South African National Department of Health

Brief Report of Rapid Review

Component: COVID-19

TITLE: LOPINAVIR–RITONAVIR (LPV/r) FOR TREATMENT OF COVID-19: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 24 November 2020

NOTE: This rapid review will be updated when the results from the WHO SOLIDARITY trial are available in peer review format.

Key findings

- We conducted a rapid review of available published clinical evidence regarding use of lopinavir-ritonavir with or without other medicines for patients with COVID-19.
- We found two small randomized controlled trials of lopinavir-ritonavir versus standard of care conducted in China.
- From the available studies, it is unclear whether the use of lopinavir-ritonavir as part of the treatment of COVID-19 has any effect on outcomes critical for decision-making (e.g. clinical improvement, mortality or decreased need for mechanical ventilation).
- Lopinavir-ritonavir did not increase risk of serious adverse effects. Use of lopinavir-ritonavir was associated with an increase in non-serious gastrointestinal adverse effects.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

There is currently insufficient evidence to support inclusion of lopinavir-ritonavir in treatment guidelines for COVID-19 in South Africa.

Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

Therapeutic Guidelines Sub-Committee of the COVID-19 Management Clinical Guidelines Committee: Andy Parrish, Andy Gray, Tamara Kredo, Gary Maartens, Gary Reubenson, Karen Cohen, Renee De Waal, Marc Blockman, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

The COVID-19 pandemic continues to spread, and there is an urgent need for medicines effective against the SARS CoV-2 virus.

Lopinavir a potent inhibitor of HIV-1 protease, is used in the treatment of HIV infection in combination with ritonavir (2). There is in vitro and observational data suggesting that lopinavir-ritonavir (LPV/r) may have been of some benefit in treating the 2003 severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome coronavirus (MERS-CoV), but data from randomized studies is lacking (2–8). When used in management of HIV, LPV/r is generally well tolerated, but gastrointestinal adverse effects are common (9,10).

LPV/r has been suggested as an option for treating COVID-19. We reviewed current evidence for efficacy and harms of LPV/r in treating patients with confirmed COVID-19.

REVIEW QUESTION: Should lopinavir-ritonavir be used for the management of COVID-19 in ambulant and hospitalised patients?

METHODS

We conducted a rapid review of the evidence including systematic searching on two electronic databases (Epistemonikos and PubMed). The search strategy is shown in Appendix 1. We also searched medrxiv.org, a pre-print website for health science studies, for relevant studies. Screening of records and data extraction was conducted by one reviewer (ST), with data extraction reviewed and checked by another reviewer (KC). Relevant records were extracted in a narrative table of results. We included systematic reviews and randomised controlled trials (RCTs) aligned to the PICO (Population, Intervention, Comparators, Outcomes) framework in the evidence synthesis. We searched two trials registers for planned and ongoing trials, www.clinicaltrials.gov (11 April 2020) and the COVID-19 specific register of studies and guidelines, www.covid-nma.com (19 April 2020). The latter database includes a register of living (regularly updated) systematic reviews of interventions for COVID-19.

Eligibility criteria for review

Population: Ambulant and hospitalised patients with confirmed COVID-19, no restriction to age.

Intervention: LPV/r either alone or in combination with other medicines. No restriction on dose, frequency.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality; duration of hospitalisation; progression to hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse events, adverse reactions.

RESULTS

Results of the search: We searched on 11 April 2020 and found 64 records. Of these there was 6 studies that were relevant to the PICO question, and on reviewing the full texts we identified one systematic review (Epistemonikos 23 March 2020) and two RCTs (Cao 2020 and Yueping Li 2020) (11–13). The systematic review included the trial by Cao 2020). The 4 excluded studies were observational (2 retrospective cohort studies and 2 single case descriptive studies). In the COVID-19 register covid-nma.com we found forest plots including both LPV/r trials (the populations are different, hence no meta-analysis) which we report below. In clinicaltrials.gov we identified 22 ongoing trials.

Included studies: The two trials (Cao 2020 and Yueping Li 2020) were conducted in China. The included trials are summarised in Table 1. Cao 2020 included severe adult cases (most required oxygen) (n = 199); Yueping Li 2020 included mild to moderate adult cases, few required oxygen or had pneumonia clinically or radiologically (n = 37). Neither trial enrolled children or pregnant women. Both trials had a LPV/r (400/100 BD) arm compared to standard of care (SOC). The Yueping Li 2020 trial included a third arm with umifenovir. Both trials were appraised as moderate risk of bias due to lack of blinding. Details available in Table 1.

Effectiveness of intervention: In the RCT by Cao et al, 2020, the primary endpoint was time to clinical improvement, which was a composite of either discharge from hospital or an improvement by two points on a 7 point ordinal scale ranging from discharged well through worsening stages of hospitalisation and pulmonary support. The investigators considered the trial underpowered after recruiting 160 patients and decided to stop recruitment at 199 patients. There was no difference between study arms in the primary endpoint (median time to clinical improvement 16 days, HR 1.31, 95% CI 0.95 to 1.85, p=0.09). This trial was underpowered to provide clear evidence on reduction in 28-day mortality, ICU stay or duration of ventilation. There was no difference in the frequency of adverse events. Gastrointestinal adverse events were more commonly reported in the LPV/r group.

Yueping Li et al, 2020 (preprint in medrxiv.org) did not report on mortality, hospitalisation or other clinical endpoints we have specified. They report that the time to-negative conversion of SARS-CoV- 2 was similar in both groups, 8.5 days (IQR 3, 13) for LPV/r vs. 7.0 days (IQR 3, 10.5) for umifenovir vs. 4.0 days (IQR 3, 10.5) for standard treatment; p = 0.751. See Figure 2, mean difference between umifenovir and LPV/r was -1.07 (95%CI -4.79 to 2.65). Adverse events were more common in the LPV/r group. Five (23.8%) patients in the LPV/r group experienced adverse events including diarrhoea (n=3), loss of appetite (n=2) and elevation of ALT over 2.5-fold upper normal limit (n=1). No apparent adverse events occurred in the umifenovir group or in the standard treatment group. The relative risk estimates of adverse event occurrence had high imprecision, RR 0.12 (95%CI 0.01, 1.98). See Figure 2.

Forest plots representing the two trials are extracted from a living systematic review of COVID-19 studies from the https://covid-nma.com/the-project/ date: 22 April 2020).

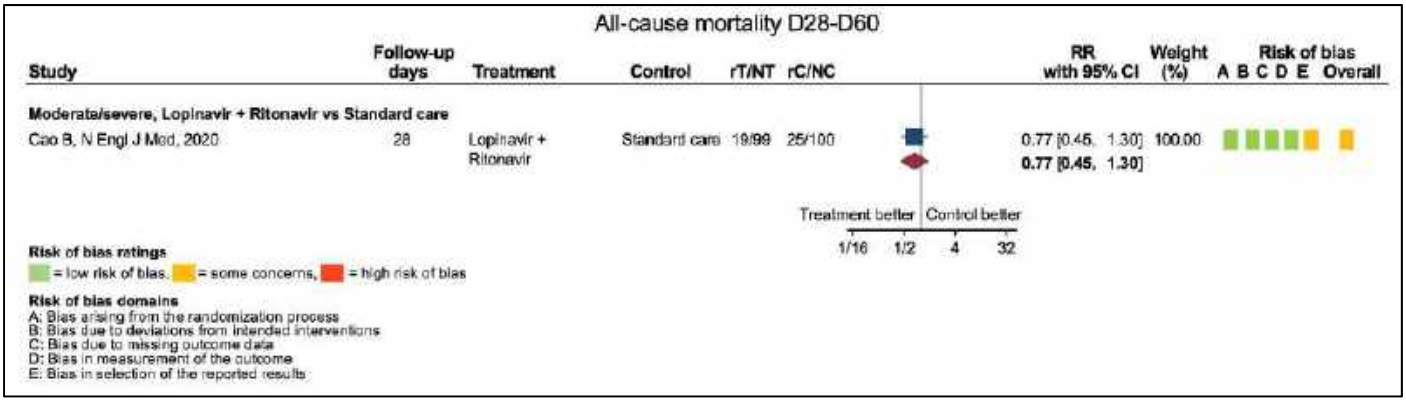


Figure 1. Forest plot of outcome: mortality

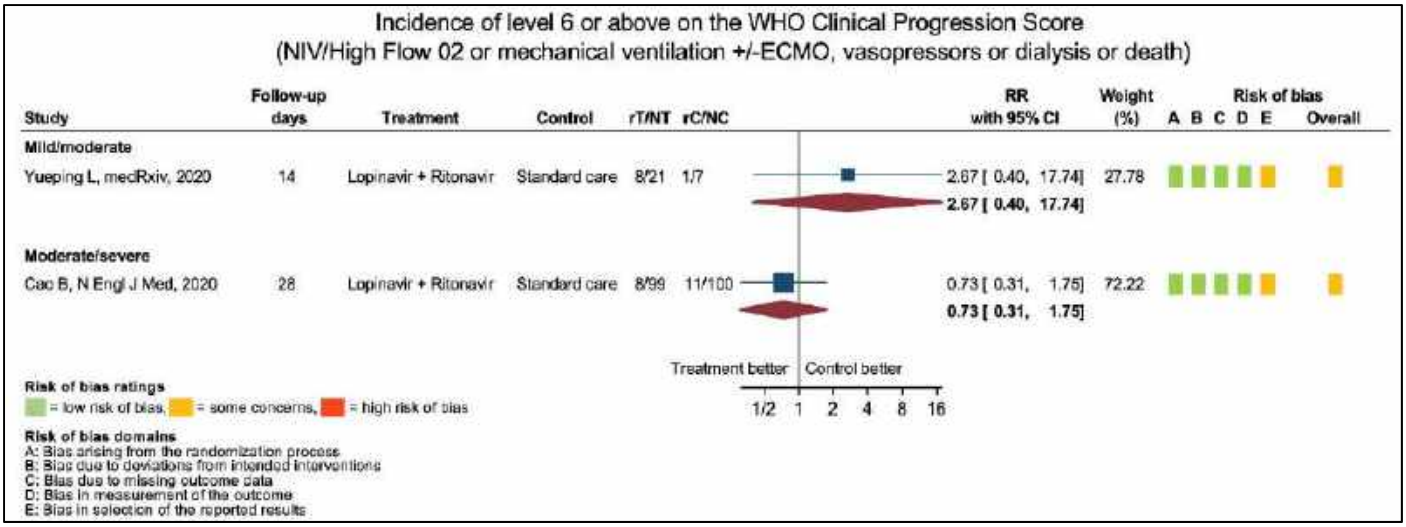


Figure 2. Forest plot of outcome: Incidence of level 6 or above WHO clinical progression score

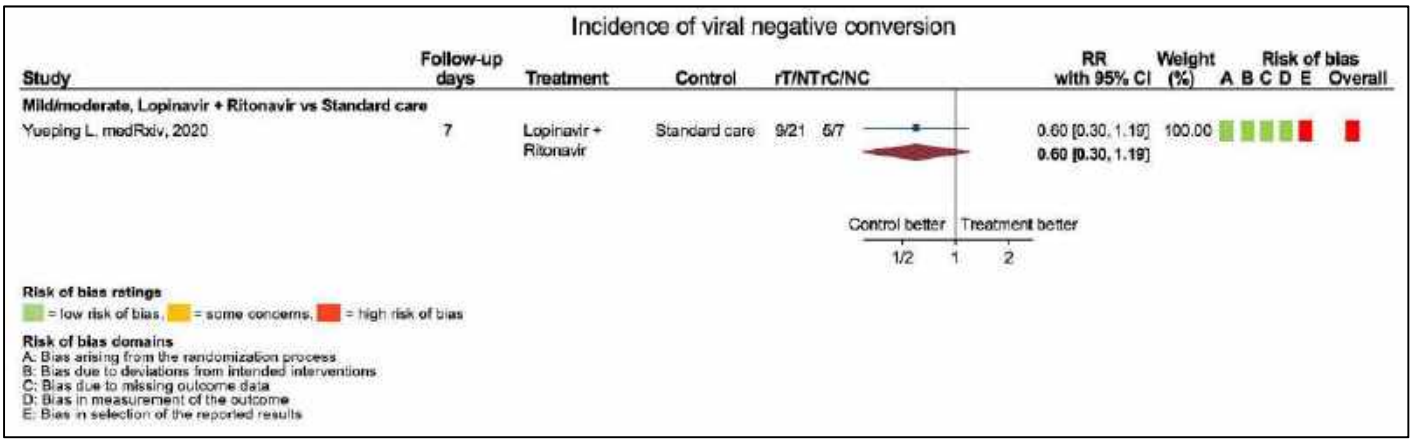


Figure 3. Forest plot of outcome: Incidence of viral negative conversion

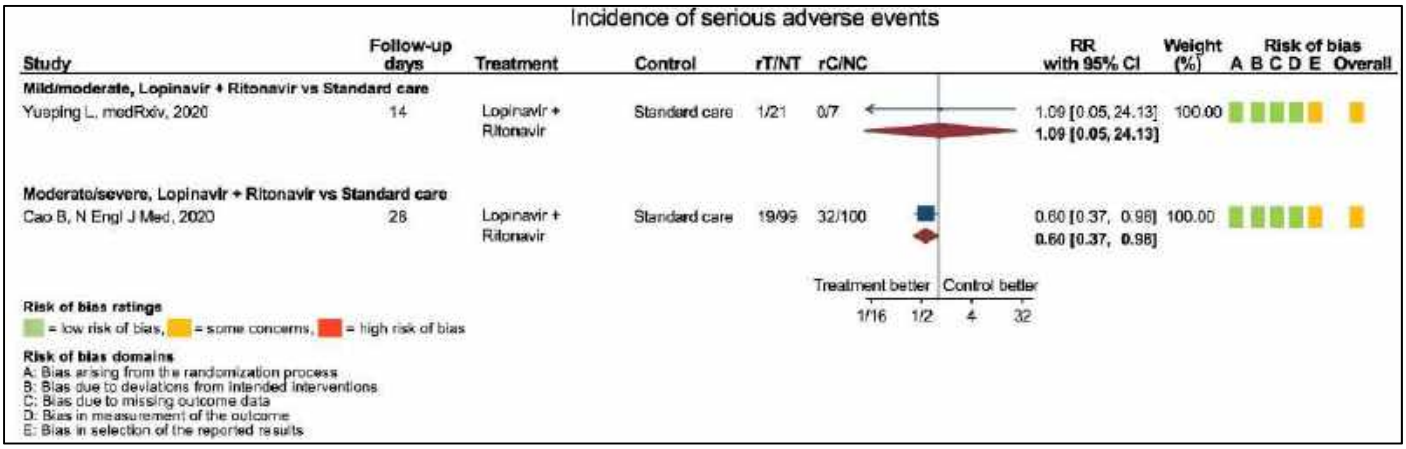


Figure 4. Forest plot of outcome: Incidence of serious adverse events

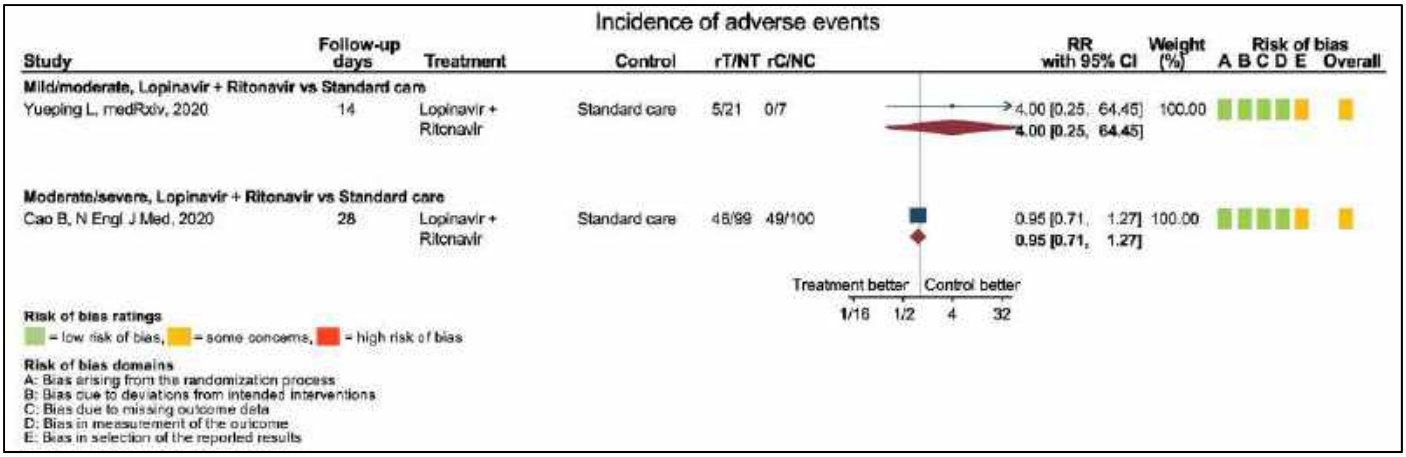


Figure 5. Forest plot of outcome: Incidence of adverse events

CONCLUSION

There is currently insufficient evidence to support inclusion of LPV/r in treatment guidelines for COVID-19 in South Africa.

Currently there are at least 22 registered RCTs evaluating LPV/r in COVID-19 treatment (alone or with other antivirals, antibacterials or interferons) - appendix 2.

Eligible patients in South Africa should be considered for enrolment in randomised controlled clinical trials of potential therapies for COVID-19 so that robust data on efficacy and safety of LPV/r can be generated to inform treatment policies going forward.

This review will be updated as more studies are completed and published

Reviewers: Simbarashe Takuva: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand and School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria**.**

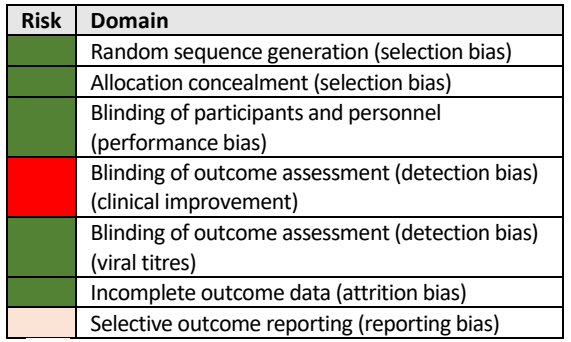
Secondary reviewer: Karen Cohen: Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town.

Additional reviewer(s): Tamara Kredo: Cochrane South Africa, South African Medical Research Council); Andrew Parrish: Department of Internal Medicine, Frere and Cecilia Makiwane Hospitals, East London, South Africa; Trudy Leong: National Department of Health, Affordable Medicines – Essential Drugs Programme, South Africa;

Declaration of interests: ST, KC, AP, TK and TL have no interests to declare in respect of LPV/r.

Table 1 Summary of included studies

Citation	Study design	Population	Intervention and Comparator	Main Findings	Comments
Cao et al 2020 (12)	Randomised Controlled Trial (single-centre in China)	Adults hospitalised with severe COVID-19 at single hospital centre in China (n=199) Male and non-pregnant females ≥18 years; 60.3% of the patients were men. Median age of patients was 58 years. At enrollment 14.1% did not require supplemental oxygen, 69. 8% required supplemental oxygen, 15.6% required high flow nasal canula/noninvasive mechanical ventilation, 0.5% required extracorporeal membrane oxygenation and/or mechanical ventilation. Baseline demographics: More patients with cancer in LPV/r cohort.	LPV/r (400/100mg 12 hourly) + Standard of Care (SoC) (n=99) *vs* SoC only (n=100) *(SoC included as necessary, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO))* 11.1% (9.1% vs 13%) were receiving interferon at enrolment. During the trial, systemic glucocorticoids were administered in 33.7% study participants (32.3% vs 35.0%). Treatment duration: 14 days	**LPV + SoC *vs* SoC only:** *Mortality:* RR 0.77 (95% CI 0.45 to 1.33); 57 less patients per 1000 (95% CI 138 less to 75 more patients); ns – ITT analysis *Mechanical ventilation or extracorporeal membrane oxygenation (ECMO):* RR 1.48 (95 % CI 0.43 to 5.09); 21 more patients per 1000 (95% CI: 25 less to 176 more patients); ns - ITT analysis *Duration of hospitalisation:* Average difference: 1 day less (95% CI: 3 to 0 less) - ITT analysis *Development of respiratory failure or acute respiratory distress syndrome (ARDS):* RR 0.56 (95% CI 0.32 to 0.99); 120 less patients per 1000 (95% CI: 185 to 3 less patients); ns – per protocol analysis *Serious adverse events:* RR 0.62 (0.38 to 1.01); 123 less patients per 1000 (95% CI: 200 less to 3 more patients); ns – per protocol analysis *Total adverse effects:* Gastrointestinal adverse events including nausea, vomiting, and diarrhoea were more common in lopinavir–ritonavir group than in the standard-care group. *Viral loads:* No difference between groups.	• The trial included was a small single center open-label study (Cao, 2020). • This cohort of severely ill patients with advanced disease started treatment very late, this may have blunted benefit and meaningful differences if any. • *Risk of bias concerns with selection of reported results:* Multiple primary outcomes specified in the registry that could be considered definitions of "time to clinical improvement" is unclear (multiple definitions possible). Neither the protocol nor the statistical analysis plan were reported. Risk assessed to be "some concerns" for the outcomes: Time to clinical improvement. Mortality. Length of ICU stay. Length of stay hosp. Adverse and serious adverse events. • *Overall judgement with regards to risk:* Moderate. See breakdown below. **Risk** / **Domain** Random sequence generation (selection bias) Allocation concealment (selection bias) Blinding of participants and personnel (performance bias) Blinding of outcome assessment (detection bias) (clinical improvement) Blinding of outcome assessment (detection bias) (viral titres) Incomplete outcome data (attrition bias) Selective outcome reporting (reporting bias) **Key:** High risk Moderate risk Low risk
Yueping Li et al (preprint under peer-review)(13)	Randomised Controlled Trial (single-centre in China)	Adult patients hospitalised with (mild to moderate) COVID-19 (n=44) *mild:* mild clinical symptoms but no signs of pneumonia on imaging;	LPV (400/100mg BID); n=21 *vs* Umifenovir (200mg TID); n=16 *vs* No antivirals (control); n=7	**Primary outcome:** • *Time to negative SARS-CoV2 PCR on nasopharyngeal swab in days – mean (SD), iTT analysis:* LPV: 9.0 (5.0); 95% CI 7.2 to 10.8 *vs* Umifenovir: 9.1 (4.4); 95% CI 7.6 to 10.2 *vs* Control: 9.3 (5.2); 95% CI 6.7 to 11.9	• This study is not peer reviewed. This was an inadequately powered single center small study with no placebo group. The main outcome was a non-clinical endpoint and it is unclear how this would relate to clinical improvement. • *Risk of bias concerns with selection of reported results:* In the clinical trial registry there are multiple dates of

		moderate: fever, respiratory symptoms and pneumonia on imaging. Severity: Mild: n=4 / Moderate: n=40/ Severe: n=0 Mean age of 49.4 years (SD 14.9, range 27-79), 21 men and 23 women.	Standard care (control) - all three groups were treated with supportive care and effective oxygen therapy as needed. Treatment administered for 7 to 14 days	**Secondary outcomes:** • *Conversion rate from moderate to severe/critical clinical status (%):* LPV: 8/34(23.5%) *vs* Umifenovir: 3/35(8.6%) *vs* Control: 2/17(11.8%); p= 0.206 • *At 14 days after initiating treatment: Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%):* LPV/r: 29/34(85.3%) *vs* Umifenovir: 32/35(91.4%) *vs* Control: 13/17(76.5%), p=0.352 (no statistical difference among groups) • *Adverse events:* LPV/r: Overall 12 (35.3% patients experienced adverse events - diarrhea (9/34, 26.5%), loss of appetite (5/34, 14.7%) and ALT increased 2.5-fold above the normal limit (1/21, 4.8%); SAE in a 79-year-old man with comorbid diabetes and hypertension – severe diarrhea on day 3 and withdrew from study. Umifenovir: Overall 5 (14.3%) patients experienced adverse events - diarrhea (3/35, 8.6%) and nausea (2/34, 5.9%). Control: No adverse events occurred in the control group.	measurement for the primary outcomes, whilst in the report only day 21 results are reported; and neither protocol nor statistical analysis plan was reported. • *Overall judgement with regards to risk:* Low to moderate. See breakdown below.  **Key:** High risk Moderate risk Low risk

Risk	Domain
	Random sequence generation (selection bias)
	Allocation concealment (selection bias)
	Blinding of participants and personnel (performance bias)
	Blinding of outcome assessment (detection bias) (clinical improvement)
	Blinding of outcome assessment (detection bias) (viral titres)
	Incomplete outcome data (attrition bias)
	Selective outcome reporting (reporting bias)

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Appendix 1: Search strategy

Adapted from a published search strategy in Epistemonikos. This was modified for PubMed.

Epistemonikos and PubMed

((coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome")) AND ((lopinavir* OR "ABT-378" OR "ABT 378" OR ABT378)) AND ((ritonavir* OR Norvir)).

Appendix 2: Clinical trials evaluating LPV/r for COVID-19 treatment

There are currently at least 22 trials investigating the use of LPV/r in treating COVID-19 (2 have recently been completed, but results are not available as yet).
See appendix 2 downloaded on 24 April 2020, from https://clinicaltrials.gov/