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Protease inhibitors give wings to combination therapy

The first antiretroviral therapies (ARTs) for people with HIV were nucleoside reverse-transcriptase inhibitors (NRTIs), but these drugs were only partially effective. The addition of an orally administered protease inhibitor, the first of which was approved in 1995, reduced HIV plasma concentrations and increased $CD4^+$ cell counts to levels that enabled patients to have fairly normal life expectancies. This combination—two nucleoside analogs and a protease inhibitor—is now the cornerstone of ART.

The HIV genome encodes a long polypeptide that must be cleaved into functional proteins by the HIV protease. Following virus uncoating and reverse transcription of the RNA genome, a polypeptide is produced that contains all viral gene products, including the structural proteins and enzymes. The HIV protease then cleaves this polypeptide into its constituent viral proteins. Inhibiting the activity of the protease is therefore an attractive means to prevent virion production.

The first protease inhibitors were peptidomimetic molecules designed to look like the peptide linkages in the precursor polypeptide and therefore compete with the substrate. However, like most peptidomimetic proteins, the early protease inhibitors had poor pharmacokinetic properties, namely, low oral absorption and rapid elimination. Key medicinal chemistry–led structural changes improved these properties. For example, substituting a pyridine with the less electron-rich thiazole to produce ritonavir improved both metabolic stability and aqueous solubility. This molecule was also more potent in animal studies than its parent, predominantly because it also had a lower inhibitory constant (K_i).

These drugs wowed the community in early clinical trials. The addition of a protease inhibitor to two NRTIs approximately halved the number of patients whose disease progressed to AIDS or death. In 90% of patients taking the three-drug combination, the number of HIV RNA particles in the blood went from >20,000 particles per milliliter to <500 in 24 weeks.

The first protease inhibitor to be approved by the US Food and Drug Administration (FDA) was saquinavir, in December 1995, a mere 97 days after the FDA received its marketing application. Within months, two other protease inhibitors, ritonavir and indinavir, were also approved. There are currently ten FDA-approved protease inhibitors on the market for HIV.

The remarkable results from the clinical trials of this first wave of protease inhibitors also highlighted important aspects of the biology of HIV infection. First, the clearance rate of virus was independent of initial viral loads and suggested that, on average, half of plasma virions turn over every two days. Second, the number of $CD4^+$ cells destroyed and replenished each day was close to the total number of infected cells. The potential to generate viral diversity (and resulting drug-resistant clones) is therefore substantial, arguing for early initiation of ART.

ART has changed the course of HIV. In the US, mortality among patients with advanced HIV infection declined from 29.4 per 100 person-years in 1995 to 8.8 once ART including a protease inhibitor became the standard of care. In geographic locations with high rates of HIV infection, ART has also changed economics and demographics. Places with high rates of infection, such as Swaziland, saw a 10- to 15-year decrease in life expectancy during the peak of HIV deaths. In the neighboring rural KwaZulu-Natal region of South Africa, where an estimated 29% of adults are HIV positive, adult life expectancy (the mean age to which a 15-year-old could expect to live) increased from 49 to 61 years in the ~10 years after government programs for HIV treatment were initiated. Because many people with HIV were dying during their most economically productive years, the knock-on societal and economic effects are substantial.

Since 1995, new protease inhibitors and combinations with improved dosing have become available, but the protease inhibitors developed in the mid-1990s changed the course of the disease and formed the foundations of ART.

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> “The addition of a protease inhibitor […] halved the number of patients whose disease progressed to AIDS or death”

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