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Lopinavir

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Contents

Abstract

▲ Lopinavir is a protease inhibitor with high specificity for HIV-1 protease. Ritonavir strongly inhibits lopinavir metabolism; coadministration of lopinavir and ritonavir in healthy volunteers increased the area under the lopinavir plasma concentration-time curve >100-fold.

▲ Trough plasma concentration : antiviral 50% effective concentration ratio for lopinavir was >75 for wild-type HIV at the dose used in clinical trials, compared to values of ≤4 for other commonly used protease inhibitors.

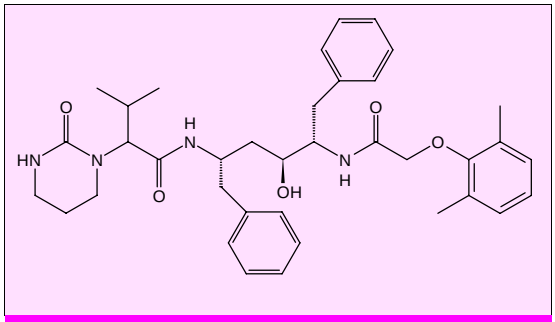
▲ Coformulated lopinavir and ritonavir (lopinavir/ritonavir) 400/100mg twice daily for 48 weeks suppressed HIV replication in significantly more antiretroviral-naive patients than nelfinavir 750mg 3 times daily (all patients also received stavudine and lamivudine).

▲ Suppression of viral replication was observed in most protease inhibitor-experienced patients with lopinavir/ritonavir (400/100, 400/200 or 533/133mg twice daily for 48 or 96 weeks) in combination with ≥2 nucleoside reverse transcriptase inhibitors (NRTIs) and either efavirenz or nevirapine.

▲ 48 weeks of treatment with twice daily lopinavir/ritonavir (230/57.5 or 300/75 mg/m^2 for the first 12 weeks and then 300/75 mg/m^2) in combination with 1 or 2 NRTIs, with or without nevirapine, suppressed viral replication in the majority of antiretroviral-naive and -experienced paediatric patients (aged 6 months to 12 years).

▲ Diarrhoea, nausea and asthenia were the most frequently reported adverse effects in patients receiving lopinavir/ritonavir-based regimens. Elevated total cholesterol, triglyceride and hepatic enzyme levels were also reported.

Features and properties of lopinavir (ABT-378)	
Indications	
HIV infection	Late phase clinical trials
Mechanism of action	
Antiviral	Protease inhibitor
Dosage and administration	
Usual dosage in clinical trials	400mg coformulated with ritonavir 100mg
Route of administration	Oral
Frequency of administration	Twice daily (with food)
Steady-state pharmacokinetic profile of lopinavir 400mg twice daily (after coadministration with ritonavir 100mg twice daily for 3 or 4 weeks)	
Peak plasma concentration	9.6 mg/L
Time to peak plasma concentration	4.2h
Trough plasma concentration	5.5 mg/L
Area under the plasma concentration-time curve over a 12-hour dosing interval	82.8 mg/L • h
Clearance	6.4 L/h
Elimination half-life	5.8h
Adverse effects	
Most frequent	Diarrhoea, nausea, asthenia; elevations in total cholesterol, triglyceride and AST/ALT levels.



Lopinavir

Current guidelines for the first-line treatment of HIV infection include treatment combinations with 2 nucleoside reverse transcriptase inhibitors (NRTIs) and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI), or 2 NRTIs and 2 protease inhibitors.[1-3]

Many currently available HIV protease inhibitors have low oral bioavailability and a short half-life,[4] and pharmacokinetic interactions (with food, plasma proteins or other medications) are common.[5] These factors can complicate treatment regimens and may result in suboptimal drug concentrations that allow development of drug-resistant HIV strains.[4]

Lopinavir is a protease inhibitor which is rapidly metabolised *in vitro*. However, coadministration with ritonavir (an inhibitor of the cytochrome P450 3A isoenzyme) inhibits lopinavir metabolism, significantly increasing plasma concentrations of the drug (section 2) and affording high and consistent levels of lopinavir. Thus, a coformulation of lopinavir and ritonavir (lopinavir/ritonavir) has been developed for clinical use.

1. Pharmacodynamic Profile

In Vitro Anti-HIV Activity

• Lopinavir 0.5 nmol/L inhibited 93% of wild-type HIV-1 protease activity *in vitro*; the drug has a high specificity for HIV-1 protease (≥10^5-fold) over mammalian aspartic proteinases.[4] Lopinavir was highly active against HIV-1 cultured in peripheral blood mononuclear cells, with a mean antiviral 50% effective concentration (EC_{50}) of 6.5 nmol/L (range 4 to 11 nmol/L) against 6 viral isolates.

• Lopinavir and ritonavir bind to alpha-1 acid glycoprotein and also to serum albumin.[6] EC_{50} values for ritonavir against HIV-1 in the presence of 50% human serum were 20- to 30-fold higher than those observed in the absence of serum; in contrast, EC_{50} values for lopinavir increased by only 5- to 8-fold.[7] The EC_{50} for lopinavir against HIV-1 in MT-4 cells was 17 nmol/L, increasing to 102 nmol/L in the presence of 50% human serum; EC_{50} values for ritonavir were 58 and 1044 nmol/L, respectively.[4]

Viral Resistance

• *In vitro* binding of lopinavir to variant isolates of HIV protease (V82A, V82F or V82T mutations) decreased <4-fold compared with binding to wild-type protease.[4] In comparison, the binding of ritonavir decreased by 12- to 52-fold.

• Serial passage of HIV-1 in MT-4 cells in the presence of increasing concentrations of lopinavir resulted in the development of a highly resistant (EC_{50} increased 338-fold) isolate after 142 days. This isolate had multiple protease mutations [occurring in the sequence I84V, L10F, M46I, T91S, V32I (which subsequently reverted back to wild-type sequence), I47V, V47A, G16E, H69Y], and mutations at both p1/p6 and p7/p1 *gag* proteolytic cleavage sites; the EC_{50} values for ritonavir and saquinavir against this variant were increased 21-fold and 4-fold, respectively, compared with wild-type HIV-1.[8]

• Virologic response at 24 weeks was predicted by the baseline lopinavir mutation score, defined as the number of mutations in HIV protease present out of 11 mutations (at positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90) found to be statistically associated with reduced *in vitro* susceptibility to lopinavir, and by the baseline lopinavir phenotype in 2 studies involving antiretroviral-experienced patients (n = 57[9] and n = 70;[10] see section 3).[11] Response rates (viral load < 400 copies/ml) were 91, 81 and 33% for patients with 0 to 5, 6 to 7 and

8 to 10 baseline mutations, respectively ($p = 0.0015$); the probability of virologic response at week 24 was ≥50% in patients with baseline isolates with ≤38-fold reductions in lopinavir susceptibility.[11]

• Plasma concentration of lopinavir just prior to the morning dose (C_{trough})/EC_{50} (inhibitory quotient) was associated with virologic response, according to stepwise logistic regression analysis, with predicted response rates of 70, 80 and 100% for inhibitory quotient values of <4, 4-15 and >15, respectively, in 57 antiretroviral-experienced patients ($p < 0.026$).[12]

• Viral rebound (>400 copies/ml at week 24) was not associated with the development of resistance to lopinavir or any significant protease mutations for 18 viral isolates from patients receiving lopinavir/ritonavir (n = 326) in a randomised double-blind comparative trial (see section 3;[13] n = 653); in contrast, 15 of 40 isolates from patients experiencing viral rebound during treatment with nelfinavir were identified as having evidence of genotypic resistance.[14]

• Phenotypic protease resistance at rebound on lopinavir/ritonavir therapy (9- to 99-fold increase in EC_{50} relative to wild-type HIV) was seen in only 4 patients (with prior protease inhibitor experience) whose baseline viral isolates had 4 or 5 protease mutations associated with lopinavir resistance.[15] Isolates for 2 patients without prior saquinavir experience remained fully sensitive to saquinavir, 2 isolates that were tested against tipranavir were fully sensitive, and all 4 isolates remained fully sensitive or were only moderately resistant (≤8.5-fold) to amprenavir.

• In patients previously treated with a protease inhibitor, a >4-fold increase in baseline lopinavir EC_{50} against viral isolates (*vs* wild-type) was not significantly correlated with response to lopinavir/ritonavir-based treatment, probably because lopinavir C_{trough} remained >12-fold above the mean EC_{50} for lopinavir in subjects with phenotypic data.[16] Results were from a randomised double-blind trial (n = 70) involving treatment with lopinavir/ritonavir 400/100 or 400/200mg twice daily; at day 15, nevirapine (200mg daily for 14 days, then 200mg twice daily) was added, and the current NRTIs were changed to include at least 1 that was new to the patient (see section 3[17]). The number of HIV protease mutations at baseline known to be associated with resistance to currently available protease inhibitors was also not correlated with response to lopinavir/ritonavir-based treatment at 48 weeks.[16]

2. Pharmacokinetic Profile

• *In vitro* studies indicate that in humans lopinavir undergoes rapid NADPH- and cytochrome P450 3A4/5-dependent metabolism. Ritonavir inhibits the metabolism of lopinavir in a concentration-dependent manner, with an apparent inhibition constant (K_i) of 0.013 μmol/L.[18] The major metabolites, M1, M3 and M4, are less active against HIV-1 than lopinavir.[18,19] A radiolabelled lopinavir study in humans showed that 89% of the plasma radioactivity after a single dose of lopinavir/ritonavir 400/100mg was due to parent drug.[20]

• Lopinavir was 98.2 to 99.2% protein bound in both healthy volunteers and HIV-infected patients.[21,22] Protein binding was not concentration-dependent within the therapeutic range.[21]

• The area under the plasma concentration-time curve (AUC) for lopinavir (100 to 800mg) increased >100-fold when coadministered with ritonavir (50 to 200mg) in a placebo-controlled single dose study in 48 healthy volunteers.[23]

• At steady state, lopinavir C_{max} was 9.6 mg/L and time to C_{max} (t_{max}) was 4.2 hours after 3 to 4 weeks of treatment with twice-daily lopinavir/ritonavir 400/100mg (taken without regard to meals) in 21 antiretroviral-naive patients with HIV infection.[21,24] The AUC over a 12-hour dosing interval (AUC_{12}) was 82.8 mg/L · h; C_{trough} was 5.5 mg/L, the elimination half-life ($t_{½}$) was 5.8 hours and clearance was 6.4 L/h.[21,24] Pharmacokinetic parameters did not differ significantly from weeks 3 to 24. The mean lopinavir inhibitory quotient for the lopinavir/ritonavir 400/100mg registrational dose (protein

binding corrected) was >75 in antiretroviral-naive patients.[24] In contrast, the inhibitory quotient (protein binding corrected) for other single protease inhibitors (i.e., ritonavir, indinavir, nelfinavir, amprenavir, saquinavir) at approved clinical doses is ≤4.[25] In single protease inhibitor-experienced patients, lopinavir C_{trough} was greater than the EC_{50} for all viral isolates phenotyped at baseline.[21]

- AUC point estimate values for soft elastic capsule and liquid formulations of single dose lopinavir/ritonavir (400/100mg) were reduced by 36 and 44%, respectively, in fasting healthy volunteers, compared with those who received a moderate fat meal in a randomised crossover study (n = 54).[26] The coformulated capsule and the liquid formulation are bioequivalent under nonfasting conditions.

- Mean AUC and C_{trough} values for lopinavir were reduced by ≈20 to 25% and 40 to 45%, respectively, during coadministration of lopinavir/ritonavir 400/100mg twice daily and efavirenz 600mg once daily in healthy volunteers (n = 30) and protease inhibitor-experienced patients with HIV infection (n = 24).[27] Increasing the dosage of lopinavir/ritonavir to 533/133mg twice daily in patients with HIV infection (n = 26) produced similar concentrations to those achieved with lopinavir/ritonavir 400/100mg in the absence of efavirenz.

- Mean lopinavir C_{trough} and AUC_{12} values were reduced by ≈20 to 30% and ≈25 to 30%, respectively, during coadministration with nevirapine in a randomised nonblind trial involving 100 children (aged 6 months to 12 years) who received lopinavir/ritonavir 230/57.5 or 300/75 mg/m^2 twice daily with (antiretroviral-experienced) or without (antiretroviral-naive) nevirapine and 1 or 2 other NRTIs (see section 3).[28] When coadministered with nevirapine, the higher dosage of lopinavir/ritonavir (a 30% increase) resulted in similar lopinavir plasma concentrations to those observed in adults receiving lopinavir/ritonavir 400/100mg twice daily without coadministration of nevirapine.

- Similar or moderately increased AUC and substantially higher C_{trough} values were observed for single doses of saquinavir 800mg, indinavir 600mg and nelfinavir 750mg in healthy volunteers (numbers not stated) receiving multiple doses of lopinavir/ritonavir 400/100mg twice daily compared with the steady-state pharmacokinetic parameters in patients receiving clinical dosages of these protease inhibitors alone.[29] Similar results were seen with multiple doses of lopinavir/ritonavir 400/100mg twice daily and 5 days of amprenavir 750mg twice daily. These results suggest that nelfinavir, indinavir, saquinavir and amprenavir can be given at reduced dosages twice daily with lopinavir/ritonavir, although optimal dosages have not been determined.

- In healthy volunteers (n = 12), C_{max}, AUC and C_{trough} for atorvastatin 20mg once daily for 4 days were all significantly increased when coadministered with lopinavir/ritonavir 400/100mg twice daily (ratios for values with/without lopinavir/ritonavir were 4.67, 5.88 and 2.28, respectively); the pharmacokinetic parameters of lopinavir were unaffected.[30] There was no clinically significant pharmacokinetic interaction between lopinavir and pravastatin.

- Lopinavir/ritonavir 400/100mg twice daily for 10 or 14 days significantly decreased plasma concentrations of methadone and ethinyl estradiol in healthy volunteers (n = 11 and n = 12, respectively).[30] Alternative or additional contraceptive methods are suggested in patients using estrogen-based contraception. Significant increases in rifabutin plasma concentrations were observed during coadministration with lopinavir/ritonavir; dosage reductions of ≥75% were recommended.[30] Coadministration of rifampicin significantly decreased lopinavir plasma concentrations, and these drugs should not be coadministered.

3. Therapeutic Use

Antiretroviral-Naive Patients

- Significantly more patients achieved viral suppression (<400 or <50 copies/ml) at 48 weeks with lopinavir/ritonavir-based treatment than with nelfinavir-based treatment in a multicentre, double-blind, randomised study involving 653 antiretro-

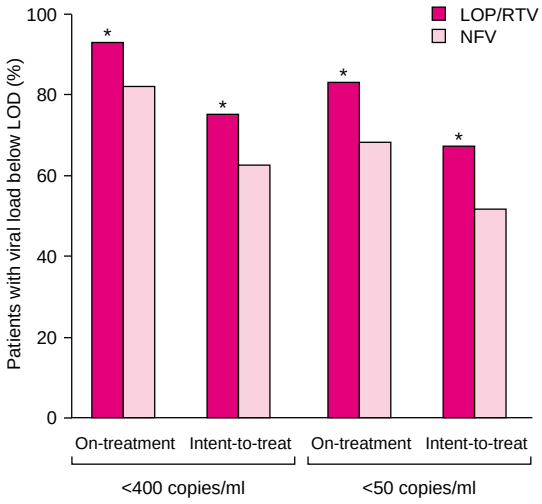


Fig. 1. Comparative efficacy of lopinavir/ritonavir (LOP/RTV)- and nelfinavir (NFV)-based treatment, assessed using plasma HIV RNA levels at 48 weeks. On-treatment and intent-to-treat analysis of data (percentage of patients with HIV RNA levels <50 or <400 copies/ml) from a multicentre, double-blind, randomised study involving 653 antiretroviral-naive patients; all patients received stavudine and lamivudine at standard dosages in addition to either LOP/RTV 400/100mg twice daily (n = 326) or NFV 750mg 3 times daily (n = 327).[13] Baseline plasma HIV RNA levels were similar in both treatment groups. **LOD** = limit of detection; * p < 0.001 *vs* NFV.

viral-naive patients (fig. 1).[13] All patients received stavudine and lamivudine at standard dosages in addition to either lopinavir/ritonavir 400/100mg twice daily or nelfinavir 750mg 3 times daily. There were no significant differences between treatment groups in baseline HIV RNA or CD4+ cell count,[13] and antiviral efficacy was not affected by positive baseline hepatitis B and/or C serology.[31] Mean increase from baseline CD4+ cell count at week 48 was 207 cells/μl in lopinavir/ritonavir recipients and 195 cells/μl in those receiving nelfinavir.[13]

- Based on results from an on-treatment analysis, 99% of patients on treatment had a viral load <400 copies/ml through 108 weeks of treatment in an ongoing randomised double-blind phase II trial evaluating lopinavir/ritonavir in combination with stavudine and lamivudine (n = 100); 80% had viral loads <400 copies/ml according to intent-to-treat analysis (fig. 2); mean increase from baseline CD4+ cell count was 299 cells/μl.[32] All patients received twice daily lopinavir/ritonavir 200/100mg (n = 16), 400/100mg (n = 51) or 400/200mg (n = 33) for 48 weeks, then nonblind treatment with lopinavir/ritonavir 400/100mg twice daily.[24,32] Patients also received stavudine 40mg and lamivudine 150mg, both twice daily, from either day 22 (all patients receiving lopinavir/ritonavir 200/100mg and 16 of those receiving 400/100mg) or day 1. The baseline mean plasma HIV RNA level was 4.9$\log_{10}$ copies/ml.[24] At 96 weeks, plasma HIV RNA levels were <50 copies/ml in 78% of patients based on results from an intent-to-treat analysis.[32]

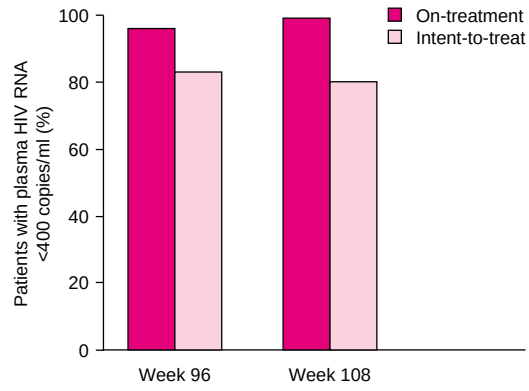


Fig. 2. Antiviral efficacy of lopinavir/ritonavir-based treatment in antiretroviral-naive patients, assessed using plasma HIV RNA levels. On-treatment (n = 78) and intent-to-treat (n = 100) analysis of data [percentage of patients with plasma HIV RNA levels below the limit of detection (LOD); i.e. 400 copies/ml] from a double-blind study involving antiretroviral-naive patients, who were randomised to receive twice daily lopinavir/ritonavir in doses of either 200/100mg (n = 16), 400/100mg (n = 51) or 400/200mg (n = 33) for at least 48 weeks; all patients then received nonblind lopinavir/ritonavir 400/100mg twice daily.[24,32] Patients also received twice daily stavudine 40mg and lamivudine 150mg from day 22 (all patients receiving lopinavir/ritonavir 200/100mg and 16 of those receiving 400/100mg) or day 1. Mean baseline plasma HIV RNA level was 4.9$\log_{10}$ copies/ml.

Antiretroviral-Experienced Patients

• At 96 weeks, results from an intent-to-treat analysis indicated that 63% of patients who received lopinavir/ritonavir (either 400/100 or 400/200mg twice daily; results pooled for both dosages) had plasma HIV RNA levels <400 copies/ml (fig. 3) in a randomised double-blind trial (n = 70).[10] All patients had previously received a single protease inhibitor and 2 NRTIs for ≥3 months, but had not received prior treatment with any other protease inhibitor or an NNRTI; at study entry all patients were changed from their current protease inhibitor to lopinavir/ritonavir.[10,17,33] At day 15 nevirapine (200mg daily for 14 days, then 200mg twice daily) was added and the 2 current NRTIs were changed to include at least 1 that was new to the patient. Baseline viral isolates from 32% of patients demonstrated ≥4-fold reduction in susceptibility to 3 or more protease inhibitors.[10] Mean increase from baseline CD4+ cell count at week 96 was 188 cells/μl.[10] During the first 2 weeks of the study, before the addition of nevirapine, 80% of patients had a decrease in HIV RNA ≥1$\log_{10}$ copies/ml; viral load decline was independent of previous protease inhibitor experience.[10]

• Plasma HIV RNA levels were <400 copies/ml in 65% of patients (intent-to-treat analysis) after 48 weeks in a randomised nonblind trial in 57 multiple protease inhibitor-experienced, NNRTI-naive patients; all patients received lopinavir/ritonavir (400/100 or 533/133mg, twice daily; data pooled for both dosages), efavirenz 600 mg/day and NRTIs (as selected by the investigator).[9,34,35] Sixty-eight percent of patients had baseline viral isolates demonstrating cross-resistance (≥4-fold increase in EC_{50} relative to wild-type virus) to at least 3 licensed protease inhibitors.[34] From 24 weeks, all patients began conversion to lopinavir/ritonavir 533/133mg twice daily; at week 48, 80% of patients had plasma HIV RNA levels <400 copies/ml according to on-treatment analysis, and mean increases from baseline CD4+ cell counts in patients receiving lopinavir/ritonavir 400/100 or 533/133mg were 116 and 67 cells/μl, respectively.[9]

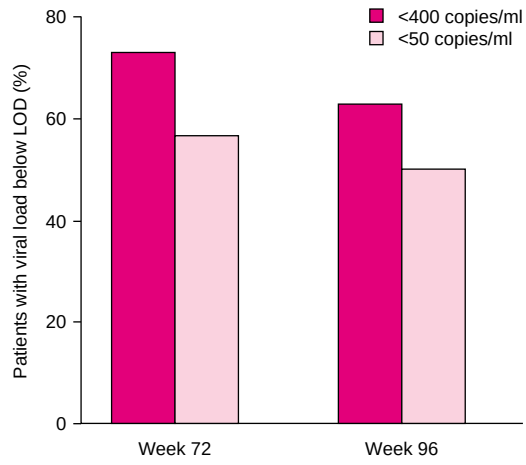


Fig. 3. Antiviral efficacy of lopinavir/ritonavir-based treatment in antiretroviral-experienced patients, assessed using plasma HIV RNA levels. Intent-to-treat analysis of data from a randomised double-blind trial involving 70 patients who received twice daily lopinavir/ritonavir (either 400/100 or 400/200mg) for 96 weeks; results are pooled for both lopinavir/ritonavir dosages and show the percentage of patients with plasma HIV RNA levels <50 or <400 copies/ml.[10,17,33] All patients had previously received a single protease inhibitor and 2 NRTIs for ≥3 months, but had not received previous treatment with any other protease inhibitor or an NNRTI. At day 15 nevirapine (200mg daily for 14 days, then 200mg twice daily) was added and the NRTIs were changed to include at least 1 that was new to the patient. **LOD** = limit of detection; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor.

Paediatric Patients

• Based on results from an intent-to-treat analysis, 84% of 44 antiretroviral-naive and 75% of 56 antiretroviral-experienced paediatric patients (aged 6 months to 12 years) had plasma HIV RNA levels <400 copies/ml after 48 weeks of treatment with lopinavir/ritonavir (230/57.5 or 300/75 mg/m^2 twice daily; all patients received 300/75 mg/m^2 twice daily after week 12) in a randomised nonblind study (fig. 4).[36,37] Treatment-naive patients also received stavudine and lamivudine; treatment-experienced patients received nevirapine and 1 or 2 NRTIs, although dosages were not stated. Mean increases from baseline CD4+ cell count at 48

weeks were 404 and 238 cells/μl in antiretroviral-naive and experienced patients, respectively.

4. Tolerability

• Incidence rates of adverse effects at 48 weeks were similar with lopinavir/ritonavir-based treatment and nelfinavir-based treatment in a randomised double-blind trial involving 653 antiretroviral-naive patients.[13] Adverse effects considered to be moderate or severe (and of probable or possible relationship to lopinavir/ritonavir) that occurred in >2% of patients included diarrhoea, nausea, asthenia, abdominal pain, vomiting and headache. Patients with hepatitis B surface antigen and/or hepatitis C antibodies at baseline were more likely to experience elevations in AST or ALT to ≥5 times the upper limit of normal than patients without these results (relative risk of 5.2 with lopinavir/ritonavir and 50.8 with nelfinavir).[31] However, these elevations did not lead to treatment discontinuation or clinical hepatitis in either treatment group.

• Lopinavir was well tolerated in the randomised double-blind study in 100 antiretroviral-naive patients who received lopinavir/ritonavir-based treatment (see section 3), with only 3 discontinuations related to lopinavir/ritonavir through 108 weeks of treatment.[32] Moderate or severe adverse effects considered to be related to lopinavir/ ritonavir included diarrhoea (>3 loose stools/day; 24% of patients), nausea (15%) and abnormal stools (≤3 loose stools/day; 8%); grade 3/4 laboratory abnormalities included elevations in total cholesterol (15%), triglyceride (13%) and hepatic enzyme AST/ALT (10%) levels. Lipid elevations observed with lopinavir/ritonavir therapy responded to treatment with statins or fibrate agents.[38]

• Diarrhoea (26%) and asthenia (7%) were the most commonly reported drug-related adverse effects of at least moderate severity during 96 weeks of lopinavir/ritonavir-based treatment in a double-blind trial involving 70 single protease inhibitor-experienced patients with HIV infection (all patients also received nevirapine and 2 NRTIs; see section 3).[17] Grade 3/4 laboratory abnormalities included total cholesterol level >3 g/L (29%), triglyceride level >7.5 g/L (26%), γ-glutamyl transferase levels >5 times upper limit of normal (29%) and AST/ALT levels >5 times upper limit of normal (17%). At 96 weeks, 4 patients had discontinued treatment for drug-related reasons.[10]

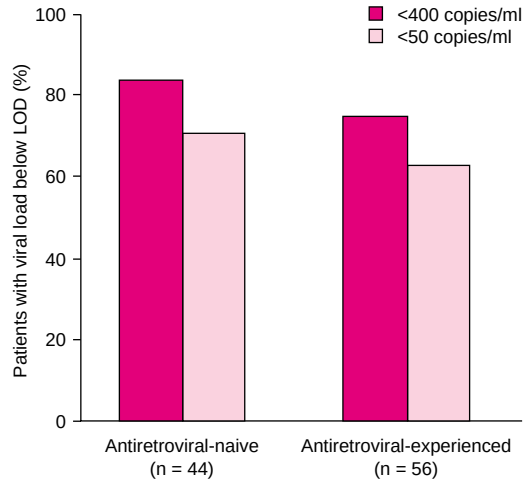


Fig. 4. Antiviral efficacy of lopinavir/ritonavir-based treatment in paediatric patients, assessed using plasma HIV RNA levels at 48 weeks. Intent-to-treat analysis of data from a randomised nonblind study involving 100 antiretroviral-naive and experienced paediatric patients (aged 6 months to 12 years); percentages of patients with plasma HIV RNA levels below the limit of detection (LOD; 50 or 400 copies/ml).[36,37] Patients received twice daily lopinavir/ritonavir 230/57.5 or 300/75 mg/m^2 (all patients received 300/75 mg/m^2 after week 12) and either stavudine and lamivudine (naive patients; n = 44) or nevirapine and 1 or 2 NRTIs [NRTI-experienced patients (n = 32) and NRTI- and protease inhibitor-experienced patients (n = 24)]; dosages were not stated.

• Lopinavir/ritonavir-based treatment was also well tolerated through 48 weeks in a randomised nonblind trial involving 100 children aged 6 months to 12 years (section 3).[36,37] The most common adverse effect of at least moderate severity was rash (2% of patients); the most common grade 3/4 laboratory abnormalities were hyperamylasaemia (6%), thrombocytopenia (4%), elevated bilirubin levels (3%), hypernatraemia (3%), elevated AST/ALT levels (3%) and hyponatraemia (3%).

5. Lopinavir: Current Status

Lopinavir is a protease inhibitor approved for use in the US. The metabolism of lopinavir is sensitive to inhibition by ritonavir, and coadministration with ritonavir substantially and significantly increases the lopinavir area under the plasma concentration-time curve above values observed with lopinavir alone. The steady-state inhibitory quotient (C_{trough}/EC_{50}) is >75 in treatment-naive patients receiving lopinavir/ritonavir 400/100mg twice daily. Treatment with coformulated lopinavir and ritonavir in combination with other antiretroviral therapies is well tolerated and has shown clinical efficacy and durability in both antiretroviral-naive and -experienced adults and children with HIV infection.

References

1. Carpenter CCJ, Cooper DA, Fischl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society - USA panel. JAMA 2000 Jan 19; 283: 381-90
2. Gazzard B, Moyle G, Bhiva GWC. 1998 revision to the British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals. Lancet 1998 Jul 25; 352: 314-6
3. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. MMWR Morb Mortal Wkly Rep 1998 Apr 24; 47 Suppl. RR-5: 43-83
4. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. Antimicrob Agents Chemother 1998 Dec; 42: 3218-24
5. Rana KZ, Dudley MN. Human immunodeficiency virus protease inhibitors. Pharmacotherapy 1999; 19 (1) I: 35-59
6. Molla A, Vasavanonda S, Kumar G, et al. Human serum attenuates the activity of protease inhibitors toward wild-type and mutant human immunodeficiency virus. Virology 1998 Oct 25; 250: 255-62
7. Molla A, Vasavanonda S, Denissen J, et al. Effect of human serum proteins on the antiretroviral activity of ritonavir and ABT-378, potent inhibitors of HIV protease. 4th Conference on Retroviruses and Opportunistic Infections; 1997 Jan 22-26, Washington DC
8. Carrillo A, Stewart KD, Sham HL, et al. In vitro selection and characterization of human immunodeficiency virus type 1 variants with increased resistance to ABT-378, a novel protease inhibitor. J Virol 1998 Sep; 72: 7532-41
9. Rockstroh J, Brun S, Bertz R, et al. Kaletra (ABT-378/ritonavir) and efavirenz: 48-week safety/efficacy evaluation in multiple PI-experienced patients [poster no. F150]. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
10. Feinberg J, Brun S, Marsh T, et al. Durable suppression of HIV+ RNA after two years of Kaletra (ABT-378/ritonavir) therapy in single protease inhibitor experienced patients. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
11. Kempf DJ, Isaacson J, King M, et al. Interpretation of phenotypic and genotypic resistance to Kaletra™ (ABT-378/ritonavir) in protease inhibitor experienced patients [poster no. F148-F149]. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
12. Hsu A, Granneman GR, Kempf DJ, et al. The C_{trough} inhibitory quotient predicts virologic response to ABT-378/ritonavir (ABT-378/r) therapy in treatment-experienced patients. 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
13. Johnson M, Beall G, Badley A, et al. A phase III, randomized, double-blind trial of Kaletra™ (ABT-378/r) + stavudine (d4T) and lamivudine (3TC) vs. nelfinavir + d4T/3TC. Handout accompanying oral presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
14. Bernstein B, Kempf D, Moseley J, et al. Lack of resistance to Kaletra™ (formerly known as ABT-378/r) observed through 24 weeks of therapy in antiretroviral-naïve subjects. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
15. Molla A, Brun S, Mo H, et al. Genotypic and phenotypic analysis of viral isolates from subjects with detectable viral load on therapy with ABT-378/ritonavir (ABT-378/r) [abstract no. 39]. 4th International Workshop on HIV Drug Resistance and Treatment Strategies; 2000 Jun 12-16; Sitges
16. Kempf D, Xu Y, Brun S, et al. Baseline genotype and phenotype do not predict response to ABT-378/ritonavir (ABT-378/r) in PI-experienced HIV+ patients at 24 and 48 weeks [poster no. 731]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco (CA)
17. Deeks S, Brun S, Xu Y, et al. ABT-378/ritonavir (ABT-378/r) suppresses HIV RNA to <400 copies/mL in 86% of PI-experienced HIV+ patients at 48 weeks [poster no. 532]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco (CA)
18. Kumar GN, Dykstra J, Roberts EM, et al. Potent inhibition of the cytochrome P-450 3A-mediated human liver microsomal metabolism of a novel HIV protease inhibitor by ritonavir: A positive drug-drug interaction. Drug Metab Dispos 1999 Aug; 27: 902-8
19. Kumar GN, Jayanti V, Lee RD, et al. In vitro metabolism of the HIV-1 protease inhibitor ABT-378: species comparison and metabolite identification. Drug Metab Dispos 1999 Jan; 27: 86-91
20. Kaletra™. US product label information [online]. Available from: URL: http://www.kaletra.com [Accessed 2000 Nov 17]
21. Bertz R, Lam W, Brun S, et al. Multiple-dose pharmacokinetics (PK) of ABT-378/ritonavir (ABT/r) in HIV+ subjects [poster no. #0327]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco (CA)
22. Lal R, Hsu A, Granneman GR, et al. Multiple dose safety, tolerability and pharmacokinetics of ABT-378 in combination with ritonavir [abstract no. 647]. 5th Conference on Retroviruses and Opportunistic Infections, 1998 Feb 1-5; Chicago (IL)
23. Lal R, Hsu A, Chen P, et al. Single dose pharmacokinetics of ABT-378 in combination with ritonavir [abstract no. 279]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28-Oct 1; Toronto
24. Murphy RL, Brun S, Hicks S, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. AIDS 2001. In press

25. Gulick R, King M, Brun S, et al. ABT-378/ritonavir (ABT-378/r) in antiretroviral-naive HIV+ patients: 72 weeks [poster no. 515]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco (CA)
26. Gustavson L, Lam W, Bertz R, et al. Assessment of the bioequivalence and food effects for liquid and soft elastic capsule co-formulations of ABT-378/ritonavir (ABT-378/r) in healthy subjects. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto
27. Bertz R, Lam W, Hsu A, et al. Assessment of the pharmacokinetic interaction between ABT-378/ritonavir (ABT-378/r) and efavirenz in healthy volunteers and in HIV+ subjects. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto
28. Hsu A, Bertz R, Renz C, et al. Assessment of the pharmacokinetic interaction between Kaletra™ (lopinavir/ritonavir or ABT-378/r) and nevirapine in HIV-infected paediatric subjects [poster no. 440]. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
29. Hsu A, Bertz R, Ashbrenner E, et al. Interaction of ABT-378/ritonavir with protease inhibitors in healthy volunteers. 1st International Workshop on Clinical Pharmacology of HIV Therapy; 2000 Mar 30-31; Noordwijk
30. Bertz R, Hsu A, Lam W, et al. Pharmacokinetic interactions between Kaletra™ (lopinavir/ritonavir or ABT-378/r) and other non-HIV drugs [poster 438]. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
31. Arribas J, Barros C, Gonzalez-Lahoz J, et al. Treatment of HIV+ subjects co-infected with hepatitis B or C safety and efficacy comparison of Kaletra™ (ABT-378/ritonavir) vs. nelfinavir from a phase III blinded randomized clinical trial. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
32. Stryker R, Brun S, King M, et al. Kaletra (ABT-378/ritonavir) in antiretroviral-naïve HIV+ patients: follow up beyond two years and viral load suppression below 3 copies/ml. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
33. Thompson M, Brun S, Xu Y, et al. Analysis of duration of virologic response in two phase II studies of ABT-378/ ritonavir (ABT-378/r) at 72 weeks [Abstract TuPeB3197]. Poster presentation, 13th International AIDS Conference; 2000 Jul 9-14; Durban
34. Becker S, Brun S, Bertz R, et al. ABT-378/ritonavir (ABT-378/r) and efavirenz: 24 week safety/efficacy evaluation in multiple PI experienced patients. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto
35. Clumeck N, Brun S, Xu Y, et al. ABT-378/ritonavir (ABT-378/r) and efavirenz: 24-week safety/efficacy evaluation in multiple PI-experienced patients [Abstract TuPeB3196]. Poster presentation, 13th International AIDS Conference; 2000 Jul 9-14; Durban
36. Cahn P, Violari A, Saez-Llorens X, et al. Kaletra™ (ABT-378/ritonavir) in HIV-infected children at 48 weeks. Poster presentation, 5th International Congress on Drug Therapy in HIV Infection; 2000 Oct 22-26; Glasgow
37. Violari A, Saez-Llorens X, Renz C, et al. ABT-378/ritonavir in HIV-infected children. Poster presentation, 13th International AIDS Conference; 2000 Jul 9-14; Durban
38. Kessler H, Brun S, King M, et al. Analysis of safety data from ABT-378/ritonavir (ABT-378/r) in two phase II clinical trials [Abstract TuPeB3198]. Poster presentation, 13th International AIDS Conference; 2000 Jul 9-14; Durban

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