# Major HIV-1 Drug Resistance Mutations

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## Major Nucleoside RT Inhibitor (NRTI) Resistance Mutations

| | Non-TAMs | | | | | TAMs | | | | | | MDR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 184 | 65 | 70 | 74 | 115 | 41 | 67 | 70 | 210 | 215 | 219 | 69 | 151 |
| Cons | M | K | K | L | Y | M | D | K | L | T | K | T | Q |
| 3TC | **VI** | R | | | | | | | | | | **Ins** | **M** |
| FTC | **VI** | R | | | | | | | | | | **Ins** | **M** |
| ABC | VI | **R** | E | **VI** | **F** | L | | | W | FY | | **Ins** | **M** |
| TFV | *** | **R** | E | | F | L | | R | W | FY | | **Ins** | **M** |
| ZDV | *** | *** | * | * | | **L** | **N** | **R** | **W** | **FY** | QE | **Ins** | **M** |

**Bold underline**: High-level reduced susceptibility or virological response. **Bold**: Reduced suceptibility or virological response. Plain text: Reduced susceptibility in combination with other NRTI-resistance mutations. Asterisk: Increased susceptibility.

**M184VI**: Although they cause high-level *in vitro* resistance to 3FTC, they are not contraindications to 3FTC because they increase TFV and AZT susceptibility and decrease viral replication fitness.

**K65R**: The most common DRM in patients with VF on a TFV-regimen. It causes a clinically relevant 2-fold reduction in TFV susceptibility. However, K65R+M184VI reduces TFV susceptibility <1.5-fold. INSTI-/PI-naive patients with K65R+M184VI who receive TFV/3FTC and a highly potent 3rd drug (e.g., DTG or DRV/r) respond as well or better than those receiving AZT/3TC even though K65R increases AZT susceptibility.

**TFV, TDF, & TAF**: Tenofovir (TFV) disoproxil fumarate (TDF) and TFV alafenamide (TAF) are TFV triphosphate prodrugs. Although TDF and TAF have similar resistance profiles, TAF attains higher intracellular levels. Additional TFV-selected mutations of uncertain phenotypic and clinical significance include A62V, K65N, K70GQNTdel, and L74I.

**TAMs**: Thymidine analog mutations. Selected by AZT and d4T; facilitate primer unblocking. Non-TAMs prevent NRTI incorporation. T215SCDEIVALN (T215 revertants) emerge from T215YF in the absence of NRTIs. **MDR**: Multidrug resistance mutations. T69 insertions occur with TAMs. Q151M occurs with non-TAMs and the accessory mutations A62V, V75I, F77L, and F116Y.

**References**: hivdb.org/s/nrtinotes

## Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations

| | 100 | 101 | 103 | 106 | 181 | 188 | 190 | 227 | 230 |
|---|---|---|---|---|---|---|---|---|---|
| Cons | L | K | K | V | Y | Y | G | F | M |
| DOR | I | E | | **AM** | IV | **L** | S**E** | **LC** | **L** |
| EFV | **I** | E**P** | **NS** | **AM** | CIV | **L** | **ASE** | L**C** | **L** |
| ETR | **I** | E**P** | | | **CIV** | L | AS**E** | **C** | **L** |
| RPV | **I** | **EP** | | | **CIV** | **L** | AS**E** | **C** | **L** |
| NVP | **I** | **EP** | **NS** | **AM** | **CIV** | **L** | **ASE** | **LC** | **L** |

**Bold underline**: High-level reduced susceptibility or virological response. **Bold**: Reduced susceptibility or virological response. Plain text: Reduced susceptibility in combination with other NNRTI-resistance mutations.

**Abbreviations**: Doravirine (DOR), efavirenz (EFV), etravirine (ETR), rilpivirine (RPV), nevirapine (NVP).

**Additional Mutations**: A98G (DOR, EFV, ETR, NVP, RPV); E138GQKR are nonpolymorphic mutations associated with intermediate/high-level RPV resistance. E138A is a polymorphic mutation associated with low-level RPV resistance. Y188CH are associated with intermediate / high-level resistance to EFV; G190Q is a rare mutation which may have an effect similar to G190E; P225H (DOR, EFV); L234I (DOR), Y318F (DOR, NVP).

**Synergistic combinations**: V179D+K103R reduce NVP and EFV susceptibility >10-fold. Y181C+V179F cause high-level ETR and RPV resistance.

**DOR and ETR often require multiple mutations:** DOR - high level with Y188L, V106A, F227L/C, M230L or any combination of V106 and F227 mutations. ETR: L100I, K101P, Y181C/I/V, M230L. But multiple non-DOR mutations at common positions such as Y181 and G190 can produce intermediate levels of reduced DOR susceptibility.

**References**: hivdb.org/s/nnrtinotes

## Major Integrase Inhibitor (INSTI) Resistance Mutations

| | 66 | 92 | 118 | 138 | 140 | 143 | 148 | 155 | 263 |
|---|---|---|---|---|---|---|---|---|---|
| Cons | T | E | G | E | G | Y | Q | N | R |
| BIC | K | Q | **R** | KAT | SAC | | **HRK** | H | **K** |
| CAB | K | Q | **R** | KAT | SAC**R** | | **HRK** | **H** | **K** |
| DTG | K | Q | **R** | KAT | SAC | | **HRK** | H | **K** |
| EVG | **AIK** | **Q** | **R** | **KAT** | **SAC** | | **HRK** | **H** | **K** |
| RAL | AI**K** | **Q** | **R** | **KAT** | **SAC** | **RCH** | **HRK** | **H** | K |

**Bold underline**: High-level reduced susceptibility or virological response. **Bold**: Low-level reduced susceptibility or reduced suceptibility or virological response. Plain text: Rreduced susceptibility in combination with other INSTI-resistance mutations.

**Abbreviations**: Bictegravir (BIC), dolutegravir (DTG), cabotegravir (CAB), elvitegravir (EVG), raltegravir (RAL).

**Additional mutations**: T97A is a polymorphic mutation (1%-4%) in INSTI-naive patients. In combination with Q148 + G140/E138 DRMs, it causes high-level BIC/DTG resistance. H51Y, F121Y, S147G, S153YF, and S230R are additional nonpolymorphic INSTI DRMs. E92GV, Y143HKSGA, P145S, Q146LP, Q148N, G149A, V151AL, and N155ST are rare nonpolymorphic IN mutations that reduce RAL and/or EVG susceptibility. L74M, V151I, E157Q, G163KR, and D232N are common polymorphic accessory DRMs. Mutations outside of IN in the polypurine tract have also rarely been reported to reduce INSTI susceptibility.

**References**: hivdb.org/s/instinotes

## Major Protease Inhibitor (PI) Resistance Mutations

| | 32 | 46 | 47 | 48 | 50 | 54 | 76 | 82 | 84 | 88 | 90 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cons | V | M | I | G | I | I | L | V | I | N | L |
| ATV/r | **I** | IL | V | **VM** | **L** | VTALM | | ATFS | **V** | **S** | **M** |
| DRV/r | **I** | | VA | | **V** | **LM** | **V** | F | **V** | | |
| LPV/r | **I** | IL | V**A** | VM | **V** | **VTALM** | **V** | **AFTS** | **V** | | M |

**Bold underline**: High-level reduced susceptibility or virological response. **Bold**: Reduced suceptibility or virological response. Plain text: Reduced susceptibility in combination with other PI-resistance mutations.

**Abbreviations**: atazanavir (ATV), darunavir (DRV), lopinavir (LPV), '/r' (ritonavir).

**Additional mutations**: L10F, V11I, K20TV, L23I, L33F, K43T, F53L, Q58E, A71IL, G73STCA, T74P, N83D, and L89V/T are common nonpolymorphic accessory resistance mutations. L10F, V11IL, L33F, T74P, and L89V are accessory resistance mutations associated with reduced DRV/r susceptibility. D30N and N88D are nonpolymorphic resistance mutations selected by NFV. L10RY, V11L, L24F, M46V, G48ASTLQ, F53Y, I54S, V82CM, I84AC, N88TG are rare nonpolymorphic variants.

**Hypersusceptibility**: I50L (each PI except ATV); L76V (ATV).

**References**: hivdb.org/s/pinotes

## Mutations for Drug Resistance Surveillance

| NRTIs*† | | NNRTIs* | | PIs* | | INSTI‡ | |
|---|---|---|---|---|---|---|---|
| **M41** | L | **L100** | I | **L23** | I | **T66** | A,I,K |
| **K65** | R | **K101** | E,P | **L24** | I | **E92** | G,Q |
| **D67** | N,G,E | **K103** | N,S | **D30** | N | **G118** | R |
| **T69** | D,Ins | **V106** | M,A | **V32** | I | **F121** | Y |
| **K70** | R,E | **V179** | F | **M46** | I,L | **E138** | A,K,T |
| **L74** | V,I | **Y181** | C,I,V | **I47** | V,A | **G140** | A,C,S |
| **V75** | M,T,A,S | **Y188** | L,H,C | **G48** | V,M | **Y143** | C,H,R,S |
| **F77** | L | **G190** | A,S,E | **I50** | V,L | **S147** | G |
| **Y115** | F | **P225** | H | **F53** | L,Y | **Q148** | H,R,K |
| **F116** | Y | **M230** | L | **I54** | V,L,M,A,T,S | **N155** | H |
| **Q151** | M | | | **G73** | S,T,C,A | **S230** | R |
| **M184** | V,I | | | **L76** | V | **R263** | K |
| **L210** | W | | | **V82** | A,T,F,S,C,M,L | | |
| **T215** | Y,F,I,S,C,D,V,E | | | **N83** | D | | |
| **K219** | Q,E,N,R | | | **I84** | V,A,C | | |
| | | | | **I85** | V | | |
| | | | | **N88** | D,S | | |
| | | | | **L90** | M | | |

*Bennett DE, Camacho RJ, Otelea D, et al. Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update. *PLoS ONE*. 2009;4:e4724.

†K65N, T69del, K70QNSTG, and K70del are nonpolymorphic DRMs that have been reportedly more commonly since TDF/XTC has become the standard NRTI backbone worldwide. These mutations should also be examined in studies of HIVDR surveillance. A62V would be included on this list except for the fact that it is common in subtype A6 sequences due to a founder effect. (Rhee SY, Varghese V, Holmes SP, et al. Mutational Correlates of Virological Failure in Individuals Receiving a WHO-Recommended Tenofovir-Containing First-Line Regimen: An International Collaboration. *EBioMedicine*. 2017 Apr;18:225-235.)

‡Tzou PL, Rhee SY, Descamps D, et al. Integrase Strand Transfer Inhibitor Resistance Mutations for Surveillance of Transmitted HIV-1 Drug Resistance. *J Antimicrob Chemother*. doi:10.1093/jac/dkz417.

**References**: hivdb.org/s/who