# Should lopinavir/ritonavir be used in the treatment of COVID-19?

**Authors:** Ian Theodore G. Cabaluna, RPh, MD, GDip (Epi) ; Michelle D. Villanueva, MD, DPPS
**Date of Review:** 31 March 2020 (version 1)
**Last Updated**: 14 April 2020 (version 3)

## KEY FINDINGS

Based from two RCTs, there is inconclusive evidence on clinical improvement, 28-day mortality and viral shedding among patients with mild to moderate and severe COVID-19 treated with lopinavir/ritonavir.

- Lopinavir/ritonavir (LPV/r) is a combination drug used primarily in HIV infections. Lopinavir is a protease inhibitor while ritonavir increases the concentration of lopinavir.
- Patients with SARS treated with LPV/r appeared to reduce the viral load, and LPV/r was recommended for patients with MERS-CoV
- Early case reports have shown that lopinavir/ritonavir may be beneficial in patients with COVID-19.[1-3] Two observational studies have shown that lopinavir/ritonavir if administered early (within 10 days) may decrease duration of viral shedding. [4, 5]
- Based on two open-label randomized controlled trials, lopinavir/ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with COVID-19. [6,7]
- There are at least 16 on-going clinical trials on lopinavir-ritonavir including a WHO-initiated worldwide clinical trial.
- Most common adverse events were nausea, vomiting, headache, increased in cholesterol level and hypertriglyceridemia [6-8]. WHO interim guidance does not recommend any specific anti-viral or biologic agents and only recommends symptomatic treatment for patients with COVID-19.[9] National Health Commission of the People's Republic of China, suggest the use of lopinavir/ritonavir in COVID-19 [10].

## RESULTS

We found two (2) randomized controlled open label trials on lopinavir/ritonavir. Both trials were conducted in China among hospitalized adults patients with confirmed SARS-COV-2 infection. The LOTUS trial involved 199 patients with severe case of COVID-19 while the ELACOI trial was a 3-arm controlled trial which evaluated the efficacy and safety of LPV/r against arbidol and standard treatment alone in the treatment of mild/moderate COVID-19 patients.

Variation on the severity of illness in the population and two different sets of outcome measures prevented the authors from performing a meta-analysis. The results of each trials are briefly discussed here.

In the LOTUS trial [6], LPV/r group had no significant difference from the control in the time to clinical improvement (HR for clinical improvement, 1.24; 95%CI , 0.90 to 1.72). Lopinavir/ ritonavir also did not show benefit on mortality at 28 days (RR 0. 77; 95%CI 0.45 to 1.30). The percentages of patients with detectable viral RNA at various time points were similar for both groups.

In the ELACOI trial [7], both LPV/r, arbidol and standard treatment had no significant difference regarding the time of positive-to-negative conversion of COVID-19 nucleic acid ($P$=0.751). There was also no significant difference in the rate of defervescence, cough improvement and radiologic improvement at day 7 and day 14 ($P$>0.05).

Both RCTs were found to be of good quality. Both underwent randomization, and allocation concealment to treatment assignment. Primary efficacy analysis was on an intention-to-treat basis and included all the patients who had undergone randomization. However, clinicians were not blinded in both RCTs, their judgement on clinical improvement may have been influenced by the treatment assignment. The ELACOI study has a very small sample size (n=44) to reach the adequate power (1-Beta error > 0.8) in many parameters. It still on pre print, so it still has to be peer reviewed.

For HIV patients, several studies regarding adverse effects of LPV/r treatment has already been published. A review by Croxtall et al, enumerated the following adverse events reported in phase II/III trials: diarrhea, nausea, vomiting, headache, increased in cholesterol level and hypertriglyceridemia[18]. A meta analysis of RCTs on the efficacy and biological safety of LPV/r based anti-retroviral therapy(ART) in HIV1 infected patients by Huang et al documented Grade 3 or 4 treatment related hyperlipidemia as most notable adverse effect. In two of the studies included in the meta analysis the incidence of dyslipidemia in ART-naïve patients were 23% and 18%. [8]

WHO interim guidance does not recommend any specific anti-viral or biologic agents and only recommends symptomatic treatment for patients with COVID-19 [9]. The National Health Commission (NHC) of the People's Republic of China, in their latest version of the Diagnosis and Treatment of Pneumonia Caused by COVID-19, suggest the use of lopinavir/ritonavir (adult: 200mg/50mg/tablet, 2 tablets twice daily; the length of treatment should not exceed 10 days).[10]

## CONCLUSION

Based from two RCTs, there is inconclusive evidence on clinical improvement,28-day mortality and viral shedding among patients with mild to moderate and severe COVID-19 treated with lopinavir/ritonavir. Clinical trials that investigate the efficacy and safety of lopinavir/ritonavir combination for COVID-19 patients are still limited. We are awaiting the results of other clinical trials.

## Declaration of Conflict of Interest

No conflict of interest

## REFERENCES

1. Deng, L., et al., *Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study.* J Infect, 2020.
2. Lim, J., et al., *Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR.* J Korean Med Sci, 2020. **35**(6): p. e79.
3. Wang, Z., et al., *Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment.* Biosci Trends, 2020. **14**(1): p. 64-68.
4. Yan, D., et al., *Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in patients with SARS-CoV-2 infection (pre-print).* medRxiv preprint, 2020.
5. Ye X.T., et al., *Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019.* European Review for Medical and Pharmacological Sciences, 2020. **24**: p. 3390-3396.
6. Cao, B., et al., *A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.* N Engl J Med, 2020.
7. Li, Y., et al., *An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI) (Preprint).* medRxiv preprint, 2020.
8. Huang, X., et al., *Efficacy and biological safety of lopinavir/ritonavir based anti-retroviral therapy in HIV-1-infected patients: a meta-analysis of randomized controlled trials.* Sci Rep, 2015. **5**: p. 8528.
9. WHO, *Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. V1.2*. 2020, WHO: Geneva.
10. China, N.H.C.N.o.t.P.s.R.o., *The diagnosis and treatment guide of COVID-19 pneumonia caused by new coronavirus infection. 7th Edition*. 2020.
11. Chu, C.M., et al., *Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings.* Thorax, 2004. **59**(3): p. 252-256.
12. Chan KS, L.S., Chu CM, et al, *Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study.* Hong Kong Medical Journal = Xianggang yi xue za zhi., 2003. **9**(6): p. 399-406.
13. de Wilde, A.H., et al., *Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture.* Antimicrob Agents Chemother, 2014. **58**(8): p. 4875-84.
14. Chan, J.F., et al., *Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset.* J Infect Dis, 2015. **212**(12): p. 1904-13.
15. Spanakis, N., et al., *Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen.* Int J Antimicrob Agents, 2014. **44**(6): p. 528-32.
16. Kim, U.J., et al., *Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome.* Antivir Ther, 2016. **21**(5): p. 455-9.
17. Zhu, Z., et al., *Arbidol Monotherapy is Superior to Lopinavir/ritonavir in Treating COVID-19.* J Infect, 2020.
18. Croxtall, J.D. and C.M. Perry, *Lopinavir/Ritonavir A Review of its Use in the Management of HIV-1 Infection.* Drugs, 2010. **70**(14): p. 1885-1915.

## Appendix 1. Characteristics of included studies

| No. | Title/Author | Study design | Country | Population | Intervention Group(s) | Comparison Group(s) | Outcomes | Key findings |
|---|---|---|---|---|---|---|---|---|
| 1 | A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19 | Randomized-controlled open-labeled trial | China | 199 | LPV/r plus standard of care | Standard of care alone | Time to clinical improvement (time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.) | No benefit was observed with lopinavir–ritonavir treatment beyond standard care. Although delayed administration of the treatment may partially explain the the ineffectiveness of LPV/r. |
| 2 | An Exploratory Randomized Controlled Study on the Efficacy and Safety of Lopinavir/Ritonavir or Arbidol Treating Adult Patients Hospitalized with Mild/Moderate COVID 19 (ELACOI) | Exploratory randomized controlled trial | China | 44 | LPV/r Arbidol | No anti-viral treatment | Time of positive to negative conversion of SARS Cov2 Nucleic Acid and conversion rates at Day 7 and Day 14 Improvement of clinical signs and symptoms and Chest CT | The mean time to positive-to-negative conversion of SARS-CoV-2 nucleic acid during the 21-day follow-up period was 8.5 (IQR, 3-13) in the LPV/r group, 7 (IQR, 3-10.5) in the arbidol group and 4 (IQR, 3-10.5) in the control group, with no statistical difference among them (*P* =0.751)<br><br>The positive-to-negative conversion rates of SARS-CoV-2 nucleic acid at day 7 and 14 did not show significant differences in the LPV/r group (42.9%, 76.2%), the arbidol group (62.5%, 87.5%) and the control group (71.4%, 71.4%) (all *P*>0.53).<br><br>No statistical differences were found among three groups in the rates of antipyresis, cough alleviation, improvement of chest CT (All P> 0.05) |
| 3 | Factors Associated with prolonged viral shedding and impact of Lopinavir/Ritonavir Treatment in Patients with SARS-Cov-2 Infection | Retrospective cohort | China | 120 | LPV/r | No LPV/R | Risk factors associated with duration of viral shedding | Older age and lack of LPV/r treatment were independently associated with SARS- CoV-2 RNA shedding in patients with COVID-19. Earlier administration of LPV/r treatment could shorten viral shedding. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| 4 | Clinical Efficacy of Lopinavir/Ritonavir in The Treatment of Corona Virus Disease 2019 | Retrospective Cohort | China | 47 | LPV/r plus Adjuvant medicine | Adjuvant medicine alone | Mean number of days to lysis of fever<br>Improvement in the Abnormal proportions of Blood tests (WBC, Lymphocytes, CRP and PLT)<br>Number of Days for nCoV RNA to turn negative | Patients in the test group returned to normal body temperature in a shorter time (4.8 +/- 1.94 days) compared to control (7.3+/- days p=0.0364).<br>Abnormal proportion of WBC, lymphocytes, CRP and PLT n the Test group was generally lower compared to control after 3 three treatments.<br>Patients in the test group are able to turn negative for nCOV RNA after 7.8 +/- 3.09 days vs control 12 +/- 0.82 days, p=0.0219) |
| 5 | Arbidol Monotherapy is Superior to Lopinavir/Ritonavir in Treating COVID 19 | Retrospective Cohort | China | 34 | Lopinavir/Ritonavir | Arbidol | Duration of positive RNA test/Viral load | No significant difference in fever duration between the two groups (P=0.61). Arbidol group thad a shorter duration of positive RNA test compared to those in the LPV/r group (P <0.01). On day 14 after the admission, no viral load was detected in arbidol group, but the viral load was found in 15(44.1%) patients on LPV/r |

## Appendix 2. Characteristics of ongoing clinical trials

| Clinical Trial Identifier (Location) | Official Title | Methodology | Groups | Estimated Date of Completion |
|---|---|---|---|---|
| ISRCTN83971151<br>(Multicountry) | Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients | Open-label randomized multicountry clinical trial | 1. Local standard of care alone<br>OR local standard of care plus one of<br>2. Remdesivir<br>3. Chloroquine or hydroxychloroquine<br>4. Lopinavir + ritonavir<br>5. Lopinavir + ritonavir plus interferon-beta | March 2021 |
| ISRCTN50189673<br><br>EudraCT number<br>2020-001113-21<br><br>(United Kingdom) | A randomised trial of treatments to prevent death in patients hospitalised with COVID-19 (coronavirus) | Randomized controlled trial | 1.Lopinavir/ritonavir<br>2. Interferon-B1a<br>3. Corticosteroid (dexamethasone)<br>4. Hydroxychloroquine | June 2021 |
| NCT04307693<br>(South Korea) | Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19) | Multicenter open labelled, parallel randomized clinical trial | Experimental: Lopinavir/ritonavir<br>Cleic Acid<br>Active Control:<br>Hydroxychloroquine<br><br>Control: No intervention | May 2020 |
| NCT04261907 | Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection | Multicenter open labelled, parallel randomized clinical trial | Experimental:<br>ASC09/ritonavir group + conventional standardized treatment<br><br>Control:<br>Lopinavir/ritonavir tablet+conventional standardized treatment | June 30,2020 |
| NCT04276688<br>(Hong Kong) | Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment | Randomized, open label parallel controlled clinical trial | Experimental: Lopinavir/ritonavir + ribavirin + Interferon Beta-1B<br><br>Active Control: Lopinavir+ritonavir | July 31,2022 |
| NCT04255017<br>(China) | A Prospective/Retrospective,<br>Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia | Randomized single-blinded parallel controlled clinical trial | Experimental: Abidol HCl + standard treatment<br><br>Experimental: Oseltamivir + standard treatment<br><br>Experimental: Lopinavir/ritonavir + standard treatment<br><br>Control: Standard treatment alone | July 1, 2020 |
| NCT04315948<br>(France) | Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) | Randomized multi-center, open label, parallel controlled clinical trial | Experimental: Remdesivir<br><br>Experimental: Lopinavir/ritonavir<br><br>Experimental: Lopinavir/ritonavir plus Interferon B-1a<br><br>Experimental: Hydroxychlorquine | March 2023 |

| | | | | |
|---|---|---|---|---|
| NCT04303299<br>(Thailand) | Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19 : A Randomized Control Trial | Randomized multi-center, open label, parallel controlled clinical trial | Experimental groups: Various combinations of protease inhibitors, oseltamivir, favipriavir, and chlroquine | November 30, 2020 |
| ChiCTR2000030187<br>(China) | Clinical study for Lopinavir and Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) | Randomized controlled clinical trial | Experimental group: Lopinavir/ritonavir<br><br>Control:<br>Routine symptomatic support treatment | March 25 2020 |
| ChiCTR2000029741<br>(China) | Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study | Randomized multi-center, open label, parallel controlled clinical trial | Experimental group:<br>Chloroquine<br><br>Control: Lopinavir/ritonavir | December 2020 |
| ChiCTR2000029548<br>(China) | Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients | Randomized open label, parallel controlled clinical trial | Experimental groups:<br>1. Baloxavir Marboxil<br>2. Favipiravir<br>3. Lopinavir-Ritonavir | June 2020 |
| ChiCTR2000029541<br>(China) | A randomised, open, controlled trial for darunavir/cobicistat or Lopinavir/ritonavir combined with thymosin a1 in the treatment of novel coronavirus pneumonia (COVID-19) | Randomized open label, parallel controlled clinical trial | Experimental groups:<br>1. Darunavir/cobicistant + thymosin<br>2. Lopinavir/ritonavir + thymosin<br>3. Conventional treatment + thymosin | December 2020 |
| ChiCTR2000029539 (China) | A randomized, open-label study to evaluate the efficacy and safety of Lopinavir-Ritonavir in patients with mild novel coronavirus pneumonia (COVID-19) | Randomized open label, parallel controlled clinical trial | Experimental : Lopinavir ritonavir + conventional treatment<br><br>Control: conventional treatment | February 2021 |
| ChiCTR2000029468 (China) | A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of novel coronavirus pneumonia (COVID-19) | Non-randomized controlled clinical trial | Experimental : Lopinavir/litonavir (LPV/r)+ emtritabine (FTC)/ Tenofovir alafenamide Fumarate tablets (TAF) in combination<br><br>Historical Control: Lopinavir/Ritonavir | June 2020 |
| ChiCTR2000029387 | Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha and ribavirin plus lopinavir/ritonavir plus interferon-alphain in patients with mild to moderate novel coronavirus pneumonia | Randomized controlled clinical trial | Experimental groups:<br>1. Ribavirin + Interferon alpha-1b<br>2. lopinavir / ritonavir + interferon alpha-1b<br>3. Ribavirin + LPV/r+Interferon alpha-1b | January 2021 |
| ChiCTR2000029308 | A randomized, controlled open-label trial to evaluate the efficacy and safety of lopinavir-ritonavir in hospitalized patients with novel coronavirus pneumonia (COVID-19) | Randomized open label, parallel controlled clinical trial | Experimental group: Lopinavir ritonavir<br><br>Control group:<br>Conventional treatment | January 2021 |