# Naturally Occurring Mutations in HIV-1 Protease Gene Among People Living With HIV

**Zahra Hasanshahi, Ava Hashempour, Javad Moayedi, Zahra Musavi, Behzad Rezaei, Behzad Dehghani, Farzane Ghasabi**

*Shiraz HIV/AIDS Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran*

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**Abstract-** The emergence of resistance to antiretroviral drugs is the main problem in their long-term efficacy and by considering the wide use of protease inhibitors (PIs), monitoring drug resistance mutations is necessary. Therefore, this study aimed to investigate the PIs drug resistance mutations in Iranian patients as well as subtyping using bioinformatics analysis. Fifteen Iranian patients living with Human Immunodeficiency Virus (HIV) (PLWH) were examined. RNA was used to amplify and sequence the HIV protease gene; also, HIV viral load was determined for all samples. The sequencing results were analyzed by several strong bioinformatics tools to determine the drug-resistance mutations and HIV subtypes. Some polymorphisms in the protease gene were recognized; however, there was no significant rate of major or minor drug resistance mutations in our studied patients. Subtyping analysis revealed the new subtype (D) and the previously reported ones, A and CRF-AD 35, in patients. This study confirmed that the resistance mutations and genetic polymorphisms of the protease region are rare in Iranian-infected patients that can be concluded that prescribing protease inhibitor class in HIV-infected patients is promising in controlling HIV in Iran. In addition, conducting periodic studies to determine the new mutations and the rate of drug resistance to PIs in Iranian individuals highlights the importance of WHO guidelines that recommends monitoring of genotypic-resistance testing and investigation of mutations in HIV-related genes.

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**Keywords:** Human immunodeficiency viruses (HIV); Protease; Drug resistance

## Introduction

Acquired immune deficiency syndrome (HIV/AIDS) is a very complex and complicated disease that often requires intensive care support; however, the life expectancy of HIV-infected individuals has improved with the expansion of antiretroviral therapy (ART) (1). Retroviruses like HIV can respond effectively to selective pressures such as drug treatment by several mutations which occur rapidly since the conversion from the RNA genome to DNA is error-prone (2).

The availability and accessibility of ART have profoundly reduced the mortality and morbidity of HIV-related infections; however, the treatments cannot eradicate the virus (3). While about 25 drugs that belong to seven classes targeting different stages in the life cycle of HIV have been introduced, there is no permanent cure or vaccine to control AIDS. The introduction of antiviral treatment could improve the quality and life expectancy of HIV-infected patients. However, low drug adherence, toxicity, high pill burden, and the error-prone mechanism of HIV reverse transcriptase have caused the rise of drug resistance in HIV-infected patients (4).

Protease has always been one of the main therapeutic targets for developing antiviral drugs against HIV-AIDS and nine FDA-approved protease inhibitors have been improved, including Saquinavir (SVQ), Indinavir (IDV), Ritonavir (RTV), Nelfinavir (NFV), Amprenavir (APV), Lopinavir (LPV), Atazanavir (ATV), Tipranavir (TPV), and Darunavir (DRV). Due to the great anti-AIDS potential of protease inhibitors, they are essential components of antiretroviral therapy (ART) (5).

Bioinformatics tools have been established during the last few years and have been the main means to analyze

**Corresponding Author:** A. Hashempour
Shiraz HIV/AIDS Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 7137386272, E-mail address: thashem@sums.ac.ir

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sequences is CRF35-AD, which has been reported in several studies from Iran. However, investigations have shown several subtypes in Iranian patients with lower prevalence, including subtypes B, C, CRF01-AE, and CRF-BF.

The difference in the subtyping findings may result in different numbers of enrolled patients, and different genomes and geographical regions which were used in different subtyping tools.

Altogether, the results of this study revealed the lack of presence of either major or minor PIs drug resistance mutations in patients that suggest the current PIs can be effective in People Living with HIV (PLWH). However, this data should be combined with the results of previous studies to make a better decision for the planning of the treatment strategy. The necessity of PIs-resistance mutation monitoring in Iranian HIV-infected patients before determining the treatment regimen can be useful. Furthermore, the present finding showed the new subtype (D) in Iranian HIV-infected patients, indicating the importance of HIV subtyping among Iranian patients periodically. This can help us predict the transmission route and the plausible level of virus pathogenicity as well as define subtype-dependent resistance in Iranian society.

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