	-
heterosexual	5	39	-
hemophiliacs	11	16	-
unknown	15	17	-
Naïve patients, *n* (%)	3 (4.9%)	33 (7.0%)	-
SCr, mean ± SD mg/dL	2.09 ± 3.10	0.93 ± 0.19	< 0.05
eGFR, mean ± SD ml/min	60.7 ± 30.4	76.2 ± 32.5	< 0.05
AST, mean ± SD IU/L	28.2 ± 24.0	28.9 ± 28.2	0.85
ALT, mean ± SD IU/L	31.6 ± 35.7	41.2 ± 68.7	0.54
LDL, mean ± SD mg/dl	104 ± 34.2	107 ± 31.0	0.51
TG, mean ± SD mg/dl	201 ± 143	135 ± 113	< 0.05
CD4*, mean ± SD /μL	508 ± 201	507 ± 266	0.97
HIV-RNA < 50 copy/mL*, *n* (%)	55 (90.1%)	378 (80.6%)	-

*at initiation of the regimen.

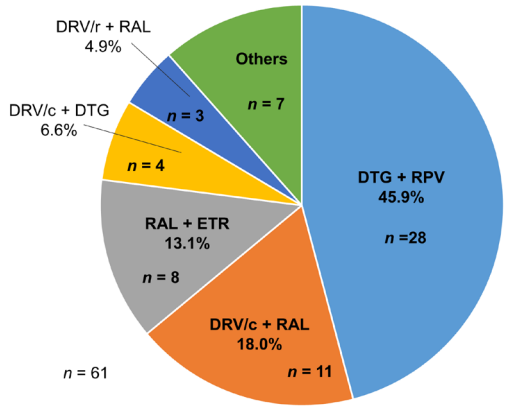

Figure 1. Details of the nucleos(t)ide reverse transcriptase inhibitor-sparing regimens used in this study. NRTI-sparing regimens accounted for only 61 (2.6%) of all (2,317) ART treatments in the study. DTG, dolutegravir; RPV, rilpivirine; DRV, darunavir; r, ritonavir; RAL, raltegravir; ETR, etravirine; c, cobicistat.

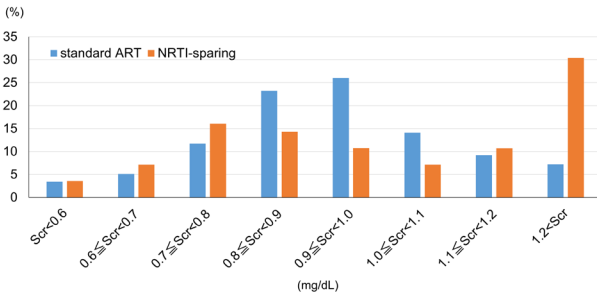

Figure 2. Frequencies of NRTI-sparing and standard ART groups usages in each serum creatinine (SCr) level. Frequencies of each group in each creatinine level were calculated dividing the number of patients in each group in each creatinine level by all NRTI-sparing regimens usage (n = 61) or all the standard ART regimen (n = 469), respectively.

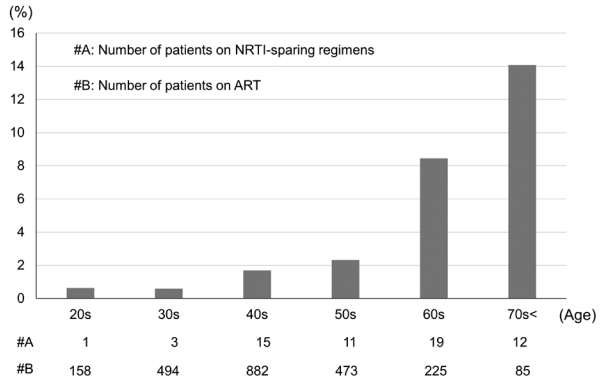

Figure 3. Connection of age and NRTI-sparing regimens. Denominator was number of all patients on ART in each age group.

failure nor developed drug resistance, and all patients exhibited viral suppression at week 48 after initiating the NRTI-sparing regimen.

Discussion

We evaluated characteristics of recent status of NRTI-sparing regimens in Japanese HIV-1-infected patients and found that use of NRTI-sparing regimens increased well with aging. This could be attributed to the age-related physical status decline in HIV-1-infected patients. For example, elderly patients have a decline in their renal function, develop lifestyle-related comorbidities, have increased concomitant drug use and their drug-drug interactions, and their side effects. Actually, renal dysfunction was the main reason for changing to NRTI-sparing regimens in this study. The standard regimens contained tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) until 2017. However, neither can be used for patients with CrCl < 50 mL/min unless their dose was reduced. For example, if renal function declined to CrCl < 50 mL/min, TDF/FTC must be given every other day. This can lead to poor adherence. Therefore, the NRTI-sparing regimens are reasonable options for elderly patients. In Japan, we tried to demonstrate safety merit of a NRTI-sparing regimen of DRV/r + RAL switching from TDF/FTC + lopinavir/r in a randomized clinical trial (*5*). In this trial, we could not document significant recovery of renal function.

In contrast, drug-drug interactions between NRTIs and other drugs are rare (*6*), and thus changing to another regimen is rarely reported. This could happen in the use of a booster drug such as ritonavir or cobicistat.

Another reason why NRTI-sparing regimens are possible is that recently some drugs such as DRV or DTG have high genetic barriers, suggesting a lower risk of emergence of drug resistance and subsequent treatment failure (*2,3,7,8*). However, for example, even using a combination of DTG + RPV, it should be prescribed carefully with drug resistance of RPV to avoid functional monotherapy with DTG. Otherwise, emergence of DTG resistance will markedly decrease future treatment options.

There are three reasons when we think of NRTI-sparing regimens. One is due to avoidance of side effects caused by NRTIs. Decreased renal function in the elderly is that reason. This type of NRTI-sparing regimen use can be said to be a negative selection. Second one is a neutral reason for long-time safety and simplicity of ART, namely maintenance therapy. Development of a long acting drug makes it possible. Large clinical trials demonstrated safety and efficacy of this type of treatment strategy (*9,10*). The last one is an active reason in the choice of this regimen for ART naïve patients. Development of the strong drug, DTG, is the key. A large, double blind, randomized study documented the non-inferiority between DTG + 3TC and DTG + FTC/TAF (*11*). Although this regimen (DTG + 3TC) contains 3TC, it can be classified as one of the NRTI-sparing regimens and listed in the first line choice in the DHHS Guideline (*1*). This type of choice can be said to be a positive or active selection. According to our data, reasons for our NRTI-sparing regimens have been still limited in negative selection.

This study has some limitations. First, this was a single-center cross-sectional study with a smaller sample size. Therefore, strictly speaking, we cannot evaluate the efficacy of each regimen. However, in our efficacy analysis, all NRTI-sparing regimens achieved virus suppression after 48 weeks, consistent with the results of previous clinical trials (*2-4*). Second, duration of the study was limited. Therefore, we were not able to document the real-world long-term safety and efficacy of the NRTI-sparing regimens. Further and longer analyses could answer these clinical questions. However, it is noteworthy that this study first illustrated the current situation of NRTI-sparing regimens in Japan.

In conclusion, use of NRTI-sparing regimens have increased with age. They were more frequently used in patients aged ≥ 60 years and those with decreased renal function. In our limited data, we did not have treatment failure in patients treated with NRTI-sparing regimens.

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ViiV Healthcare, Merck Sharp & Dohme, Janssen Pharmaceutical K.K., and Torii Pharmaceutical, Co. Other authors declared none.

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