**HIV-1 Protease Summary**

Human Immunodeficiency Virus (HIV) is a virus that infects cells involved in immune response and ultimately leads to Acquired Immunodeficiency Syndrome (AIDS), a condition that according to the World Health Organization caused an estimated 1.2 million deaths worldwide in 2012. The detection and treatment of HIV is of utmost importance to prevent not only the progression to AIDS in infected individuals but also the spread of the virus, and considerable effort has gone into researching novel drug targets in HIV. One popular target for antiviral drug therapy in HIV is HIV-1 protease. Like many viruses HIV assembles its proteins as one continuous polypeptide that must be cleaved to appropriate lengths and at precise times to allow the maturation of the virus—HIV1 protease serves this purpose.

HIV-1 protease is a homodimer, that is, it is two separate but identical chains that come together to form the active protein. HIV-1 protease consists mainly of beta strands with only two alpha helices. The two helices (purple) run from positions 86-94 of each chain, and are comprised of the amino acids GRNLLTQLG. These helices may influence the active site of the enzyme in some way: the mutation I93L has been demonstrated to be related to an increased risk of virological failure in patients. The active site is comprised of an active site triad of Asp25-Thr26-Gly27 (orange), a highly conserved sequence that is present in all aspartic protease such as pepsin and renin. Asp is the main catalytic residue, while Thr is essential in the binding of the two chains. It has been show that upon a T26A mutation the protein is unable to dimerize, and thus unable to function. Interestingly, mutation in an already dimerized protein results in residual function, implying that the “fireman’s grip” is not essential for function, but is incredibly important to form the dimer. The precise role of Gly has yet to be elucidated, however, it is known that Asp25 forms a hydrogen bond with the backbone N of Gly27. Although any amino acid should be able to serve this function, due to the incredibly high rate of conservation of the glycine residue it would not be unreasonable to expect some sort of steric hindrance from the insertion of any other residue.
amino acid bigger than glycine.

During catalysis the flap region of HIV-1 protease (red), consisting of beta strands with Gly residues on the ends open up to allow the viral polyprotein to enter the active site and undergo hydrolysis. In the hydrolysis reaction a water molecule that is retained in the active site between the two aspartate residues acts as a nucleophile and attacks the carbonyl C atoms on the substrate, leaving the acidic proton on OD2 of Asp25 (see “figure 9” on page 1).

Developing drugs to target HIV-1 protease has been a goal of several pharmaceutical companies for decades, and there are several compounds able to inhibit the activity of the enzyme. Along with the considerable effort that has been poured into the development of novel treatment options involving the inhibition of HIV-1 protease the enzyme itself has accrued various mutations that contribute to drug resistance. As previously mentioned, the mutation I93L has been implicated in virological failure (the failure of antiviral drug therapy). Other important mutations that have been indentified are M46I/L shown to be responsible for Indinavir and Amprenavir resistance along with G48V connected to Saquinavir resistance. In a 2003 study Muzzamil et. al examined the drug resistance potential of active site mutations versus non-active site mutations. By starting with a “wild type” protein ANAM-11 containing both active and non-active site mutations resistant to indinavir, nelfinavir, saquinavir, and ritonavir. The A-1 protein containing only the active site mutations present in ANAM-11, and the NAM-10 protein containing only the non-active site mutations were produced, and, upon examination of the catalytic activity of both the A-1 and NAM-10 mutants similar (low, inhibited) catalytic activities to the wild type ANAM-11 protein were observed, demonstrating that both active and non-active site mutations can be sufficient on their own to produce a resistant protein. Furthermore, non-active site mutations likely alter the geometry of the binding site cavity to produce resistance.

**Figure sources:**

**Mechanism:**

**Drug Resistance:**