Infect Chemother. 2026 Mar;58(1):105-111
https://doi.org/10.3947/ic.2025.0120
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Brief Communication

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Characteristics of Drug Resistance Mutations in a Korean HIV/AIDS Cohort, and Risk Factors for Resistance Acquisition in ART-Experienced Patients

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ABSTRACT

We aimed to characterize human immunodeficiency virus (HIV) drug-resistance mutations among patients in Korea HIV/acquired immunodeficiency syndrome (AIDS) Cohort. Among 1,579 surveyed between December 2006 and December 2020, 148 had resistance mutations (64 ART-naïve and 84 ART-experienced). The most common mutations in ART-naïve patients were related to non-nucleoside reverse transcriptase inhibitors (V179F/D/E/L; 50.0%), whereas those in ART-experienced were M184V/I (73.8%), conferring resistance to nucleotide reverse

Received: Sep 30, 2025
Accepted: Jan 30, 2026
Published online: Mar 12, 2026

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transcriptase inhibitors. Multivariate logistic regression identified poor compliance (adjusted odds ratio [aOR], 18.780; 95% confidence interval [CI], 1.883–187.300; *P*=0.012) and viral load ≥1-100,000 copies/mL at ART initiation (aOR, 3.117; 95% CI, 1.160–8.374; *P*=0.024) as being associated with resistance mutations.

Keywords: HIV/AIDS; Drug resistance; Korea

Although effective antiretroviral therapy (ART) has reduced human immunodeficiency virus (HIV)-related mortality and morbidity [1], drug resistance mutations remain an important issue. These mutations are influenced by viral burden, prior exposure to ART, and patient compliance with treatment [2, 3]. Korea established the Korea HIV/ acquired immunodeficiency syndrome (AIDS) cohort to monitor more than 1,500 patients with HIV, accounting for about 10% of all HIV/AIDS cases in Korea [4]. Here, we aimed to characterize drug resistance mutations in ART-naïve and ART-experienced patients in the Korea HIV/AIDS cohort. In addition, we tried to identify factors associated with resistance mutations in ART-experienced patients by comparison with an extracted control group without resistance mutations.

From December 2006 to December 2020, 1,579 HIV patients were monitored in the Korea HIV/AIDS Cohort, which includes HIV patients aged ≥18 years from 21 tertiary hospitals (listed in the Acknowledgements). Among these patients, 646 had undergone HIV drug resistance mutation tests, and 217 had positive results. After excluding patients carrying resistance mutations not included in World Health Organization (WHO) surveillance (n=47), patients who were well suppressed after ART initiation (n=11), and those with missing data (n=11), 148 patients with drug resistance mutations were enrolled in the study (ART-naïve, n=64; ART-experienced, n=84).

During early cohort period, the HIV drug resistance mutation test was performed only by the Korean Centers for Disease Control and Prevention; therefore, a limited number of patients received the test (*e.g.*, those who did not achieve viral suppression after 12 to 24 weeks of ART). This meant that many ART-experienced patients with viral suppression had not been tested. In order to select a control group, we tried to find well-suppressed (presumably without drug-resistant mutations) patients as matched control group. Therefore, we used the following operational definition; experience of ART (>6 months), good suppression of viral load throughout the observation period (HIV RNA <50 copies/mL within 24 weeks of ART initiation) and maintenance of HIV RNA <500 copies/mL throughout the observation period.

They were balanced by propensity score matching using a greedy matching algorithm. The propensity score was calculated via logistic regression, with age, sex, and ART duration as matching variables. Nearest-neighbor matching was performed with a 0.2 caliper on the logit scale. The observation period for the ART-experienced group with resistance mutations (ART-experienced resistance group) began at the time of ART initiation and ended on the date of a positive resistance test, whereas that for the control group began at the time from ART initiation and ended at the time when the mean ART duration of the resistance group had elapsed.

AIDS-defining illnesses followed the revised surveillance case definition [5]. Poor adherence was defined as missing medication more than once every 2 weeks. Resistance mutations included in the WHO surveillance were analyzed [6]. Multiple mutations in a single patient were counted individually. Continuous variables were compared using the Mann–Whitney *U*-test, and categorical variables were compared using Pearson's chi-square or Fisher's exact test. Variables with *P*<0.200 in univariate analyses, or those of clinical importance (except for multi-collinear variables), were included in multivariate logistic regression, with 0.1 as the cut-off value for elimination. *P*<0.050 was considered statistically significant. All statistical analyses were performed using SPSS (version 27.0, IBM, Armonk, NY, USA).

Of the 64 ART-naïve patients carrying drug resistance mutations, 62.5% were aged 20–39 years, and 98.4% (63/64) were male. At the time of ART initiation, 10.9% (7/64) had AIDS-defining illnesses, the median CD4 cell count was 274 cells/mm^3, and 18.8% (12/64) had viral loads ≥100,000 copies/mL (**Table 1**). The most common drug resistance mutations in ART-naïve patients were related to non-nucleoside reverse transcriptase inhibitors (NNRTIs), with V179F/D/E/L (50.0%, 32/64) being the most common, followed by K103H/N/S/T (12.5%, 8/64),

Table 1. Demographic characteristics of the enrolled patients

Variable	ART-naïve group with drug resistance mutations[a] (N=64), n (%)	ART-experienced resistance group[a] (N=84), n (%)	Control group[a] (N=84), n (%)
Age group			
<20 years	4 (6.3)	0	0
20–39 years	40 (62.5)	43 (51.2)	47 (56.0)
40–59 years	18 (28.1)	35 (41.7)	31 (36.9)
≥60 years	2 (3.1)	6 (7.1)	6 (7.1)
Age at detection of resistance mutation, median (IQR)	NA	39 (33–48)	37 (30–46.3)
Male sex	63 (98.4)	82 (97.6)	83 (98.8)
Sexual orientation			
Homosexual	31 (48.4)	31 (36.9)	34 (40.5)
Heterosexual	17 (26.6)	29 (34.5)	29 (34.5)
Bisexual	15 (23.4)	22 (26.2)	18 (21.4)
Unknown	1 (1.6)	2 (2.4)	3 (3.6)
Mode of transmission			
Sexual contact	63 (98.4)	82 (97.6)	81 (96.4)
Unknown	1 (1.6)	2 (2.4)	3 (3.6)
Comorbidities at ART initiation			
Hypertension	3 (4.7)	3 (3.6)	2 (2.4)
Dyslipidemia	0	2 (2.4)	1 (1.2)
Hepatitis B virus infection	1 (1.6)	1 (1.2)	2 (2.4)
Hepatitis C virus infection	0	1 (1.2)	0
Diabetes mellitus	0	0	1 (1.2)
AIDS-defining illness at ART initiation	7 (10.9)	24 (28.6)	18 (21.4)
Laboratory findings at ART initiation			
CD4 cell count, cells/mm^3, median (IQR)	274 (144–427)	140.5 (78.3–242.3)	251.5 (95.8–343.3)
HIV viral load			
<100,000 copies/mL	27 (42.2)	31 (36.9)	62 (73.8)
≥100,000 copies/mL	12 (18.8)	26 (31.0)	18 (21.4)
Unavailable	25 (39.1)	27 (32.1)	4 (4.8)

[a]The results are presented as the median value. The value in parentheses is the percentage, and the range is the interquartile range.
Values are presented as n (%) or median (interquartile range).
ART, antiretroviral therapy; IQR, interquartile range; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

K103R (12.5%, 8/64), and V106I/M/A (7.8%, 5/64). In the context of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors, the most common mutations were T69D/G/Del/Ins (6.3%, 4/64) and M46I/L/V (4.7%, 3/64), respectively (**Table 2**).

Among the 84 patients in the ART-experienced resistance group, the median age was 39 years (interquartile range 33–48), and 97.6% (82/84) were male (**Table 1**). At the time of ART initiation, 28.6% (24/84) had AIDS-defining illnesses, commonly *Pneumocystis jirovecii* pneumonia (13.1%, 11/84) and tuberculosis infection (9.5%, 8/84). At ART initiation, the median CD4 cell count was 140.5 cells/mm^3, and 31.0% (26/84) had a viral load ≥100,000 copies/mL (**Table 3**). In ART-experienced patients, the most common drug resistance mutation was M184V/I (73.8%, 63/84), which is related to NRTIs. The second most common was K103H/N/S/T (36.9%, 31/84), linked to NNRTIs. Other NRTI mutations included T215A/C/D/E/F/I/L/N/S/V/Y (20.2%, 17/84), L74V/I (16.7%, 14/84), and M41L (15.5%, 13/84). Common NNRTI mutations included V179F/D/E/L (15.5%, 13/84) and L100I/V (11.9%, 10/84). PI-related mutations included M46I/L/V and V82A/T/F/S/C/M/L (both 15.5%, 13/84) (**Table 2**).

Table 3 compares variables between the ART-experienced resistance group and the control group. At ART initiation, the CD4 cell count in the ART-experienced resistance group was significantly lower than that in the control group (140.5 cells/mm^3 *vs.* 251.5 cells /mm^3, respectively; *P*=0.004). The median HIV viral load in the ART-experienced resistance group at ART initiation was higher than that in the control group (72,600 copies/mL *vs.* 23,900 copies/mL, respectively; *P*=0.012). The proportion of patients with poor drug adherence was also significantly higher in the ART-experienced resistance group (18/84 [21.4%] *vs.* 4/84 [4.8%] in the control group; *P*=0.001). The two groups received different ART regimens. Regimens comprising 2NRTIs + NNRTI or

Table 2. Frequency of drug resistance mutations in ART-naïve and ART-experienced HIV patients

Variable[a]	ART-naïve patients N=64, n (%)	ART-experienced patients N=84, n (%)
NRTI resistance mutations		
T69D/G/Del/Ins	4 (6.3)	3 (3.6)
T215A/C/D/E/F/I/L/N/S/V/Y	3 (4.7)	17 (20.2)
M184V/I	2 (3.1)	63 (73.8)
M41L	2 (3.1)	13 (15.5)
L74V/I	1 (1.6)	14 (16.7)
K70E/G/N/Q/R/S/T	-	8 (9.5)
D67E/G/H/N/S/T/Del	-	5 (5.9)
L210W	-	5 (5.9)
K219Q/E/N/R/W	-	4 (4.8)
K65E/N/R	-	4 (4.8)
A62V	-	3 (3.6)
V75A/I/M/S/T	-	2 (2.4)
E44A/D	-	1 (1.2)
NNRTI resistance mutations		
V179F/D/E/L	32 (50.0)	13 (15.5)
K103H/N/S/T	8 (12.5)	31 (36.9)
K103R	8 (12.5)	3 (3.6)
V106I/M/A	5 (7.8)	4 (4.8)
E138G/K/Q/R	3 (4.7)	2 (2.4)
G190A/C/E/Q/S/T/V	2 (3.1)	8 (9.5)
E138A	2 (3.1)	-
V108I	1 (1.6)	6 (7.1)
Y181C/F/G/I/S/V	1 (1.6)	4 (4.8)
K238N/T	1 (1.6)	3 (3.6)
L100I/V	-	10 (11.9)
K101E/H/P	-	5 (5.9)
Y188C/F/H/L	-	5 (5.9)
H221Y	-	4 (4.8)
P225H	-	4 (4.8)
A98G	-	1 (1.2)
M230I/L	-	1 (1.2)
V179D/E	-	1 (1.2)
Major PI resistance mutations		
M46I/L/V	3 (4.7)	13 (15.5)
I54V/L/M/A/T/S	1 (1.6)	10 (11.9)
I84V/A/C	1 (1.6)	4 (4.8)
Q58E	1 (1.6)	1 (1.2)
L33F	1 (1.6)	-
V82A/T/F/S/C/M/L	-	13 (15.5)
I50V/L	-	7 (8.3)
L90M	-	3 (3.6)
V32I	-	3 (3.6)
F53L/Y	-	2 (2.4)
I47V/A	-	2 (2.4)
L10F	-	1 (1.2)
L76V	-	1 (1.2)

[a]Multiple mutations in a single patient were counted individually.
ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

2NRTIs + PI were more common in the ART-experienced resistance group (24/84 and 40/48, respectively *vs.* 12/84 and 14/84, respectively). The 2 NRTIs + integrase strand transfer inhibitor (INSTI) regimen was more common in the control group (34/84 *vs.* 17/84; **Table 3**). Multivariate analysis identified an HIV viral load ≥1100,000 copies/mL at ART initiation (adjusted odds ratio [aOR], 3.117; 95% confidence interval [CI], 1.160–8.374; *P*=0.024) and poor adherence (aOR 18.780; 95% CI, 1.883–187.300; *P*=0.012) as being associated with resistance mutations in ART-experienced patients. INSTI-containing regimens were inversely associated with resistance mutations compared with NNRTI-containing regimens (aOR, 0.189; 95% CI, 0.057–0.623; *P*=0.006).

Among the 1,579 HIV patients enrolled in the Korea HIV/AIDS Cohort and monitored between December 2006 and December 2020, 646 underwent HIV drug resistance mutation tests and 148 had WHO monitored-HIV drug resistance-positive results (9.27% positivity; repeat tests (including the first positive test) were counted just once per patient). INSTI resistance mutation data were not collected from the Korea HIV/AIDS Cohort during the study period; however, another conducted between 2014 and 2015 in Korea showed low INSTI resistance, suggesting that the clinical impact of this limitation might be minimal [7].

In the ART-naïve patients included in this study, common mutations were V179F/D/E/L (50%, 32/64) and K103H/N/S/T (12.5%, 8/64). A previous study conducted in Korea between 2006 and 2012 also identified K103N as the most common mutation in ART-naïve patients, accounting for 21.9% (7/32) [8]. A more recent study conducted from 2012 to 2020 reported that V179D/E and K103N were the most common mutations, each found in 29.6% (8/27) of cases [9]. In neighboring China, V179A/D (38.1%, 72/189) was the most prevalent mutation in 2018, showing an increasing trend compared with 2015 [10]. Considering the introduction of long-acting injectable ART including rilpivirine into Korea, NNRTI resistance monitoring, including rilpivirine resistance-associated mutations such as K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C and M230I/L, might be an important source of monitoring data for the Korea HIV/AIDS Cohort in the future.

Among ART-experienced patients, M184V/I (73.8%, 63/84) was the most common mutation, followed by K103H/N/S/T (36.9%, 31/84). A study conducted in Korea from 2007 to 2011 also identified M184V (50.0%, 11/22) and K103N (40.9%, 9/22) as common mutations in ART-experienced patients [11]. The WHO report on countries in Africa, the Americas, Southeast Asia, and the Western Pacific region, aligns with our findings, identifying

https://doi.org/10.3947/ic.2025.0120

Table 3. Comparison of variables between the ART-experienced resistance group and the control group

Variable	ART-experienced resistance group, N=84	Control group, N=84	*P*-value
Clinical features at ART initiation			
AIDS-defining illness	24 (28.6)	18 (21.4)	0.285
Pneumocystis jirovecii pneumonia	11 (13.1)	12 (14.3)	0.822
Tuberculosis	8 (9.5)	3 (3.6)	0.119
Cytomegalovirus disease	4 (4.8)	2 (2.4)	0.682
Laboratory findings at ART initiation			
CD4 cell count, cells/mm^3, median (IQR)	140.5 (78.3-242.3)	251.5 (95.8-343.3)	0.004
HIV viral load, copies/mL, median (IQR)	72,600 (2,400–240,302)	23,900 (1,478.5-82,150.75)	0.012
<100,000 copies/mL	31 (36.9)	62 (73.8)	<0.001
≥100,000 copies/mL	26 (31.0)	18 (21.4)	0.160
Unavailable	27 (32.1)	4 (4.8)	<0.001
ART regimen at resistance mutation detection			
Poor compliance	18 (21.4)	4 (4.8)	0.001
2 NRTIs + NNRTI	24 (28.6)	12 (14.3)	0.024
2 NRTIs + PI	40 (47.6)	14 (16.7)	<0.001
2 NRTIs + INSTI	17 (20.2)	34 (40.5)	0.004
Others	2 (2.4)	2 (2.4)	>0.999
Unknown	1 (1.2)	22 (26.2)	<0.001
Clinical features at resistance mutation detection			
AIDS-defining illness	4 (4.8)	0	0.121
Pneumocystis jirovecii pneumonia	1 (1.2)	0	>0.999
Tuberculosis	2 (2.4)	0	0.497
Laboratory findings at resistance mutation detection			
CD4 cell count, cells/mm^3, median (IQR)	266.5 (105.8–369.5)	575 (448.5-719.5)	<0.001
HIV viral load, copies/mL, median (IQR)	13,100 (2,774.25–64,475)	19 (0–22)	<0.001
<100,000 copies/mL	66 (78.6)	57 (67.9)	0.117
≥100,000 copies/mL	16 (19.0)	NA	NA
Unavailable	2 (2.4)	27 (32.1)	<0.001

Values are presented as n (%) or median (interquartile range).
Laboratory findings were evaluated among available data.
ART, antiretroviral therapy; IQR, interquartile range; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; AIDS, acquired immunodeficiency syndrome.

M184V/I and K103H/N/S/T as the most common mutations in patients under ART with unsuppressed viral loads [6].

Factors associated with resistance mutations in ART-experienced patients include a high viral load at ART initiation, and poor adherence (defined as less than 93%). An unsuppressed viral load during ART is a well-established risk factor for acquiring resistance mutations [12,13]. Several studies report that a higher viral load is related to virologic failure due to resistance mutations [14,15]. This might be due to prolonged viremia under ART [16], which is linked to the development of the resistance mutations [12,13]. INSTI-containing regimens better protect against resistance mutations than NNRTI-containing regimens, which is a finding consistent with a previous report [17]. This can be explained by the higher resistance barrier of INSTIs, along with better tolerability and fewer treatment discontinuations compared with NNRTIs [18,19].

This analysis provides important information about the distribution of HIV drug resistance mutations among this Cohort (9.27%) [20]. However, this study has some limitations. We selected the control group using operational definitions, not based on the test results. Only 10% of the Korean HIV patients were included in this cohort and the ART regimens were not analyzed between the two groups. INSTI-related drug-resistant mutations were not included in this study since they were not monitored during the study period.

ACKNOWLEDGEMENTS

Korea HIV/AIDS Cohort Study.

Sites: Ajou University Hospital, Asan Medical Center, Chungbuk National University Hospital, Ewha Womans University Mokdong Hospital, Gacheon University Gil

Medical Center, Hallym University Kangdong Sacred Heart Hospital, Hallym University Kangnam Sacred Heart Hospital, Hallym University Sacred Heart Hospital, Hanyang University Seoul Hospital, Inha University Hospital, Kangbuk Samsung Hospital, Korea University Anam Hospital, Korea University Ansan Hospital, Korea University Guro Hospital, Kyungpook National University Hospital, Soonchunhyang University Seoul Hospital, The Catholic University of Korea, Seoul ST. Mary's Hospital, The Catholic University of Korea, ST. Vincent's Hospital, Yeungnam University Medical Center, Yonsei University Severance Hopital, Yonsei University Wonju Severance Christian Hospital.

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Funding

This study was supported by the National Institute of Infectious Diseases, National Institute of Health, Korea Disease Control and Prevention Agency (#2025-E1903-00).

Conflict of Interest

JYC, HJC, JYS are editorial board of *Infect Chemother*; however, they did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Ethics statement

This study was approved by the institutional review board of Chungbuk National University Hospital (No. 2022-05-006-006). All subjects provided written informed consent to participate. Personal identifiers were removed before data processing.

Author Contributions

Conceptualization: JHK, JYC, JHK, YKK, SIK, SWK, JH, YK, HJC, JYS, HWJ. Data curation: ML, SMK, JHK, BP, OJ, MJG, SR, HSK, HWJ. Formal analysis: ML, SMK, BP. Funding acquisition: JYC. Investigation: ML, JHK. Methodology: BP, OJ, MJG, SR, HSK. Project administration: JYC. Resources: SMK, JHK, JYC, JHK, YKK, SIK, SWK, JH, YK, HJC, JYS, HSK. Software: BP. Supervision: HWJ. Validation: HWJ. Visualization: ML. Writing - original draft: ML, HWJ. Writing - review & editing: HWJ.

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