Case Report
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A Case Report of Lenacapavir Use in a Patient with Multidrug-Resistant HIV: The First Experience in Asia

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Lenacapavir is a novel, first-in-class, capsid inhibitor, which has been approved as an adjunctive therapy for multidrug-resistant human immunodeficiency virus (HIV)-1 virus in combination with optimized background regimen (OBR). Lenacapavir has demonstrated a significant decrease in viral load and high rate of virologic suppression in patients with multidrug-resistant HIV-1 infection with limited treatment options. Here, we report a case of 43-year-old male who was diagnosed with HIV-1 infection in 2005 but failed to achieve viral suppression due to multiclass resistance. After lenacapavir use with OBR, viral suppression was achieved, and recovery of $CD4^+$ T-cell count was observed for 8 months. This case report shows the first lenacapavir experience in Asia in a heavily treatment-experienced HIV patient with limited treatment options.

Key Words: HIV, acquired immunodeficiency syndrome, drug resistance, anti-retroviral agents

INTRODUCTION

Human immunodeficiency virus (HIV) drug resistance is a global concern. In antiretroviral therapy (ART)-naïve people living with HIV (PLWH), transmitted drug resistance rates have increased from 3.3%–12.1% (2009–2013) to 4.2%–14.2% (2014–2019).[1] Drug resistance in ART-experienced PLWH occurs much more frequently than in treatment-naïve PLWH.[2] Twenty-one percent of ART-experienced PLWH had resistance mutations for non-nucleoside reverse transcriptase inhibitors (NNRTIs) compared to 7.8% of treatment-naïve patients.

A study conducted between 1999 and 2012 found that 4.8% of treatment-naïve patients in Korea had resistance mutations,[3] and the prevalence of resistance mutations increased to 12.9% in 2018–2020.[4] For treatment-experienced patients, the Korea Centers for Disease Control reported that 48.3% had at least one drug class resistance mutation, and 9.8% had triple-class resistance.[5] HIV drug resistance mutation is an important determinant of treatment failure, necessitating the development of new treatment options.

Lenacapavir is a novel, first-in-class, multistage, selective inhibitor of HIV capsid protein, which was approved by the European Commission in August 2022 and by the United States Food and Drug Administration in December 2022 as a component of therapy for multidrug-resistant HIV-1 virus in combination with optimized background regimen (OBR).[6] In the CAPELLA trial, a phase 2/3 clinical trial, lenacapavir resulted in a significant decrease in viral load and high rate of virologic suppression in participants with multidrug-resistant HIV-1 infection with limited treatment options.[7]

In this case report, we present our experience with the use of lenacapavir in a heavily treatment-experienced PLWH with limited treatment options. Although lenacapavir is not yet available in the Korean domestic market, we expect that our experience will contribute to the treatment of multidrug-resistant HIV.

CASE REPORT

A 43-year-old male was diagnosed with HIV-1 infection in 2005 and was treated with various combinations antiretroviral ther-

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apy (cART) from 2005 to 2016 at another hospital, but his virus was not suppressed, and he presented to our clinic in November 2017. At the time of his visit, the patient had oral candidiasis. $CD4^+$ T-cell count was 256/μL and viral load was 79200 copies/mL. HIV-1 genotype demonstrated high-level resistance to nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs), as well as resistance to almost all drugs currently available in the country (Table 1).

The patient then tried several combinations of dolutegravir, tenofovir alafenamide fumarate, emtricitabine, etravirine, darunavir/cobicistat, maraviroc, rilpivirine, atazanavir/cobicistat, and bictegravir, to treat multidrug-resistant HIV virus, but they were not effective (Table 2). Additional genotype resistance test in October 2019 showed more resistance mutation accumulated (Table 1). Later, as there were no treatment options available in the domestic market, the patient was treated with doravirine, islatravir, and fostemsavir through a clinical trial in May 2020, but the virus was not suppressed. In August 2022, the viral concentration was 55800 copies/mL, and the $CD4^+$ T cell count was 27/μL.

Therefore, the use of lenacapavir through a compassionate use program was considered. After informed consent was obtained from the patient, the combination of dolutegravir twice a day, tenofovir disoproxil fumarate, fostemsavir, and lenacapavir was initiated in September 2022. Oral lenacapavir 600 mg was administered on days 1 and 2, and 300 mg was administered on day 8 as the loading dose. Subsequently, subcutaneous lenacapavir 927 mg was administered on day 15.

Viral load was suppressed to 102 copies/mL after a month on medication, 38.2 copies/mL after 3 months, and <20 copies/mL after 6 months. The patient's $CD4^+$ T-cell count increased to 131/μL (May 2023) (Fig. 1). He had no adverse events other than transient skin rash after 3 months of medication. He has been receiving subcutaneous lenacapavir 927 mg every 6 months with OBR, and self-reported adherence to cART was assessed as 100%.

DISCUSSION

This case demonstrates successful use of lenacapavir in a heav-

Table 1. Results of Genotyping Resistance Test

Drugs	Mutations and drug susceptibility	
	Feb. 2017	Oct. 2019
NRTIs	M41L, M184V, L210W, T215F	M41L, L74LV, M184V, L210W, T215F
Lamivudine	High-Level Resistance	High-Level Resistance
Abacavir	High-Level Resistance	High-Level Resistance
Zidovudine	High-Level Resistance	High-Level Resistance
Stavudine	High-Level Resistance	High-Level Resistance
Didanosine	High-Level Resistance	High-Level Resistance
Emtricitabine	High-Level Resistance	High-Level Resistance
Tenofovir	Intermediate Resistance	Intermediate Resistance
NNRTIs	K103S	L100I, K103S, E138Q, P225H
Efavirenz	High-Level Resistance	High-Level Resistance
Etravirine	Susceptible	Intermediate Resistance
Nevirapine	High-Level Resistance	High-Level Resistance
Rilpivirine	Susceptible	High-Level Resistance
PIs	V32VI, M46MI, I47IV, I54ILV, V82VA, I84IV	V32I, M46I, I47IV, I50IL, I54ILV, I84V, L90M
Atazanavir	High-Level Resistance	High-Level Resistance
Darunavir	High-Level Resistance	High-Level Resistance
Fosamprenavir	High-Level Resistance	High-Level Resistance
Indinavir	High-Level Resistance	High-Level Resistance
Lopinavir	High-Level Resistance	High-Level Resistance
Saquinavir	High-Level Resistance	High-Level Resistance
Tipranavir	High-Level Resistance	High-Level Resistance
INSTIs	E138K, G140S, Q148H	E138K, G140S, Q148H
Dolutegravir	High-Level Resistance	High-Level Resistance
Elvitegravir	High-Level Resistance	High-Level Resistance
Raltegravir	High-Level Resistance	High-Level Resistance

NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors.

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Table 2. History of Changes of Regimens for Combination Antiretroviral Therapy

Start date	Combination of antiretroviral therapy regimens
Sep. 2022	LEN+DTG BID+TDF/FTC+Fostemsavir
Mar. 2022	DTG BID+TDF/FTC
Nov. 2021	DTG BID+TDF/FTC+DOR/ISL/Fostemsavir
Nov. 2020	DTG BID+TDF/FTC+DRV+r+DOR/ISL/Fostemsavir
May 2020	ATV/c+TAF/FTC+DOR+ISL
Dec. 2019	MVC+BIC/TAF/FTC+DRV/c
Feb. 2019	MVC+ATV/c+ABC/3TC
Nov. 2018	RPV+TDF/FTC+DRV/c
May 2018	DTG BID+TAF/FTC+ETR BID+LPV/r BID+DRV BID
Feb. 2018	DTG BID+TAF/FTC+ETR BID+DRV/c
Jul. 2017	DTG BID+TDF/FTC+ETR BID+DRV/c
Feb. 2017	DTG BID+TDF/FTC+RPV
May. 2016	DTG+TDF/FTC
Jan. 2016	DRV+ LPV/r
Jan. 2013	DRV+r+TDF/FTC
Mar. 2012	LPV/r+TDF/FTC
Feb. 2011	RAL+ZDV/3TC
Oct. 2010	ABC+3TC+EFV
Jun. 2010	ZDV/3TC+EFV
Jun. 2007	ZDV/3TC+LPV/r
Dec. 2006	ZDV+ATV
Oct. 2006	ZDV+3TC+LPV/r
Apr. 2005	ZDV+3TC+EFV

LEN, lenacapavir; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; DOR, doravirine; ISL, islatravir; DRV, darunavir; r, ritonavir boosting; ATV, atazanavir; c, cobicistat; TAF, tenofovir alafenamide fumarate; MVC, maraviroc; BIC, bictegravir; ABC, abacavir; 3TC, lamivudine; RPV, rilpivirine; ETR, etravirine; LPV, lopinavir; RAL, raltegravir; ZDV, zidovudine; ABC, abacavir; EFV, efavirenz; BID, twice a day.

ily treatment-experienced patient with multidrug-resistant HIV-1. This patient was diagnosed with HIV-1 in 2005 but was in virologic failure due to resistance to multiple drug classes. After the initiation of lenacapavir, viral load decreased from 55800 copies/mL to 102 copies/mL (-2.74 $\log_{10}$) in a month. Viral suppression to <50 copies/mL was achieved after 2 months. $CD4^+$ T-cell count also recovered from 18/μL at the start of lenacapavir to 128/μL at week 25.

The CAPELLA trial, a phase 2/3 study of lenacapavir, also showed successful results in patients with multidrug-resistant HIV.[7] The study included patients who were resistant to at least three of the four major drug classes, and 17% of participants had no fully active agents in their OBR. Despite their limited treatment options, 88% of participants achieved a significant reduction in HIV viral load to -2$\log_{10}$ or greater at day 15. At week 26, 81% of cohort 1 and 83% of cohort 2 achieved virologic suppression, with improved $CD4^+$ T-cell counts. This result is compatible with successful treatment outcome in our case.

There was a lack of preexisting resistance mutations in ART-naïve or experienced PLWH, even in PI-experienced people with emergence of PI resistance mutations.[8] In vitro viral breakthrough selections performed with lenacapavir identified several HIV capsid variants, with Q67H and N74D being the most predominantly observed variants.[9] In a study reported in 2020, no capsid variants was observed in participants with prior PI failure, suggesting that neither previous PI failure nor emergence of PI resistance mutations are anticipated to affect lenacapavir activity.

Lenacapavir-associated capsid substitutions were observed

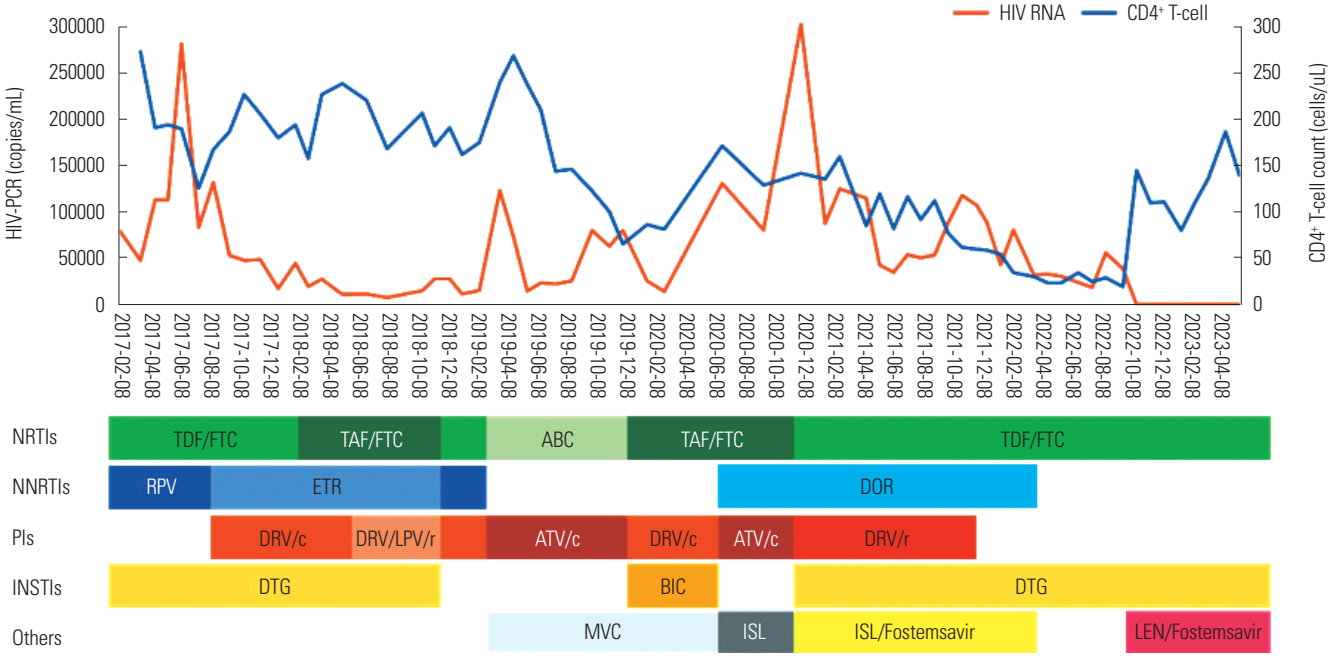

Fig. 1. $CD4^+$ T-cell count and viral load dynamics according to combination antiretroviral therapy. NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors; LEN, lenacapavir; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; DOR, doravirine; ISL, islatravir; DRV, darunavir; r, ritonavir boosting; ATV, atazanavir; c, cobicistat; TAF, tenofovir alafenamide fumarate; MVC, maraviroc; BIC, bictegravir; ABC, abacavir; RPV, rilpivirine; ETR, etravirine; LPV, lopinavir.

in the CAPELLA trial.[7] Capsid mutations were found in nine of 72 participants, with the M66I mutation as the most common capsid mutation found. However, all participants continued on lenacapavir, and four of nine participants had resuppression of HIV. Most HIV-1 variants that are resistant to lenacapavir have reduced replication capacity, which suggests that such variants may have a reduced ability to establish or maintain infection.[10] The nature of these capsid variants may support the continuation of lenacapavir despite the occurrence of lenacapavir-associated capsid substitutions.

In conclusion, successful virologic suppression could be achieved with a lenacapavir-based regimen in this heavily treatment-experienced HIV-infected patient with multiple drug resistance mutations. This case is significant, as it is the first use of lenacapavir in Asia. We expect that lenacapavir will play an important role in the treatment of multidrug-resistant HIV-1.

This study was approved by the institutional review board of Yonsei University Health System Clinical Trial Center (4-2023-0629).

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AUTHOR CONTRIBUTIONS

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