



한국에서의 HIV-1 약제 내성 돌연변이와 임상적 의미

HIV-1 Drug Resistance Mutations and Their Clinical Implications in South Korea

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Background: While the incidence of new human immunodeficiency virus (HIV) infections has decreased, the dramatic rise in antiretroviral therapy (ART) use will likely increase the prevalence of drug resistance mutations (DRMs). This study aimed to investigate the prevalence and profile of HIV-1 DRMs in ART-naïve and ART-experienced patients in South Korea and determine the correlation between the degree of DRM and the clinical response.

Methods: Thirty-six ART-naïve and 8 ART-experienced HIV-1-infected Korean patients referred for standard genotypic resistance testing (SGRT) between 2018 and 2019 were enrolled. Their SGRT results, viral loads, and CD4+ T cell counts were analyzed.

Results: Protease inhibitor (PI)-related DRMs were the most frequently observed mutations in ART-naïve (52.8%) and ART-experienced (50.0%) groups, followed by nonnucleoside reverse transcriptase inhibitor (NNRTI)-related and integrase inhibitor (INSTI)-related DRMs. Major DRMs were observed only as NNRTI-related DRMs. The prevalence of transmitted drug resistance (TDR) was 55.6%, which was markedly higher than that previously reported. The changes in viral loads and CD4 counts in ART-naïve patients showed no correlation with the degree of DRM (major, minor, and none). All ART-naïve patients were treated with INSTI-based regimens, and most showed very good responses.

Conclusions: The distribution of HIV-1 DRMs in Korean patients was biased toward PI-related and minor DRMs, and DRM severity was not associated with the clinical response. This study provides valuable information on the recent DRM profile among Korean HIV-1 patients and emphasizes the importance of drug resistance genotyping.

Key Words: HIV, Anti-HIV Agents, Drug Resistance, Viral, Genetic Profile

INTRODUCTION

The worldwide efforts for the prevention of the spread of human immunodeficiency virus (HIV) infection have successfully

decreased the incidence of new HIV infections [1]. However, the dramatic rise in the use of antiretroviral therapy (ART) will likely increase the prevalence of acquired drug resistance (ADR) among treated HIV-infected individuals and transmitted drug resistance (TDR) in newly infected patients [2]. HIV drug resistance is a common cause of treatment failure in HIV-infected patients. AIDS Info Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents suggest that therapy for a treatment-naïve patient generally comprises two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active drug from one of three drug classes, namely, an integrase strand transfer inhibitor (INSTI), a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer [3]. The guidelines recommend initial antiretroviral regimens for most people with HIV as 1 INSTI plus 2 NRTIs or plus 1

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NRTI, and additionally mention HIV drug resistance testing before the inception of treatment to guide the selection of the initial ART regimen. HIV drug resistance testing is also performed to assist the selection of active drugs while changing ART regimens, especially in patients with virologic failure and HIV RNA levels >1,000 copies/mL.

Data on DRM have been internationally published. Hattori et al. performed a drug resistance test on 3,904 HIV-1-infected cases in Japan and found the overall prevalence of TDR to be 9.1%, which was not significantly different between recent and long-term seroconverters [4]. Eleven of 127 drug-naïve and 13 of 117 first-line drug-treated HIV-1-infected individuals in Suzhou, China, had transmitted and acquired resistance mutations, respectively. Six TDR mutations (DRMs), including one major mutation, were found in the protease and reverse transcriptase regions [5]. In particular, INSTIs are the most recently introduced drug type and have been clinically used since 2007 [6]. Several recent studies have focused on uncovering INSTI resistance mutations [7-9].

According to the data from the Korea Disease Control and Prevention Agency, the prevalence of HIV in South Korea is very low, at less than 0.1%. The major subtype of HIV-1 is subtype B and the incidence of TDR ranges from 1.9% to 8.5% in South Korea [10-14]. Many HIV-1 DRMs have been reported in South Korea.

Clinical responses according to DRMs were analyzed in previous studies. Chin et al. calculated the sum of the average resistance mutation scores (SARMS) obtained from the Stanford HIV Drug Resistance Database (HIVDB) in each primary HIV-1-infected patient and found that the SARMS of patients with viral loads exceeding 100,000 copies/mL were significantly lower than those of patients with viral loads <100,000 copies/mL, suggesting that the resistant strains had decreased viral fitness [13].

The primary aim of this study was to investigate the prevalence and profile of HIV-1 DRMs in ART-naïve and ART-experienced patients in South Korea. The secondary purpose was to determine the correlation between the degree of drug resistance and the clinical response.

MATERIALS AND METHODS

1. Study design and patient population

We retrospectively enrolled HIV-1-infected patients who underwent standard genotypic resistance testing (SGRT) between

April 2018 and April 2019 at Boramae Medical Center in Seoul, South Korea. There are 15,000 HIV-infected individuals in South Korea, and approximately 340 patients have regular follow-up visits at the hospital, accounting for 2.3% of all HIV-infected people. Individual patient data were extracted from electronic hospital records. This study was approved by the Institutional Review Board of Seoul National University Boramae Medical Center (10-2019-36) and conducted in accordance with the tenets of the Declaration of Helsinki. All standard genotypic resistance tests were performed with written informed consent.

We calculated the required sample size using the World Health Organization practical manual for the determination of sample sizes in health studies [15]. The required sample sizes of ART-naïve and ART-experienced groups were 29–120 and 385, respectively. A total of 61 HIV-1-infected patients were screened. We excluded 18 HIV-1-infected patients whose history of treatment was unknown or whose SGRT results were “not assessed” due to low viral loads. We enrolled 43 patients, including 36 ART-naïve and 7 ART-experienced patients, who were initially tested with SGRT. One patient (patient #23) underwent SGRT before and after ART and was included in both the ART-naïve and ART-experienced groups in the overall analysis. Most patients were male (95.3% and 87.5% in the ART-naïve and ART-experienced group, respectively), and homosexual men accounted for 74.3% and 37.5% individuals, respectively (Table 1). The median ages were 29 and 34 years in ART-naïve and ART-experienced group, respectively.

Table 1. Baseline characteristics of the patients

	ART-naïve (N=36)	ART-experienced (N=8)
Sex		
Male	35 (97.2)	7 (87.5)
MSM	26 (74.3)	3 (37.5)
Female	1 (2.8)	1 (12.5)
Patients who died	2 (5.6)	0
Age	29 (26–33)	34 (28–53)
CD4 counts at enrollment (cells/ μ L)		
<200	12 (33.3)	3 (37.5)
200–349	14 (38.9)	3 (37.5)
350–499	4 (11.1)	0
\geq 500	6 (16.7)	2 (25.0)
HIV RNA at enrollment (copies/mL)	35,272 (12,530–185,900)	32,168 (12,511–107,303)

Data are presented as the no. (%) or median (interquartile range). Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; MSM, men who have sex with men.

2. Protocol of genotypic drug resistance testing

Viral RNA was extracted from the plasma of patients with a TANBead OptiPure Nucleic Acid Auto Tube/Plate kit and TAN-Bead instrument (Taiwan Advanced Nanotech Inc., Taoyuan, Taiwan) according to the manufacturer’s guidelines. Reverse-transcription PCR was carried out, the integrase gene (*IN*) was subjected to laboratory-developed tests, and the reverse transcriptase gene (*RT*) and protease gene (*PR*) were analyzed with an Abbott ViroSeq kit (Abbott Laboratories, Chicago, IL, USA). Samples were sequenced using an ABI 3500xl genetic analyzer (Applied Biosystems, Waltham, MA, USA). Finally, genotypic drug resistance testing elucidated the NRTI-, NNRTI-, PI-, or INSTI-related DRMs.

3. Interpretation of DRMs

The translated amino acid sequences were compared with the amino acid sequences of known DRMs. Variants in the *RT* and *PR* genes were compared with the 2019 edition of the International Antiviral Society–USA (IAS–USA) DRM list [16], and those in the *IN* gene were compared with the HIVDB [17]. We defined a variant as a major drug resistance-related mutation for a specific class when it is considered a major drug mutation for at least one drug in a class of antiretroviral drugs according to the databases.

4. Clinical responses

For the analysis of clinical responses, CD4 counts, plasma HIV viral loads (Abbott RealTime HIV-1, Abbott Laboratories), and data on treatment history and mortality were collected. The follow-up viral loads and CD4 counts could not be obtained for four of 36 ART-naïve patients due to death or follow-up loss. The median

(interquartile range) follow-up periods of viral loads and CD4 counts among 32 ART-naïve patients were both 8 (6–11) months. As ART started 2 weeks after the measurement of initial CD4 counts and viral loads, the time periods between the start of ART and the final follow-ups of CD4 counts and viral loads in the ART-naïve group were 7 months and 2 weeks (median value), respectively. Among the eight ART-experienced patients, one had no follow-up CD4 counts. The median (interquartile range) follow-up periods of viral loads in the eight ART-experienced patients and CD4 counts in the seven ART-experienced patients were both 8 (3–11) months.

5. Patient subgroup classification according to the degree of DRM

We classified the patients according to DRM subtypes. When the HIV strain harbored at least one major mutation, the patient was assigned to the major DRM subgroup. On the other hand, the patient was assigned to the minor DRM subgroup if his/her HIV strain had only minor mutations. Individuals with an HIV strain without any DRM were classified into the non-DRM subgroup.

6. Statistical analysis

The chi-squared test or Fisher’s exact test was used to compare categorical variables, and the Kruskal–Wallis test with Dunn’s multiple comparison test was used to compare continuous variables. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). *P* < 0.05 was considered statistically significant.

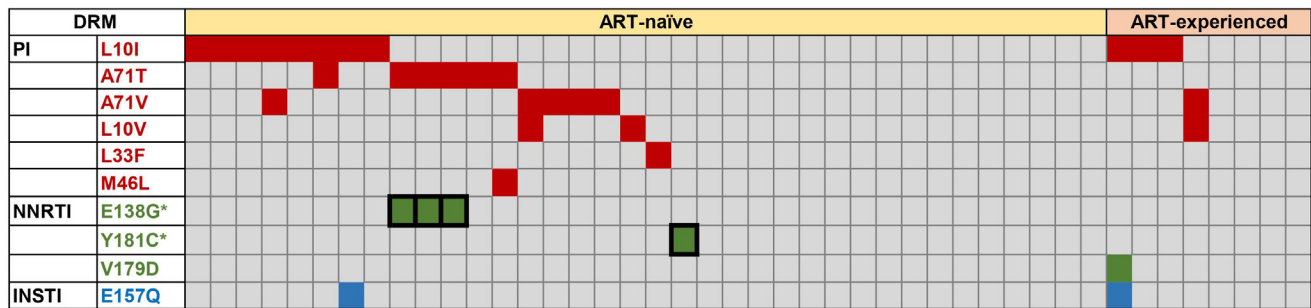


Fig. 1. Landscape of DRM in ART-naïve and ART-experienced patients in South Korea. *represents major DRMs, and the absence of *represents minor DRMs. Abbreviations: ART, antiretroviral therapy; DRM, drug resistance mutation; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor.

RESULTS

1. The landscape of DRMs

Twenty of 36 ART-naïve patients had DRMs for any one class of antiretroviral drugs, representing a TDR prevalence of 55.6%. Among ART-naïve patients, PI-related mutations were the most frequently observed DRMs (19/36, 52.8%), followed by NNRTI-related (4/36,

11.1%) and INSTI-related (1/36, 2.8%) mutations (Fig. 1). NRTI-related mutations were not noted.

Among the eight ART-experienced patients, only one patient (patient #23) had SGRT results before ART. Both the pre- and post-ART DRM of the patient were PI-related minor mutations as follows: L10I and A71V in pre-ART and L10V and A71V in post-ART. As patient #23 did not take PI, the DRM change was not inferred

Table 2. Drug resistance mutation test results in 36 ART-naïve patients and their subsequent ART

Patient No.	Drug resistance mutation	Following ART regimen			
		NRTI	NNRTI	PI	INSTI
1	None	3TC, ABC	(-)	(-)	DTG
3	None	FTC, TAF	(-)	(-)	EVG/c
5	NNRTI(E138G)*, PI(A71T)	3TC, ABC	(-)	(-)	DTG
8	NNRTI(E138G)*, PI(A71T)	FTC, TAF	(-)	(-)	EVG/c
10	None	FTC, TAF	(-)	(-)	EVG/c
11	None	3TC, ABC	(-)	(-)	DTG
12	None	FTC, TAF	(-)	(-)	DTG
15	PI(L10I)	3TC, ABC	(-)	(-)	DTG
17	None	FTC, TAF	(-)	(-)	DTG
18	PI(L10I)	3TC, ABC	(-)	(-)	DTG
19	None	FTC, TAF	(-)	(-)	DTG
21	PI(L10I)	FTC, TAF	(-)	(-)	EVG/c
22	None	3TC, ABC	(-)	(-)	DTG
23	PI(L10I, A71V)	3TC, ABC	(-)	(-)	DTG
24	PI(L10V, A71V)	3TC, ABC	(-)	(-)	DTG
25	PI(L10I)	3TC, ABC	(-)	(-)	DTG
26	None	3TC, ABC	(-)	(-)	DTG
27	None	FTC, TAF	(-)	(-)	EVG/c
30	PI(A71V)	FTC, TAF	(-)	(-)	EVG/c
32	NNRTI(Y181C)*	3TC, ABC	(-)	(-)	DTG
33	NNRTI(E138G)*, PI(A71T)	3TC, ABC	(-)	(-)	DTG
34	PI(L10I, A71T)	3TC, ABC	(-)	(-)	DTG
37	PI(A71T)	3TC, ABC	(-)	(-)	DTG
39	PI(L10V)	FTC, TAF	(-)	(-)	DTG
43	PI(L10I), INI(E157Q)	3TC, ABC	(-)	(-)	DTG
44	None	3TC, ABC, FTC, TAF	(-)	(-)	DTG, EVG/c
46	None	3TC, ABC	(-)	(-)	DTG
47	PI(A71V)	3TC, ABC	(-)	(-)	DTG
48	PI(M46L, A71T)	3TC, ABC	(-)	(-)	DTG
49	None	3TC, ABC	(-)	(-)	DTG
50	PI(L33F)	3TC, ABC	(-)	(-)	DTG
53	None	3TC, ABC	(-)	(-)	DTG
55	PI(A71V)	FTC, TAF	(-)	(-)	EVG/c
56	None	3TC, ABC	(-)	(-)	DTG
57	None	3TC, ABC	(-)	(-)	DTG
61	PI(L10I)	3TC, ABC	(-)	(-)	DTG

*represents major DRMs, and the absence of *represents minor DRMs.

Abbreviations: ART, antiretroviral therapy; DRM, drug resistance mutation; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; TAF, tenofovir alafenamide; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat.

to be ADR. Therefore, the prevalence of ADR in this study could not be evaluated. In the ART-experienced subgroup, the most common class was PI (4/8, 50.0%), followed by NNRTI and INSTI (both 1/8, 12.5%). NRTI-related mutations were absent.

Major DRMs were observed in only the NNRTI class and only the ART-naïve group (4/36, 11.1%). The total DRM count in the cohort was 32, including four major DRMs (12.5%) and 28 minor DRMs (87.5%). The median mutation count per patient was 1 and ranged from 0 to 3. The L10I variant was the most frequent mutation in both the ART-naïve subgroup (8/36, 22.2%) and the ART-experienced group (3/8, 37.5%).

2. DRMs and ART regimens

All ART-naïve patients were initially treated with INSTI-based regimens (Table 2). Only one ART-naïve patient (patient #43) harbored a minor INSTI-related drug mutation, E157Q. None of the other patients harbored NRTI- or INSTI-related DRMs. The previous ART regimens in ART-experienced patients were variable and included NNRTI-based, PI-based, and INSTI-based regimens (Table 3). Four of 8 (50.0%) patients were estimated to not have developed ADR because they did not harbor any DRMs. Three patients (patients #23, 40, and 54) showed PI-related DRMs but had not previously received PIs, and their ART regimens after SGRT were all INSTI-based regimens. Patient #36 previously took PI-(darunavir) and INSTI-based regimens and subsequently harbored minor PI- and INSTI-related mutations. However, the PI-related DRM (L10I) was a minor DRM for atazanavir and lopinavir but not

darunavir. The INSTI-related DRM that the patient harbored was E157Q, which is a common polymorphic accessory DRM and has a minimal impact on integrase strand transfer activity and viral infectivity [17, 18].

3. Correlation between the degree of drug resistance and the clinical response

Four of 32 ART-naïve and 4 of 8 ART-experienced patients with follow-up viral load data and CD4 counts did not achieve viral loads of less than 40 copies/mL (limit of detection, LoD). HIV RNA levels below the lower LoD indicate virologic suppression [3]. There

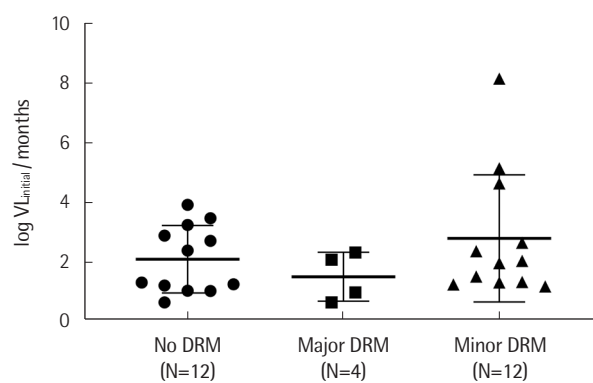


Fig. 2. Log initial viral load per months required to reach virologic suppression according to DRM subtypes in 28 ART-naïve patients. Virologic suppression means the achievement of a viral load of less than the limit of detection (40 copies/mL). Horizontal lines and vertical lines indicate mean values and standard deviations, respectively. There were no differences among the three subgroups ($P=0.3429$) or between any two groups.

Abbreviations: DRM, drug resistance mutation; VL, viral load.

Table 3. Drug resistance mutation testing results of 8 ART-experienced patients and their antiretroviral regimens before and after SGRT

Patient number	ART regimen before SGRT				ART regimen after SGRT				Drug resistance mutation
	NRTI	NNRTI	PI	INSTI	NRTI	NNRTI	PI	INSTI	
4	ZDV, 3TC	(-)	LRV/r	(-)	FTC, TAF	(-)	DRV/c	DTG	None
7	3TC, ABC	(-)	(-)	RAL	(-)	(-)	DRV/c	DTG	None
9	3TC, ABC	(-)	ATV/c	(-)	3TC, ABC	(-)	ATV/c	(-)	None
23	3TC, ABC	(-)	(-)	DTG	3TC, ABC	(-)	(-)	DTG	PI(L10V, A71V)
36	3TC, ABC, FTC, TAF	(-)	DRV/c	DTG	3TC, ABC	(-)	(-)	DTG	NNRTI(V179D), PI(L10I), INSTI(E157Q)
38	FTC, TAF	(-)	(-)	RAL	FTC, TAF	(-)	(-)	RAL	None
40	FTC, TAF, TDF	EFV	(-)	EVG/c	FTC, TAF	(-)	(-)	EVG/c	PI(L10I)
54	3TC, ZDV	EFV	(-)	(-)	3TC, ABC	(-)	(-)	DTG	PI(L10I)

All DRMs are minor DRMs.

(-) means none.

Abbreviations: ART, antiretroviral therapy; SGRT, standard genotypic resistance testing; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; EFV, efavirenz; LRV/r, lersivirine/ritonavir; ATV/c, atazanavir/cobicistat; DRV/c, darunavir/cobicistat; RAL, raltegravir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat.

Table 4. Initial CD4 counts before ART and final CD4 counts after ART in 32 ART-naïve patients according to DRM subtypes

DRM type	Initial CD4 count/ μ L before ART*				Final CD4 \geq 350/ μ L after ART†
	< 200	200–349	350–499	\geq 500	
None (N = 14)	2	9	2	1	12 (85.7%)
Minor (N = 14)	3	5	2	4	12 (80.0%)
Major (N = 4)	3	0	0	1	3 (75.0%)

* $P=0.1087$, † $P=0.8587$.

Abbreviations: ART, antiretroviral therapy; DRM, drug resistance mutation.

was no difference in the proportion of patients who achieved virologic suppression among DRM subtypes in either the ART-naïve or ART-experienced group ($P=0.7214$ and $P>0.9999$, respectively). We compared the decreased viral load rate after ART in ART-naïve patients who achieved virologic suppression among the DRM subtypes and found no difference ($P=0.3429$, Fig. 2).

We analyzed the initial CD4 counts before ART and the final CD4 counts after ART in these 32 ART-naïve patients according to DRM subtypes (Table 4). The distribution of initial CD4 counts according to DRM subtypes was not different among the subtypes ($P=0.1087$). In all the DRM subgroups, 75% or more patients from each group showed final CD4 counts of 350 copies/mL or higher ($P=0.8587$). The initial and final CD4 counts of the patients whose final CD4 counts were less than 350/ μ L were as follows: 73 and 132/ μ L and 285 and 322/ μ L in the non-DRM subgroup; 51 and 19/ μ L and 126 and 248/ μ L in the minor DRM subgroup; and 38 and 194/ μ L in the major DRM subgroup.

DISCUSSION

In the current study, we presented the landscape of DRMs in 43 Korean HIV-1-infected patients diagnosed from 2018 to 2019. Twenty of 36 (55.6%) ART-naïve patients and 4 of 8 (50.0%) ART-experienced patients carried DRMs. In both subgroups, PI DRMs were the most common mutations, followed by NNRTI and INSTI DRMs. The majority of the observed DRMs were minor mutations, and major DRMs were reported in only NNRTI-related mutations. Kim et al. showed the prevalence and profile of HIV-1 DRMs in 50 ART-naïve and 34 ART-experienced Korean individuals diagnosed between 2007 and 2011 [19]. These authors did not analyze the expression of IR gene. Six (12%) ART-naïve and 22 (64.7%) ART-experienced patients had HIV strains with resistance mutations. V179D (NNRTI) and M184V (NRTI) were the most common mutations

among ART-naïve and ART-experienced patients, respectively. In comparison with Kim et al.'s results, our data showed higher TDR and PI DRM prevalence. In addition, several previous studies reported that the prevalence of TDR in South Korea ranged from 1.9% to 8.5% [10–14], which was lower than the present result. Considering only the major DRMs, the prevalence of TDR was 11.1% in this study. We speculated that the discrepancy in the prevalence of TDR may be attributed to different interpretations of DRMs among researchers, the various databases used in DRM analysis, and deviation due to small population sizes.

We could not estimate the prevalence of ADR because most of the cohort did not undergo SGRT both before and after ART. Only one patient (patient #23) underwent SGRT both before and after ART because the viral load did not decrease below the LoD on ART. The patient harbored minor PI-related DRMs (L10I and A71V) before the initiation of ART. SGRT results from both 10 and 11 months from the initiation of ART revealed only minor PI-related DRMs (L10V and A71V), and the patient was prescribed an INSTI-based regimen. The major cause of the patient's poor response was thought to be poor compliance.

In the analysis of the correlation between DRM subtypes and the clinical response, viral loads and CD4 counts in ART-naïve patients showed no correlations with the DRM subtypes. Overall, 28 of 32 (87.5%) ART-naïve patients achieved virologic suppression and 27 (84.4%) patients had CD4 counts of 350/ μ L or higher after ART. An incomplete virologic response, indicative of virologic failure, is that when two consecutive plasma HIV RNA levels are \geq 200 copies/mL after 24 weeks on an ART regimen in a patient without virologic suppression on the regimen [3]. As long as ART maintains viral suppression, CD4 counts would recover. CD4 count recovery occurs most rapidly in the first 3 months of ART and gradually increases thereafter [20–22]. The 7.5-month follow-ups of CD4 counts and viral loads in this study were sufficient to evaluate the clinical responses.

Most patients in the ART-naïve group showed very good responses. As most physicians in South Korea use INSTI-based regimens [23], all regimens used to treat ART-naïve patients in our study were INSTI-based, but the major DRMs were NNRTI-related mutations. The most common minor DRMs were PI-related, and the median number of mutations per patient was one. These factors explain why most patients did not develop treatment failure, irrespective of the DRM subtype.

The only observed INSTI-related DRM was E157Q reported in 2.8% (1/36) of the ART-naïve group and 12.5% (1/8) of the ART-experienced group. This minor DRM alone has hardly any impact on drug resistance. Other studies reported the prevalence rates of INSTI DRMs in ART-naïve patients in South Korea as 12.3% in 2014 and 2015 and 47.1% in 2007 [8, 24]. All of these were minor DRMs. The E157Q variant had prevalence rates of 8.5% in 2014–2015 and 7.1% in 2007. The low prevalence of INSTI DRMs in the current study may be owing to the small number of study participants.

Meanwhile, our cohort included two dead HIV-1-infected ART-naïve patients. One patient was a 42-year-old female who had no past medical history except postnasal drip syndrome. The patient had fever, chills, and cough 2 weeks before a visit, and the HIV screening test was positive. The patient was admitted and received trimethoprim-sulfamethoxazole (TMP-SMX) and methylprednisolone to treat severe *Pneumocystis jirovecii* pneumonia. She was then treated in the intensive care unit and died due to multiorgan failure 27 days after admission. The other patient was a 36-year-old male who presented with dyspnea a month prior. He was admitted, confirmed to have HIV infection, and treated with TMP-SMX, prednisolone, and a mechanical ventilator. The patient exhibited aggravated acute respiratory distress syndrome, probably due to cytomegalovirus pneumonia, and finally died 27 days after admission.

The potential limitations of this study were that it was based on the data from a single center and included a small number of study participants. According to the manual for the calculation of sample sizes [15], we calculated the required sample sizes. For a 95% confidence level, a desired precision of 0.05, and an expected prevalence of TDR from 1.9% to 8.5%, the minimum sample size required in the ART-naïve group ranged from 29 to 120 individuals. Given the limited data on DRM prevalence in ART-experienced patients, the acquisition of a minimum sample size for the ART-experienced group was limited. When the expected prevalence was 50% with a 95% confidence level and a desired precision of 0.05, the minimum sample size of ART-experienced patients was 385. In this study, the number of ART-naïve patients (N=36) was appropriate and the number of ART-experienced patients (N=8) was too small to present the DRM prevalence in ART-experienced patients in South Korea.

We presented the recent DRM distribution and prevalence in both ART-naïve and ART-experienced HIV-1-infected patients in

a single center in South Korea, although the number of ART-experienced patients was too small. A total of 58.3% ART-naïve and 50.0% ART-experienced patients harbored HIV strains with PI-related resistant mutations, which were all minor mutations. Two major DRMs in NNRTIs were observed in only four ART-naïve patients. Almost all Korean HIV-1-infected patients received INSTI-based regimens, and most patients had a good prognosis. Our results presented no major INSTI DRM, supporting the current use of INSTI-based treatment. The prevalence of TDR was higher than that previously reported, suggesting a difference in the interpretation of DRMs among researchers. In addition, there was no significant correlation between DRM subtypes and viral loads or CD4 counts. SGRT is necessary to select appropriate regimens in the initiation of ART or the treatment of treatment-failure cases and to monitor TDR. Surveillance of the distribution and prevalence of DRM in HIV-1 should be continued globally.

요 약

배경: 새롭게 발생하는 HIV 감염은 감소했지만, 항레트로바이러스요법 사용이 급증하면서 항HIV 약제 내성 돌연변이의 유병률이 증가할 것으로 예상된다. 본 연구에서는 항레트로바이러스요법을 받지 않은 환자 및 치료 경험이 있는 환자에서 HIV-1 약제 내성 돌연변이의 빈도 및 프로파일을 조사하고, 약제 내성 돌연변이의 정도와 임상적 반응 간의 관계를 분석하고자 하였다

방법: 2018년부터 2019년까지 표준 유전형 내성 검사(SGRT)가 의뢰된 항레트로바이러스제 치료력이 없는 36명의 환자와 치료력이 있는 환자 8명이 연구에 포함되었다. 환자들의 SGRT 결과, 바이러스 양 및 CD4 양성 T세포 수가 분석에 이용되었다.

결과: 단백분해효소 억제제 관련 내성 돌연변이는 항레트로바이러스요법 경험이 없는 그룹과 경험이 있는 그룹 모두에서 가장 흔하게 관찰되었으며(각각 52.8% 및 50.0%) 비뉴클레오시드 역전사 효소억제제 관련 및 통합효소 억제제 관련 내성 돌연변이가 그 뒤를 이었다. Major drug resistance mutation은 비뉴클레오시드 역전사 효소억제제 관련 내성 돌연변이만 관찰되었다. 본 연구에서 전파된 약제 내성(transmitted drug resistance) 유병률은 55.6%로 이전에 보고된 결과보다 현저히 높게 관찰되었다. 항레트로바이러스요법 경험이 없는 환자의 바이러스 양 및 CD4 수치 변화는 약제 내성 돌연변이의 정도(major, minor, 없음)와 상관 관계가 없는 것으로 나타났다. 치료력이 없었던 모든 환자는 통합효소 억제제 기반 요법으로 치료를 받았으며 대부분은 매우 좋은 임상 반응을 보였다.

결론: 한국인 환자에서 HIV-1 약제 내성 돌연변이의 분포는 단백

분해효소 억제제 관련 내성 돌연변이와 minor drug resistance mutation에 치우쳐 관찰되었으며, 약제 내성 돌연변이의 중증도는 임상 반응과 관련이 없었다. 본 연구는 최근 한국인 HIV-1 감염 환자의 약물 내성 돌연변이 프로파일에 대한 귀중한 정보를 제공하고 약물 내성 유전형 분석의 중요성을 강조하는 바이다.

Conflicts of Interest

None declared.

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