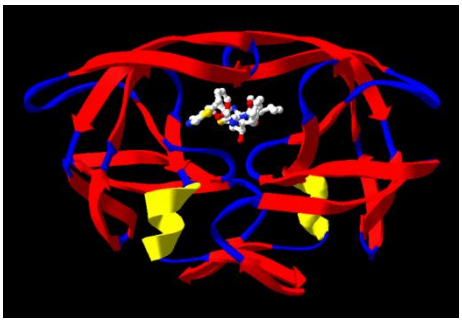
Tse Wing Lam 7S
Wong Tai Wa 7S

Kaletra

Kaletra is an HIV medication. It is in a category of HIV medicines called protease inhibitors. Kaletra prevents cells infected by HIV from producing new virus. This reduces the amount of virus in your body, and can increase the number of CD4 cells.

Lead compound discovery

The lead compound of kaletra is ritonavir, with trade name **Norvir** (Abbott Laboratories), is an antiretroviral drug from the protease inhibitor class used to treat HIV infection and AIDS.
Ritonavir was originally developed as an inhibitor of HIV protease. It is one of the most complex inhibitors. It is now rarely used for its own antiviral activity, but remains widely used as a booster of other protease inhibitors. More specifically, ritonavir is used to inhibit a particular liver enzyme that normally metabolizes protease inhibitors, cytochrome P450–3A4 (CYP3A4). The drug's molecular structure inhibits CYP3A4, so a low dose can be used to enhance other protease inhibitors. This discovery has drastically reduced the adverse effects and improved the efficacy of PI's and HAART. However, it can cause a large number of side–effects on its own.

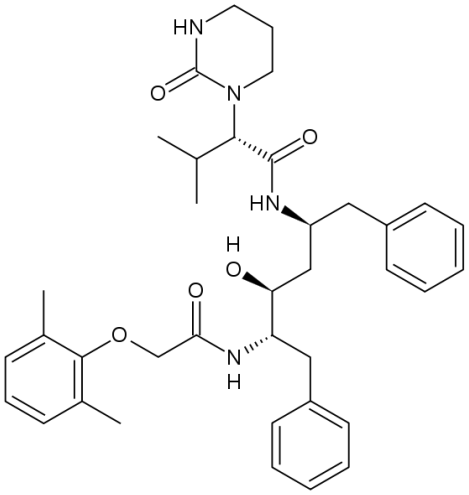


(image of HIV protesase with the bound protese inhibitor ritonavir)

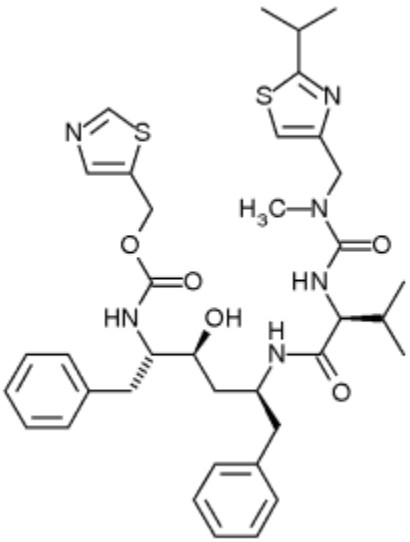
Molecular modification

There are 2 active ingredients in Kaletra: Lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV–1 protease. As co–formulated in KALETRA, ritonavir inhibits the CYP3A–mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.
Lopinavir is chemically designated as [1S–[1R*, (R*), 3R*, 4R*]]–N–[4–[[(2,6–dimethylphenoxy)acetyl]amino]–3–hydroxy–5–phenyl–1–(phenylmethyl)pentyl]tetrahydro–alpha–(1–methylethyl)–2–oxo–1(2H)–pyrimi

dineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10–hydroxy–2–methyl–5–(1–methylethyl)–1–[2–(1–methylethyl)–4–thiazolyl]–3,6–dioxo–8,11–bis(phenylmethyl)–2,4,7,12–tetraazatridecan–13–oic acid, 5–thiazolylmethyl ester, [5S–(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water. Ritonavir has the following structural formula:



Formulation development

KALETRA film–coated tablets are available for oral administration in two

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strengths:

- Yellow tablets containing 200 mg of lopinavir and 50 mg of ritonavir
- Pale yellow tablets containing 100 mg of lopinavir and 25 mg of ritonavir

The yellow, 200 mg lopinavir/50 mg ritonavir, tablets contain the following inactive ingredients:
copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene glycol 3350, yellow ferric oxide E172, and polysorbate 80.
The pale yellow, 100 mg lopinavir/25 mg ritonavir, tablets contain the following inactive ingredients:
copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350, and yellow ferric oxide E172.

Safety tests and human trials

Several human trials were conducted on patients without prior antiretroviral therapy. The study was a randomized, double-blind, multicenter trial comparing treatment with kaletra plus stavudine and lamivudine versus nelfinavir plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years old, 57% were Caucasian, and 80% were male. Mean baseline CD4+ cell count was 259 cells/mm3 (range: 2 to 949 cells/mm3) and mean baseline plasma HIV-1 RNA was 4.9 log10 copies/mL (range: 2.6 to 6.8 log10 copies/mL).

Outcome	KALETRA+d4T+3TC	Nelfinavir+d4T+3TC
Responder	75%	62%
Virologic failure	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse events	4%	4%
Discontinued for other reasons	10%	10%

Through 48 weeks of therapy, there was a statistically significantly higher

proportion of patients in the kaletra arm compared to the nelfinavir arm with HIV-1 RNA < 400 copies/mL (75% vs. 62%, respectively) and HIV-1 RNA < 50 copies/mL (67% vs. 52%, respectively).

Apart from this test, different tests were conducted in various groups of patients, like those with antiretroviral therapy of different age groups, different body conditions and so on. And these tests were approved.

Approval for marketing

Kaletra, sold as Aluvia in some parts of the world, is manufactured by Abbott Laboratories. The U.S. Food and Drug Administration (FDA) approved it for the treatment of HIV infection, in both adults and children, in 2000.

KALETRA®
(lopinavir/ritonavir)

Reference:
http://www.kaletra.com/index.cfm
http://www.rxlist.com/kaletra-tablets-drug-patient.htm
http://en.wikipedia.org/wiki/Ritonavir
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021251s022,021906s013lbl.pdf