# HIV-1 Protease Amino Acid Sequences: Wildtype and Common Mutants

## Overview

HIV-1 protease is a 99-amino acid homodimeric enzyme essential for viral replication. This document presents the amino acid sequences for the wildtype enzyme and common drug-resistant mutants, including specific variants for research purposes.

## Wildtype HIV-1 Protease Sequence

### Wildtype (Reference):

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

Note: This is the mature HIV-1 protease sequence (99 amino acids). Some laboratory constructs may have slight variations such as Q7K to prevent autoproteolysis.

## Requested Mutants

### 1. I50V Mutant

**Mutation:** Isoleucine → Valine at position 50

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGVGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

*Clinical Significance: Major resistance mutation for fosamprenavir and darunavir; affects dimer interface stability and reduces van der Waals interactions with inhibitors.*

### 2. I84V Mutant

**Mutation:** Isoleucine → Valine at position 84

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNVIGRNLLTQIGCTLNF

*Clinical Significance: Major resistance mutation for multiple protease inhibitors including atazanavir, darunavir, lopinavir, fosamprenavir, and indinavir; causes loss of van der Waals contacts with inhibitors.*

### 3. I50V + I84V Double Mutant

**Mutations:** Isoleucine → Valine at positions 50 and 84

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGVGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNVIGRNLLTQIGCTLNF

*Clinical Significance: Combination significantly reduces binding affinity to most protease inhibitors; affects both active site interactions and dimer stability.*

### 4. 5T2Z (PR-S17) - Multi-drug Resistant Variant

**Mutations:** 17 total mutations including K20R, E35D, M36I, S37D, M46L, G48V, A71V, V82S, I93L, L89V, L90M, and others

PQITLWQRPIVTIKIGGQLREALLDDGAIDDTVLEEMSLPGRWKPKLIGVIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNISGRNLLTIIGCTLNF

*Note: This represents the PR-S17 variant with 17 mutations. Despite having only one mutation (V82S) in the active site, it shows 10,000-fold weaker binding to darunavir compared to wildtype.*

## Additional Common HIV-1 Protease Mutants

### 5. D30N Mutant

**Mutation:** Aspartic acid → Asparagine at position 30

PQITLWQRPLVTIKIGGQLKEALLDTGADNTVLEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

*Clinical Significance: Primary resistance mutation for nelfinavir; rarely confers cross-resistance to other PIs.*

### 6. G48V Mutant

**Mutation:** Glycine → Valine at position 48

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIVGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

*Clinical Significance: Major mutation selected by saquinavir; increases amino acid side chain size and reduces flap interactions with inhibitors.*

### 7. V82A Mutant

**Mutation:** Valine → Alanine at position 82

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVANIIGRNLLTQIGCTLNF

*Clinical Significance: Major resistance mutation for indinavir, ritonavir, and lopinavir; lies in active site cavity.*

### 8. L90M Mutant

**Mutation:** Leucine → Methionine at position 90

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLMTQIGCTLNF

*Clinical Significance: Major resistance mutation for nelfinavir and saquinavir; affects dimer interface and can destabilize the enzyme.*

### 9. V32I Mutant

**Mutation:** Valine → Isoleucine at position 32

PQITLWQRPLVTIKIGGQLKEALLDTGADDTILEEMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

*Clinical Significance: Associated with resistance to atazanavir and lopinavir; often appears with other mutations like L33F, I54M, and I84V.*

### 10. M46I Mutant

**Mutation:** Methionine → Isoleucine at position 46

PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLEEMSLPGRWKPKIIGGIGGFIKVRQYDQILIEICGHKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

*Clinical Significance: Associated with indinavir resistance; affects flap dynamics and can stabilize closed conformation.*

## Key Structural Features

### Catalytic Triad

* **Positions 25-27:** ASP-THR-GLY (conserved in all variants)
* Each monomer contributes one Asp25 to form the active site

### Important Regions

* **Flaps:** Residues 43-58 (crucial for substrate binding and drug interactions)
* **Active Site:** Residues around positions 25, 30, 48, 50, 82, 84
* **Dimer Interface:** N- and C-terminal regions, positions 1-10 and 90-99

### Resistance Patterns

* **Major mutations:** Directly affect inhibitor binding (positions 30, 48, 50, 82, 84, 90)
* **Minor/accessory mutations:** Compensate for fitness costs and enhance resistance
* **Multiple mutations:** Often required for high-level resistance to newer inhibitors like darunavir

## Summary Table

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Mutant** | **Position** | **Change** | **Primary Resistance To** | **Type** |
| I50V | 50 | Ile → Val | Fosamprenavir, Darunavir | Major |
| I84V | 84 | Ile → Val | Multiple PIs | Major |
| D30N | 30 | Asp → Asn | Nelfinavir | Major |
| G48V | 48 | Gly → Val | Saquinavir | Major |
| V82A | 82 | Val → Ala | Indinavir, Ritonavir, Lopinavir | Major |
| L90M | 90 | Leu → Met | Nelfinavir, Saquinavir | Major |
| V32I | 32 | Val → Ile | Atazanavir, Lopinavir | Major |
| M46I | 46 | Met → Ile | Indinavir | Minor/Accessory |
| PR-S17 (5T2Z) | Multiple (17 mutations) | Complex | All clinical PIs | Multi-drug resistant |

## Clinical Implications

These mutations represent the most clinically relevant drug-resistant variants encountered in HIV-1 therapy. Understanding their structural basis helps in:

1. **Drug resistance monitoring:** Genotypic testing for these mutations guides treatment decisions
2. **New drug design:** Targeting conserved regions less prone to mutation
3. **Combination therapy:** Using drugs with different resistance profiles
4. **Fitness assessment:** Some mutations reduce viral fitness, which can be exploited therapeutically

## References

* Mutations are based on the HIV Drug Resistance Database (Stanford University)
* Structural information from Protein Data Bank entries and published crystallographic studies
* Clinical significance from WHO and IAS treatment guidelines
* PDB Structure 5T2Z: Crystal Structure of Multi-drug Resistant HIV-1 Protease PR-S17