HIV Antiretroviral Resistance Mutations Among Antiretroviral Treatment-Naive and -Experienced Patients in South Korea

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Abstract

The purpose of this study was to assess the prevalence and characteristics of HIV drug resistance mutations among antiretroviral therapy (ART)-naive and ART-experienced patients in South Korea. A total of 50 ART-naive and 34 ART-experienced Korean HIV-1-infected patients who visited an urban hospital from February 2007 to March 2011 were included. Most patients (86.9%) were infected with clade B HIV-1. Six (12%) ART-naive and 22 (64.7%) ART-experienced patients had HIV strains with resistance mutations. Among ART-naive patients, V179D was the most common mutation, being found in five ART-naive patients. Among ART-experienced patients, M184V was the most common mutation. Eight of 34 ART-experienced patients had thymidine analogue mutations (TAMs). The prevalence of drug-resistant HIV-1 in ART-naive patients was higher than in previous reports, and 50% of patients with virologic failure harbored strains with multiple resistance mutations. HIV drug resistance testing should be recommended to guide therapy of ART-naive patients in South Korea.

ALTHOUGH SOUTH KOREA HAS a relatively low HIV prevalence of less than 0.03%, HIV / AIDS poses a threat to the public health. The introduction of highly active antiretroviral therapy (HAART) for the treatment of HIV-1 has markedly changed the course of the disease. However, many HIV-1 drug-resistant mutations have been reported, and the efficacy of HAART can be limited.¹ Monitoring the prevalence of resistance mutations in populations is important to provide guidelines for antiretroviral therapy (ART) resistance testing. The aim of this study was to determine the prevalence and characteristics of HIV-1 drug resistance mutations in ART-naive and ART-experienced patients in South Korea.

A total of 84 HIV-1-infected individuals who visited a tertiary care hospital in Seoul and underwent genotypic testing for HIV resistance mutations between February 2007 and March 2011 were enrolled. HIV RNA polymerase sequences were obtained using the ViroSeg HIV genotyping system 2.0. The protease (PR) and reverse transcriptase (RT) components of the *pol* sequences were assembled, aligned to the HXB2 consensus, and manually edited using Bioedit v.7.1.3. HIV

TABLE 1. BASELINE CHARACTERISTICS OF PARTICIPANTS

Variables	Naive [n=50(%)]	Experienced [n=34(%)]
Sex		
Male	47 (94.00)	29 (85.29)
Female	3 (6.00)	5 (14.70)
Age	43.94 ± 12.51	42.32 ± 10.12
CD4 counts at enrollment (counts/μl)		
<200	13 (26.00)	19 (46.30)
200–350	21 (42.00)	11 (26.80)
>350	16 (32.00)	10 (24.40)
HIV RNA at enrollment (copies/ml)	3.71 × 10 ⁶	1.09 × 10 ⁵
Subtype		
B	45 (90.00)	28 (82.35)
AE	2 (4.00)	2 (5.88)
AG	2 (4.00)	2 (5.88)
C	1 (2.00)	0 (0.00)

Data are frequencies and percentages in parentheses, unless otherwise indicated.

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subtypes were identified using the REGA subtyping tool v.2.0 (<http://dbpartners.stanford.edu/RegaSubtyping/>, accessed October 1, 2012). Antiretroviral resistance mutations were analyzed using the Stanford HIV Drug Resistance Database version 4.2.4 (<http://sierra2.stanford.edu/sierra/servlet/JSierra?action=sequenceInput/>, accessed October 1, 2012). The *pol* gene sequences of eligible patients were submitted to GenBank as accession numbers KC 120826 through KC 120908. PhyML version 2.4.4 (<http://atgc.lirmm.fr/phyml/>, accessed October 1, 2012) was used to estimate the maximum likelihood phylogenies of *pol* sequences.

A total of 50 patients were ART-naïve and 34 were ART-experienced. The majority of the patients were male (76/84, 90.4%) (Table 1). Seventy-three of 84 (86.9%) patients harbored subtype B viruses. Among the remaining subjects, four

(4.7%) carried subtype AE virus, four (4.7%) were subtype AG, and one (1.2%) was subtype C. Phylogenetic analysis of the *pol* genes revealed distinct clustering according to the subtypes.

Six of 50 (12%) ART-naïve participants had resistance mutations for any one class of antiretroviral drugs. The patterns of drug resistance mutations among ART-naïve patients differed from those described in previous studies conducted in South Korea. In previous studies of ART-naïve patients, protease inhibitor (PI)-related mutations had not been found.² In our study, one patient (2%) harbored two PI-related mutations, encoding L10I and V71T. In addition, V179D was the most common amino acid change, which was detected in five (10%) ART-naïve patients. In previous reports, V179D was more common in Korean patients than Chinese patients

TABLE 2. CURRENT AND PAST ANTIRETROVIRAL TREATMENT REGIMENS AND ANTIRETROVIRAL RESISTANCE-ASSOCIATED MUTATIONS IN EACH PATIENT

Patient number	Age (years)	Sex	HAART regimen			Antiretroviral resistance-associated mutations
			PI	NRTI	NNRTI	
1	42	M	NFV	AZT, 3TC	(-)	L10I, V179D
2	48	M	LPV	3TC, d4T	(-)	None
3	33	M	ATV	3TC, ddI	(-)	None
4	44	M	IDV	AST, 3TC	(-)	V82A, L10I, M41L, M184V
5	46	M	ATV	ddI, 3TC	(-)	A71AV
6	61	M	LPV	AZT, 3TC	(-)	M46I, L90M, L10I, A71V, T74P, M41L, V75IMV, L210LW, T215FY, K103Q
7	22	F	LPV	AZT, 3TC	(-)	L10I
8	72	F	NFV, ATV, RTV/r	3TC, ddI, d4T	EFV	M184V, A98G, K103N, P225H, M230L
9	38	M	LPV	AZT, 3TC	EFV	L10I, M184MV
10	35	M	LPV	3TC, ddI, AZT	(-)	L33F, M184V
11	63	M	LPV	3TC, ddI	EFV	L74V, M184V
12	41	M	LPV	3TC, AZT	(-)	None
13	32	M	Medication unidentifiable			None
14	40	M	LPV	3TC, ddI	(-)	K101Q, K103N
15	36	M	LPV	AZT, 3TC	(-)	V106IV, Y188L, P225HP
16	56	M	ATV, LPV	ABV, d4T	(-)	M46IL, G48V, I50V, I54A, V82S, L10I, A71V, M41L, L74V, M184V, L210W, T215Y, K101P, K103S
17	35	M	IDV	AZT, 3TC, ddI, d4T	EFV	L10I, M41L, T215D, K103N, V179D
18	31	F	Medication unidentifiable			M46IM, I54IV, L76LV, V82AV, L10FL, A71AV, G73GS, L89MV, L74LV, M184V, T215AT
19	50	M	IDV	3TC, ddI	EFV	None
20	41	M	LPV	3TC, AZT, d4T	(-)	L10I, T69S
21	48	M	ATV, IDV	AZT, 3TC	(-)	None
22	40	F	IDV, ATV	3TC, AZT	EFV	None
23	36	M	ATV, RTV/r	AZT, 3TC	EFV	K103KN, V108IV
24	53	M	IDV, ATV	3TC, ddI	(-)	L10I
25	37	M	(-)	3TC, ddI	EFV	A71V, K103KN
26	41	M	ATV, RTV/r	3TC, d4T, ddI	EFV	M46IM, L10FIL, M184MV, V179D
27	37	M	LPV	AZT, 3TC	(-)	None
28	37	M	LPV	3TC, ddI	EFV	L10IL, A71AT, M184V, T215Y, K219N, L100I, K103N
29	45	M	LPV	3TC, ddI	EFV	None
30	35	M	(-)	AZT, 3TC	EFV	A62AGV
31	49	M	LPV	AZT, 3TC	EFV	A71V
32	46	M	LPV	AZT, 3TC	EFV	D67N, K70R, M184V, K103N, P225H
33	35	F	NFV, ATV, RTV/r	3TC, AZT, d4T, ddI	(-)	V82A, M41LM, L74LV, M184V, V179D
34	34	M	LPV	3TC, ddI	(-)	K103N

PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NFV, nelfinavir; LPV, lopinavir; ATV, atazanavir; IDV, indinavir; RTV/r, ritonavir; 3TC, lamivudine; d4T, stavudine; ddI, didanosine; AZT, zidovudine; EFV, efavirenz; ABV, abacavir.

TABLE 3. PREVALENCE OF ANTIRETROVIRAL DRUG RESISTANCE MUTATIONS

Mutation	Experienced (n=50)	Naïve (n=34)	Mutation	Experienced (n=50)	Naïve (n=34)	Mutation	Experienced (n=50)	Naïve (n=34)
PI N(%)			NRTI N(%)			NNRTI N(%)		
Minor			M41L	0	5 (14.7)	A98G	0	1 (2.9)
L10I	1 (2)	5 (14.7)	M184V	0	11 (32.4)	K103N	0	9 (26.5)
A71V	0	3 (8.8)	V75IMV	0	1 (2.9)	P225H	0	3 (8.8)
T74P	0	1 (2.9)	T215FY	0	1 (2.9)	M230L	0	1 (2.9)
L33F	0	1 (2.9)	L74V	0	2 (5.8)	K101Q	0	1 (2.9)
L10FL	0	1 (2.9)	L210W	0	2 (5.8)	V106IV	0	1 (2.9)
G73GS	0	1 (2.9)	T215Y	0	2 (5.8)	Y188L	0	1 (2.9)
L89MV	0	1 (2.9)	T215D	0	1 (2.9)	K101P	0	1 (2.9)
A71T	1 (2)	1 (2.9)	L74LV	0	2 (5.8)	K103S	0	1 (2.9)
			T215AT	0	1 (2.9)	V179D	5 (10)	2 (5.8)
Major			K219N	0	1 (2.9)	L100I	0	1 (2.9)
V82A	0	3 (8.8)	D67N	0	1 (2.9)	Y188L	0	1 (2.9)
M46I	0	2 (5.8)	K70R	0	1 (2.9)			
L90M	0	1 (2.9)						
G48V	0	1 (2.9)						
I50V	0	1 (2.9)						
I54A	0	1 (2.9)						
V82S	0	1 (2.9)						
M46IM	0	1 (2.9)						
I54IV	0	1 (2.9)						
L76LV	0	1 (2.9)						

Data are frequencies and percentages in parentheses, unless otherwise indicated.

(13.6% vs. 0%).³ No nucleoside reverse transcriptase inhibitor (NRTI) mutations were found in ART-naïve patients.

The results from ART-experienced patients were also informative. Of 34 ART-experienced patients, 22 (64.7%) harbored at least one resistance mutation. This rate is similar to previous results of 42–71%.⁴ In South Korea, PI-based regimens were used more commonly as initial antiretroviral therapy than nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens.⁴ In this study, most patients (30/34, 88.2%) were treated with PI-based regimens, and only two (5.8%) were treated with NNRTI-based regimens (Table 2). Details of drug resistance profiles among patients with virologic failure may help clinicians choose secondary drugs for salvage therapy. V82A was the most frequent major PI mutation, being detected in three (8.8%) ART-experienced patients, and was associated with lopinavir resistance. Thirteen (38.2%) patients had mutations that conferred high-level resistance to NRTIs.⁵ The most commonly detected NRTI resistance mutation was M184V, which conferred resistance to lamivudine (3TC) or emtricitabine (FTC), but could delay or prevent the emergence of thymidine analogue mutations (TAMs).⁶ Eleven (32.4%) patients had M184V. K103N was the most frequently found resistance mutation associated with NNRTIs (consistent with a previous study⁷). K103N was found in nine (26.5%) patients, which was closely related to efavirenz resistance and could lead to resistance to all first-generation NNRTIs (Table 3).

Overall, we report here the recent resistance rate and patterns of both ART-naïve and ART-experienced patients in South Korea. The prevalence of drug-resistant HIV-1 in ART-naïve patients was higher than identified previously, and many Korean HIV-1-infected patients with virologic failure

harbored strains with multiple resistance mutations. HIV drug resistance testing should be recommended to guide therapy of ART-naïve patients in South Korea.

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Author Disclosure Statement

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