Lopinavir-Ritonavir (LPV/r) for treament of COVID-19: evidence Review of clinical benefits

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: 21 December 2020 ***(second update of the initial 22 April 2020 rapid review report)***

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 (22 April 2020. Updated 18 December 2020).
- From the available studies (4 RCTs; n=8050, lopinavir-ritonavir as part of the treatment of COVID-19 does not result in clinical benefit, reduce mortality or decrease the 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.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
Type of recommendation	X				

Recommendation: The NEMLC COVID-19 sub-committee recommends against the use of lopinavir-ritonavir for the management of mild to critical COVID-19.
Rationale: RCT evidence indicates that lopinavir-ritonavir is no more effective than standard care in treating patients with COVID-19.
Level of Evidence: I RCT (high certainty evidence)
Review indicator: New high quality evidence of a clinically relevant benefit

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 (1). 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.

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

METHODS

We conducted an initial rapid review of the evidence including systematic searching on two electronic databases (Epistemonikos and PubMed). The search strategy is shown in Appendix 1. 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.

An updated search was undertaken on the 18 December 2020 of two trials registers (ST, TL) for planned and ongoing trials, www.clinicaltrials.gov and the COVID-19 specific register of studies and guidelines, www.covid-nma.com 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: In the updated search on 18 December 2020, 42 records of systematic reviews and RCTs were identified. The living systematic review of COVID-19 studies from the https://covid-nma.com/the-project/ (updated 20 November 2020) included four RCTs (Cao 2020 ,Yueping Li 2020, Pan 2020 and Horby 2020) (11–14) and compared LPV/r with standard of care (SoC) and supersedes all other reviews of RCTs. In clinicaltrials.gov we identified 51 ongoing trials.

Included studies: Two trials (Cao 2020 and Yueping Li 2020) were conducted in China. Pan 2020 was conducted in 30 countries and Horby 2020 conducted in the UK. 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). In Horby 2020, 74% of participants were classified as having moderate/severe disease at study entry (about 62% in Pan 2020). Neither trial enrolled pregnant women and Horby 2020 removed age restriction during the trial. 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, Pan 2020 additionally had remdesivir, hydroxychloroquine and interferon arms. Details on risk of bias are available in Table 1.

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).

The Recovery trial reported 374 (23%) patients in the LPV/r and 767 (22%) patients in the usual care arms died within 28 days (rate ratio 1·03, 95% CI 0·91–1·17; p=0·60). Results were consistent across all prespecified subgroups of patients. For patients not on invasive mechanical ventilation at study entry, proportions reaching the composite endpoint of invasive mechanical ventilation or death were similar (risk ratio 1·09, 95% CI 0·99–1·20; p=0·092). There was no significant difference in time until discharge alive from hospital or the proportion of patients discharged from hospital alive within 28 days among the LPV/r and usual care arms. Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion who met the composite endpoint of invasive mechanical ventilation or death (risk ratio 1·09, 95% CI 0·99–1·20). Occurrence of specific adverse events like renal dialysis or haemofiltration or occurrence of new cardiac arrythmias was similar across the two arms.

In the WHO Solidarity trial, LPV/r did not reduce mortality, overall or in any subgroup, compared to control (rate ratio 1.00; 95% CI 0.79 - 1.25). Remdesivir (rate ratio 0.95; 0.81 – 1.11), hydroxychloroquine (rate ratio 1.19; 95%CI 0.89 – 1.59) and interferon regimes (rate ratio 1.16; 95%CI 0.96 – 1.39) also had little or no effect in reducing mortality of these hospitalized patients with COVID-19. Similar lack of effect for all drugs was reported for reduced initiation of ventilation or hospitalization duration.

Effects of the intervention:
Table 2 summarizing these findings is extracted from a living systematic review of COVID-19 studies from the https://covid-nma.com/the-project/ date: 21 December 2020).

Table 2 Summary of findings - Lopinavir + Ritonavir compared to Standard Care for Mild/Moderate/Severe COVID-19

Outcomes	Anticipated absolute effects (95%): Risk with SoC	Anticipated absolute effects (95%) – Risk with LPV/r	Relative Ratio (95%CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
Viral negative conversion D7	341 per 1,000	334 per 1,000 (222 to 505)	RR 0.98 (0.65 to 1.48)	181 (2 RCTs)	⊕◯◯◯ VERY LOW
Clinical improvement D7	20 per 1,000	61 per 1,000 (13 to 293)	RR 3.03 (0.63 to 14.65)	199 (1 RCT)	⊕◯◯◯ VERY LOW
Clinical improvement D14-D28	697 per 1,000	718 per 1,000 (641 to 802)	RR 1.03 (0.92 to 1.15)	5228 (2 RCTs)	⊕⊕◯◯ LOW
WHO progression score (level 6 or above) D7	291 per 1,000	250 per 1,000 (154 to 401)	RR 0.86 (0.53 to 1.38)	250 (2 RCTs)	⊕◯◯◯ VERY LOW
WHO progression score (level 7 or above) D7	94 per 1,000	101 per 1,000 (47 to 216)	RR 1.07 (0.50 to 2.30)	250 (2 RCTs)	⊕◯◯◯ VERY LOW
All-cause mortality D7	60 per 1,000	43 per 1,000 (14 to 132)	RR 0.72 (0.24 to 2.20)	250 (2 RCTs)	⊕◯◯◯ VERY LOW
All-cause mortality D14-28	191 per 1,000	195 per 1,000 (176 to 214)	RR 1.02 (0.92 to 1.12)	8050 (4 RCTs)	⊕ ⊕⊕⊕ HIGH
Adverse events D14-D28	419 per 1,000	1000 per 1,000 (88 to 1,000)	RR 2.39 (0.21 to 27.57)	250 (2 RCTs)	⊕◯◯◯ VERY LOW
Serious adverse events D14-D28	274 per 1,000	167 per 1,000 (104 to 274)	RR 0.61 (0.38 to 1.00)	250 (2 RCTs)	⊕⊕◯◯ LOW

- *Mortality day 14-28:* There is no difference to mortality with LPV/R compared to standard of care in patients with mild/ severe COVID-19 (RR 1.02 (95% CI 0.92 to 1.12), 4 trials, 8050 patients, high certainty evidence)
- *Duration of hospitalisation:* this outcome was not reported
- *Progression to hospitalisation:* this outcome was not reported
- *Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis:* There is uncertainty about the effect of LPV/r compared to standard of care for viral negative conversion at day 7 – (RR 0.98 (95% CI 0.65 to 1.48), 2 trials, 181 patients, very low certainty evidence).
- *Time to negative SARS-CoV2 PCR on nasopharyngeal swab:* this outcome was not reported
- *Duration of ICU stay:* this outcome was not reported
- *Duration of mechanical ventilation:* this outcome was not reported
- *Adverse events day 14-28:* There may be an increase in adverse events when LPV/r is used compared to standard of care – (RR 2.39; 95% CI 0.21 to 27.57), 2 trials, 250 patients, very low certainty evidence).
- *Serious adverse events:* There may be a slight decrease in serious adverse events when LPV/r is used compared to standard of care (RR 0.61;95% CI 0.38 to 1.00), 2 trials, 250 patients, low certainty evidence)

CONCLUSION

Adding LPV/r to treatment for COVID-19 patients has little effect on mortality at day 14-28 and probably makes little or no difference to clinical improvement at day 14. The effect of LPV/r on other outcomes such as WHO progression score 6 or 7 or above at day 7 is uncertain. Considering the balance of benefits and harms, there is no added benefit and lopinavir/ ritonavir are not recommended for use in ambulant or hospitalised patients with COVID-19.

Currently there are at least 51 registered RCTs evaluating LPV/r in COVID-19 treatment (alone or with other antivirals, antibacterials or interferons) – see appendix 2. This review will continue to be updated as more relevant studies are completed and published.

Reviewer: 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: Tamara Kredo: Cochrane South Africa, South African Medical Research Council).
Additional reviewers: Trudy Leong: National Department of Health, Affordable Medicines – Essential Drugs Programme, South Africa; Karen Cohen: Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town.

Declaration of interests: ST, TK, TL and KC 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)(14)	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; *moderate:* fever,	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 **Secondary outcomes:**	• 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 measurement for the primary outcomes, whilst in the

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<td>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.</td>
<td>Standard care (control) - all three groups were treated with supportive care and effective oxygen therapy as needed.

Treatment administered for 7 to 14 days</td>
<td>• <u>Conversion rate from moderate to severe/critical clinical status (%):</u>
LPV: 8/34(23.5%) vs
Umifenovir: 3/35(8.6%) vs
Control: 2/17(11.8%); p= 0.206

• <u>At 14 days after initiating treatment: Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%):</u>
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)

• <u>Adverse events:</u>
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.</td>
<td>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.
<table><tr><th>Risk</th><th>Domain</th></tr><tr><td></td><td>Random sequence generation (selection bias)</td></tr><tr><td></td><td>Allocation concealment (selection bias)</td></tr><tr><td></td><td>Blinding of participants and personnel (performance bias)</td></tr><tr><td></td><td>Blinding of outcome assessment (detection bias) (clinical improvement)</td></tr><tr><td></td><td>Blinding of outcome assessment (detection bias) (viral titres)</td></tr><tr><td></td><td>Incomplete outcome data (attrition bias)</td></tr><tr><td></td><td>Selective outcome reporting (reporting bias)</td></tr></table>Key:
High risk Moderate risk Low risk</td>
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<td>Pan H et al, NEJM 2020(11)</td>
<td>Randomised Controlled Trial (multicenter study with 405 hospital sites in 30 countries)</td>
<td>Age ≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician’s view, with no contra-indication to any study drug.

n=2791
Mean age: not reported
1653 males</td>
<td>LPV/r, 800/200 mg daily, (n=1411)
vs
placebo (n=1380);
for 14 days

Co-Intervention:
Standard care (SoC)

Duration: 14 days</td>
<td>All-cause mortality D14-28 (LPV/r vs SoC):
• 148/1399 (10.58%) vs 146/1372 (10.64%); RR 0.99, 95% CI 0.80 to 1.23; ARR 0.06% (95% CI -2.23% to 2.36%)</td>
<td>• Interim WHO Solidarity Trial Results for the LPV/r treatment arm published in peer-review format
• ITT analysis
• Overall judgement with regards to risk: Low. See breakdown below.
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		Severity varied from mild to critical, but most were diagnosed with mild COVID-19 at study entry (n=1067)			<table><tr><td></td><td>Incomplete outcome data (attrition bias)</td></tr><tr><td></td><td>Selective outcome reporting (reporting bias)</td></tr></table> **Key:** High risk Moderate risk Low risk
Horby P et al, Lancet 2020(12)	Randomised Controlled, Open-label, Platform Trial (multicenter study with 176 hospital sites in the United Kingdom)	In-hospital patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection, no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. Aged ≥18 years initially but from May 9, 2020, this age limit was removed. n=5040 Mean age: 66.3 3077 males Severity varied from mild to critical, mild (n=1321)	LPV/r, 400/100 mg 12 hourly, (n=1616) vs SoC (n=3424); Duration: 10 days or until discharge	**All-cause mortality D28 (LPV/r vs SOC):** • 374 (23%) vs 767 (22%); RR 1.03, 95% CI 0.91 to 1.17.	• Recovery Trial Results for the LPV/r treatment arm published in peer-review format • ITT analysis • *Overall judgement with regards to risk:* Low. See breakdown below. <table><tr><th>Risk</th><th>Domain</th></tr><tr><td></td><td>Random sequence generation (selection bias)</td></tr><tr><td></td><td>Allocation concealment (selection bias)</td></tr><tr><td></td><td>Blinding of participants and personnel (performance bias)</td></tr><tr><td></td><td>Blinding of outcome assessment (detection bias) (clinical improvement)</td></tr><tr><td></td><td>Blinding of outcome assessment (detection bias) (viral titres)</td></tr><tr><td></td><td>Incomplete outcome data (attrition bias)</td></tr><tr><td></td><td>Selective outcome reporting (reporting bias)</td></tr></table> **Key:** High risk Moderate risk Low risk

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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)).
Cochrane living syntheses https://covid-nma.com/

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

There are currently at least 51 trials investigating the use of LPV/r in treating COVID-19, https://clinicaltrials.gov

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [X] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	High certainty evidence shows no mortality benefit associated with LPV/r for the treatment of COVID-19.
EVIDENCE OF BENEFIT	**What is the size of the overall effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [X] Uncertain [ ]	All-cause mortality D14-28 for LPV/r vs SoC: 191 per 1,000 vs 195 per 1,000; RR 1.02 (95% CI 0.92 to 1.12); n=8050; 4 RCTs
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	There may be a slight decrease in serious adverse events when LPV/r is used compared to SoC: RR 0.61;95% CI 0.38 to 1.00; 2 RCTs, n=250, low certainty evidence.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [x]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	LPV/r is SAHPRA registered and is readily available as second-line antiretroviral therapy in adults.

<table>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?
More intensive: X
Less intensive:
Uncertain:</td>
<td>Price of medicines/ treatment course :
<table>
<tr><th>Medicine</th><th>Tender Price (R)*</th><th>Single Exit Price (R)*</th></tr>
<tr><td>LPV/r 400/100 mg 12 hourly for 7 days</td><td>R66.75</td><td>R84.37</td></tr>
<tr><td>LPV/r 400/100 mg 12 hourly for 14 days</td><td>R133.49</td><td>R168.75</td></tr>
</table>
*Contract circular RT71-2019ARV: LPV/r 200/50mg, 112 tablets = R266.98
** SEP database. Accessed March 2020. https://medicineprices.org.za/ : LPV/r 200/50 mg, 112 tablets = R337.49</td>
</tr>
<tr>
<td>VALUES, PREFERENCES, ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor:
Major:
Uncertain: X

Is the intervention acceptable to key stakeholders?
Yes:
No:
Uncertain: X</td>
<td>There is no local survey data to determine stakeholder acceptability. However, the Subcommittee was of the opinion that clinicians</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?
Yes:
No: X
Uncertain:</td>
<td></td>
</tr>
</table>

Appendix 3: Updating of a rapid report

Date	Signal	Rationale
9 December 2020	New efficacy signal	The initial rapid review concluded that there was insufficient evidence to inform the initial recommendation. The WHO SOLIDARITY RCT results have recently been published in the NEJM.

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
First	22 April 2020	ST, TL, TK, KC	There is currently insufficient evidence to support routine use of lopinavir-ritonavir for COVID-19; may be used in a clinical trial setting.
Second	24 November 2020	n/a	Statement advising that rapid review will be updated when the results from the WHO SOLIDARITY trial are available in peer review format.
Third	21 December 2020	ST, TL, TK	WHO SOLIDARITY RCT results have recently been published in the NEJM and thus, included in the evidence synthesis. EtD framework added to guide strength of recommendation. Recommendation amended to strong.