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Commentary

SARS-CoV-2 and HIV protease inhibitors: why lopinavir/ritonavir will not work for COVID-19 infection

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Summary

Since the beginning of the outbreak of severe acute respiratory syndrome (SARS) coronavirus (CoV) 2 lopinavir/ritonavir was selected for treatment. The recent publication of Cao et al in the NEJM[1] showed that lopinavir/ritonavir treatment did not accelerate clinical improvement compared with standard of care. This raised the question if we in retrospect could have known this. The aim of this paper is to gather all the available evidence and to comprehensively discuss this issue.

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Running head: SARS-CoV-2 and HIV protease inhibitors

In December 2019, the first reports of severe acute respiratory syndrome (SARS) coronavirus (CoV) 2 infections were described. Since then, the virus rapidly expanded the world, achieving pandemic status in March 2020.

From the beginning of the outbreak various antiviral treatment regimens have been identified for the treatment of SARS-CoV-2 infection; including antiviral agents (remdesivir, favipiravir), immunomodulating agents (interferons, tocilizumab), and a combination of both (ribavirin and chloroquine). These drugs were selected based on in vitro and in vivo research performed in the field of SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV, which caused coronavirus outbreaks in Asia (2003) and Middle-East region/South-Korea (2012), respectively. Not without rational, HIV protease inhibitors (PIs) that prevent HIV viral replication by binding to its proteases, such as lopinavir, were initially suggested as antiviral agents against SARS-CoV-2.

The clinical use of lopinavir/ritonavir was quickly adapted for corona virus disease 2019 (COVID-19) treatment when the virus arrived in the Netherlands late February 2020. Lopinavir is the active PI which is pharmacokinetically enhanced by its co-formulated ritonavir [2]. In the scientific community also other HIV protease inhibitors such as atazanavir and darunavir were suggested as possible candidates for COVID-19 treatment. As all PIs inhibit HIV viral replication, why wouldn’t they also inhibit SARS-CoV-2 replication? This hypothesis was revisited with the publication of Cao et al in the New England Journal of Medicine of March 18 2020 [1]. This randomized controlled open-label
trial showed that lopinavir/ritonavir treatment does not significantly accelerate clinical improvement (16 vs 16 days), reduce mortality (19.2 vs 25%), or diminish throat viral RNA detectability (day 28 60.3 vs 58.6%) in patients with serious COVID-19 compared with standard of care [1]. The authors acknowledged that the study suffered from limitations, but results were a signal that lopinavir/ritonavir was not beneficial for COVID-19 treatment [1]. Lopinavir/ritonavir is still used for COVID-19 treatment, but in the Netherlands, the publication of Cao et al. (2020) (5) caused lopinavir/ritonavir to be removed from the national treatment guidelines.

In retrospect, the question has been raised, why does lopinavir/ritonavir not work for the treatment of COVID-19 disease and could we have known this upfront?

We extensively searched PubMed, web-based search engines (Google, Google Scholar), and preprint servers (www.medRxiv.org; www.bioRxiv.org) for publications on the use of HIV PIs for SARS-CoV, MERS-CoV, and SARS-CoV-2 treatment. We searched for all relevant publications up to May 8, 2020 by snowballing.

Data for SARS-CoV, MERS-CoV and SARS-CoV-2 are summarized in Additional table 1, and could be categorized in in silico (n=2 vs n=0 vs n=1), in vitro (n=4 vs n=3 vs n=3), and in vivo (n=1 vs n=1 vs n=8) evidence. In vitro evidence of lopinavir’s activity against SARS-CoV is contradictory. Yamamoto et al. (2004) found that lopinavir did not affect SARS-CoV replication, as measured by a reduction in cell viability [3]. Other researchers reported in vitro half maximum effective concentrations (EC50) for antiviral activity against SARS-CoV varying from 4.0 to 10.74 mg/L [4–6]. Chu et al. (2004) found that the EC50 could be further reduced from 4 mg/L to 1 mg/L when lopinavir was combined with ribavirin, suggesting a synergistic effect [4]. EC50 values for antiviral activity of lopinavir of 5.03-7.29 mg/L against MERS-CoV have been reported [5,7].

To predict in vivo efficacy of lopinavir against SARS-CoV-2, reported in vitro EC50 values found against SARS-CoV and MERS [4–7] were compared with clinical total and (predicted) unbound maximal and minimal plasma concentrations (C max and C min) reported in HIV-infected patients. C max and C min after intake of 400/100mg lopinavir/ritonavir twice daily in HIV patients are 9.8 and 5.5 mg/L with a protein binding of 98-99% [2]. In this same dose, lopinavir has an intracellular/plasma concentration ratio of 1.18 in peripheral blood mononuclear cells (PBMCs), not supporting a large difference between tissue and plasma concentrations [8].

Important is that HIV patients are, in general, relatively healthy individuals who may not be comparable with critically ill COVID-19 patients admitted to the intensive care units. These pathophysiological changes may also significantly influence pharmacokinetics.

Data initially available for the use of lopinavir against SARS-CoV-2 were mainly based on in vitro activity against SARS-CoV and MERS-CoV and were used to predict in vivo efficacy retrospectively. At the moment of writing this paper, in vitro SARS-CoV-2 data became available for lopinavir (EC50 3.6 mg/L) [9] even as pharmacokinetic data of eight COVID-19 patients treated with 400/100mg lopinavir twice daily. The median C min was 13.6 mg/L with a range from 6.2 to 23.4 mg/L which is an ~2-fold increase compared with HIV patients [10]. (Additional table 2).
Translation of such an *in vitro* parameter to clinical practice should be made cautiously considering its limited protein binding compared to plasma pharmacokinetic parameters (C<sub>max</sub> and C<sub>min</sub>). Most clinical studies report total concentrations (bound + unbound), while *in vitro* only a relatively small amount of protein is present, i.e. cell culture medium is supplemented with diluted (5-10%) animal serum. The unbound fraction of a drug is pharmacologically active, and therefore the comparison between EC<sub>50</sub> values and unbound plasma concentrations is probably more appropriate. These values reported for lopinavir against the coronaviruses are in the same concentration range as the total C<sub>max</sub>. This most likely means that *in vivo* free lopinavir plasma concentrations are too low for effective reduction of viral replication. In line with this, the PI darunavir had an EC<sub>50</sub> of ~55-165mg/L reported, largely exceeding darunavir intracellular and plasma concentrations, meaning that darunavir is not a suitable candidate for COVID-19 therapy.

Comparisons between EC<sub>50</sub> and C<sub>max</sub> were made to make assumptions about the pharmacokinetic-pharmacodynamic (PK-PD) relationship between lopinavir concentrations and SARS-CoV-2 viral load reductions. Important for the interpretation of the PK-PD relationship is that the EC<sub>50</sub> represents the concentration where *in vitro* 50% reduction of viral replication is achieved. Preferably the C<sub>max</sub> is higher than the EC<sub>50</sub>, and actually an EC<sub>90</sub> would be preferred. However, EC<sub>90</sub> values are more difficult to assess and are often not reported.

In general, when pharmaceutical companies develop antiviral drugs they aim for plasma concentrations greatly exceeding the IC<sub>90</sub> and the FDA states that a “high” inhibitory quotient (C<sub>min</sub>/EC<sub>50</sub>) indicates effective compound concentrations with minimal risk to resistance [11]. Also is stated for HIV antiretroviral drug development that dosages chosen for phase 2 trials should exceed, by several-fold, the protein binding adjusted EC<sub>50</sub> [12]. Exceeding IC<sub>90</sub> is needed to accomplish a clinically relevant viral load reduction (meaning undetectable). When comparing with HIV, the C<sub>min</sub> (5.5 mg/L) of lopinavir exceeded >75-fold the IC<sub>50</sub> (0.007 mg/L) of lopinavir for wildtype HIV resulting in undetectable HIV viral load. From a previous study in HIV infected patients it is known that lopinavir/ritonavir activity is highest when IC<sub>50</sub> values of HIV isolates were <10-fold increased compared with the wildtype; with increasing isolate IC<sub>50</sub> values the susceptibly to lopinavir decreased [13]. Based on these data it seemed unrealistic to expect any antiviral efficacy of lopinavir/ritonavir against SARS-CoV-2 as the EC<sub>50</sub> of lopinavir against SARS-CoV and MERS-CoV were approximately 4 to 10 mg/L and 5 to 7 mg/L, respectively, which is in the same concentration range as observed lopinavir C<sub>min</sub> concentrations. In addition, we also know from HIV therapy that the C<sub>min</sub> of lopinavir is an important predictor of efficacy and that the inhibitory quotient should be at least >15 [14]. This quotient takes, among others, resistance and drug distribution into cells into account. In this context, a C<sub>min</sub>/EC<sub>50</sub> ratio for lopinavir and SARS-CoV-2 of 3.8 is most likely insufficient. Such an extrapolation from the field of HIV seems warranted considering the comparable mechanism; inhibiting the viral protease instead of ‘killing’ an organism.

Of note, both plasma and intracellular (PBMC) concentrations are surrogate markers for tissue concentrations. At the moment it is unknown if and how lopinavir distributes to the site of infection, i.e. the lung in critically ill COVID-19 patients.
An important clinical consideration is the interpretation of the findings by Cao et al. (2020), is that patients were treated with monotherapy lopinavir/ritonavir [1], while other published studies in COVID-19 all used combination therapy (Additional table 1). This could be an interesting approach to evaluate for SARS-CoV-2 treatment, as combining lopinavir/ritonavir with other agents might cause a synergistic effect, which was also suggested in an in vitro study combining lopinavir with ribavirin [4].

Overall it seems that at least lopinavir/ritonavir as monotherapy would not be effective for COVID-19 treatment. Nonetheless, results of more trials remain highly anticipated, and >30 studies with lopinavir/ritonavir (and other antivirals) in COVID-19 are registered on ClinicalTrials.gov.

Author’s Contributions
ES literature search, manuscript preparation, interpretation of data; LtB interpretation of data and critically revising the paper for intellectual content; AW interpretation of data, critically revising the paper for intellectual content and final approval of the paper.

Conflict of interest and financial support
ES, DB, LtB: nothing to declare. No financial support was received for the preparation of this manuscript.

References


**Supplementary Material:**


Additional table 2: Overview of *in vivo* pharmacokinetic parameters in HIV-infected patients compared to *in vitro* antiviral activity against SARS-CoV-2.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Drugs</th>
<th>Results</th>
<th>EC$_{50}$ to mg/L</th>
<th>References</th>
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</thead>
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<tr>
<td><strong>SARS-CoV</strong></td>
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<tr>
<td><em>In silico</em></td>
<td></td>
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</tr>
<tr>
<td>Molecular dynamics simulations</td>
<td>Commercially available compounds</td>
<td>Both lopinavir and ritonavir were found to bind to the active site of SARS-CoV with similar binding affinities.</td>
<td>N/A</td>
<td>[1]</td>
</tr>
<tr>
<td>Molecular dynamics simulations</td>
<td>Commercially available compounds</td>
<td>Lopinavir, ritonavir, niclosamide and promazine show signs of inhibiting the replication</td>
<td>N/A</td>
<td>[2]</td>
</tr>
<tr>
<td><strong>In vitro</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CPE assay in Vero E6 cells Screening different drugs</td>
<td>LPV RTV Nelfinavir Saquinavir Indinavir</td>
<td>Inhibition CPE of SARS-CoV by nelfinavir EC$<em>{50}$: 0.048 µM; CC$</em>{50}$: 14.5 µM; SI: 302.1</td>
<td>Nelfinavir: 0.027 mg/L</td>
<td>[3]</td>
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<tr>
<td></td>
<td></td>
<td>No inhibition CPE of SARS-CoV of the other compounds (CC$_{50}$)</td>
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<tr>
<td></td>
<td></td>
<td>LPV 21.15 µM; RTV 13.8 µM; saquinavir 31.4 µM; indinavir 9.63 µM</td>
<td></td>
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</tr>
<tr>
<td>SARS isolates of patients used in fRhK-4 cell line and Vero E6 cells. Plague reduction in Vero cell line. Screening of several drugs + Chinese medicine.</td>
<td>LPV</td>
<td>Plague reduction assay EC$_{50}$: LPV 6 µg/mL RBV 50 µg/mL</td>
<td>LPV: 6 mg/L RBV: 50 mg/L</td>
<td>[4]</td>
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<tr>
<td></td>
<td></td>
<td>No inhibitory activity: RTV</td>
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<tr>
<td>HKU-39849 isolate used for in vitro testing.</td>
<td>LPV RBV</td>
<td>Cytopathic effect LPV 4 µg/mL RBV 50 µg/mL LPV + RBV: 1 µg/mL and 6.25 µg/mL, respectively.</td>
<td>Cytopathic effect: LPV: 4 mg/L RBV: 50 mg/L LPV + RBV: 1 mg/L and 6.35 mg/L</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Screening FDA drug library</strong>&lt;br&gt;<strong>CPE assay Vero, Vero E6, Huh7 cells</strong></td>
<td><strong>LPV</strong></td>
<td><strong>LPV has activity against SARS-CoV and HCoV-229E-GFP</strong>&lt;br&gt;LPV:&lt;br&gt;SARS-CoV&lt;br&gt;EC$<em>{50}$: 17.1 µM; CC$</em>{50}$ &gt;32 µM; SI &gt;2&lt;br&gt;HCoV-229-GFP&lt;br&gt;EC$<em>{50}$: 6.6 µM; CC$</em>{50}$ 37.6 µM; SI 5.7</td>
<td><strong>SARS: 10.75 mg/L</strong>&lt;br&gt;HCoV-229-GFP: 4.15 mg/L</td>
<td>[6]</td>
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<tr>
<td><strong>in vivo</strong></td>
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<tr>
<td><strong>Test versus historical controls treated with RBV</strong></td>
<td>400/100mg LPV/r + loading dose 4000mg followed by 1200mg RBV (n=41) RBV monotherapy (n=111) 2 weeks of treatment</td>
<td>Test vs control at 21 day:&lt;br&gt;ARDS + Death: 2.4 versus 28.8%&lt;br&gt;Age, hepatitis B carrier status, and lack of treatment with antiviral combination were independent predictors of an adverse outcome</td>
<td>N/A</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>MERS-CoV</strong></td>
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<tr>
<td><strong>In vitro</strong></td>
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</tr>
<tr>
<td><strong>Screening FDA drug library</strong>&lt;br&gt;<strong>CPE assay Vero, Vero E6, Huh7 cells</strong></td>
<td><strong>LPV</strong></td>
<td><strong>LPV has activity against MERS-CoV</strong>&lt;br&gt;LPV:&lt;br&gt;MERS EC$<em>{50}$ 8.0 µM; CC$</em>{50}$ 24.4 µM; SI 31</td>
<td>5.03 mg/L</td>
<td>[6]</td>
</tr>
<tr>
<td><strong>CPE assay in calu-3 hµMan lung cell line</strong>&lt;br&gt;Transgenic mouse model of MERS-CoV</td>
<td><strong>LPV/r + IFNb</strong>&lt;br&gt;Remdesivir + IFNb</td>
<td>Remdesivir and IFNb have superior antiviral activity compared with LPV and RTV IFNb activity does not improve when combined with LPV/r LPV EC$<em>{50}$: 11.6 µM; CC$</em>{50}$ &gt;50 µM; SI &gt;4.3&lt;br&gt;RTV EC$<em>{50}$: 24.9 µM; CC$</em>{50}$ &gt;50 µM; SI &gt;2 LPV/r EC$_{50}$: 8.5 µM</td>
<td><strong>LPV: 7.29 mg/L</strong>&lt;br&gt;RTV: 17.95 mg/L&lt;br&gt;LPV/r: 5.34 mg/L</td>
<td>[7]</td>
</tr>
<tr>
<td><strong>In vivo</strong></td>
<td></td>
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<tr>
<td>Study Type</td>
<td>Treatment Details</td>
<td>Description</td>
<td>Kd</td>
<td>Source</td>
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<tr>
<td>Primate model with severe MERS</td>
<td>LPV/r MMF Interferon-beta 1b</td>
<td>LPV/r and interferon group improved clinical, pathological and radiological scores and has lower viral loads compared with untreated and MMF group</td>
<td>N/A</td>
<td>[8]</td>
</tr>
<tr>
<td>Case report</td>
<td>400/100mg LPV/r BID 2000mg loading + 1200mg TID RBV 180µg pegIFN-alfa 2a Strat ay 4 of admission</td>
<td>No fever from day 7 onwards</td>
<td>N/A</td>
<td>[9]</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td></td>
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<tr>
<td>In silico</td>
<td></td>
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<tr>
<td>Molecule transformer-drug target interaction</td>
<td>Commercially available compounds</td>
<td>Kd: ATV: 94.94 nM EFV: 199.17 nM RTV: 204.05nM DTG: 336.91 nM</td>
<td>N/A</td>
<td>[10]</td>
</tr>
<tr>
<td>In vitro</td>
<td></td>
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</tr>
</tbody>
</table>
| VeroE6 cell line | Nelfinavir inhibits SARS-CoV-2 replication  
|                  | EC$_{50}$ 1.13 µM  
|                  | EC$_{90}$ 1.173 µM  
| Amprenavir EC$_{50}$: 31.32 µM; CC$_{50}$ >81 µM; SI > 2.59  
| Darunavir EC$_{50}$: 46.41 µM; CC$_{50}$ >81 µM; SI >1.75  
| Indinavir EC$_{50}$: 59.14 µM; CC$_{50}$ >81 µM; SI >1.37  
| Tipranavir EC$_{50}$: 13.34 µM; CC$_{50}$ 76.80 µM; SI: 5.76  
| Ritonavir EC$_{50}$: 8.63 µM; CC$_{50}$ 74.11 µM; SI 8.59  
| Saquinavir EC$_{50}$: 8.83 µM; CC$_{50}$ 44.43 µM; SI 5.03  
| Atazanavir EC$_{50}$: 9.36 µM; CC$_{50}$ >81 µM; SI >8.65  
| Lopinavir EC$_{50}$: 5.73 µM; CC$_{50}$ 74.44 µM; SI 12.99  
| **Nelfinavir**  
| **Amprenavir**  
| **Indinavir**  
| **Tipranavir**  
| **Ritonavir**  
| **Saquinavir**  
| **Atazanavir**  
| **Lopinavir**  
| **Communication unpublished data** | DRV/r  
| DRV: Viral inhibition 300 µM  
| Mean C$_{\text{in vivo}}$ 3.8µM in dose 800/100mg QD  
| Limited structural interactions SARS-CoV-2 and DRV  
| Viral inhibition DRV: 164.31 mg/L  
| **SARS-CoV-2 isolate in Caco-2 cell line** | DRV/c  
| Remdesivir | DRV EC$_{50}$ >100µM  
| Remdesivir EC$_{50}$: 0.38 µM; SI >260  
| DRV: 54.77 mg/L  
| **In vivo** |  
| **Case report (n=1)** | 400/100mg LPV/r BID start on day 10 of illness  
| Viral load decreased from day 11 onwards  
| Could be LPV/r; could be natural course of COVID  
| N/A  
<p>| [10] | [11] | [12] | [13] |</p>
<table>
<thead>
<tr>
<th>Case Report (n=1)</th>
<th>400/100mg LPV/r BID start on day 4 of illness</th>
<th>Fever subsided on day 11 of illness Improvement dyspnea day 14 of illness</th>
<th>N/A</th>
<th>[14]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series</td>
<td>2 severe COVID-19 cases</td>
<td>2 patients discharged 1 patient clinical improvement 1 patient signs of improvement</td>
<td>N/A</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td>2 mild COVID-19 cases</td>
<td></td>
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<tr>
<td></td>
<td>LPV/r 400/100 BID Arbidol 200mg TID Shufeng Jiedu Capsule 2.08 g TID 6-15 days Symptomatic support</td>
<td></td>
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</tr>
<tr>
<td>Open-label, RCT</td>
<td>SaO2 &lt;94% or PaO2/FiO2 &lt;300mmHg n = 199</td>
<td>Treatment not different from control group Time to clinical improvement 16 vs. 16 days (HR 1.31 95%CI 0.95-1.85) Mortality at day 28: 19.2 vs. 25% Days at ICU: 6 vs. 11 days Days from randomization to discharge: 12 vs 14 days No difference in RNA viral load swab (day 5, 34.5% vs. 32.9%; day10, 50.0% vs. 48.6%; day 14, 55.2% vs. 57.1%; day 21, 58.6% vs. 58.6%; and day 28, 60.3% vs.58.6%) More gastro intestinal adverse events in treatment group (any adverse event 48.4 vs 49%).</td>
<td>N/A</td>
<td>[16]</td>
</tr>
<tr>
<td>Case series (n=10)</td>
<td>Initial therapy: 400/100mg LPV/r BID + 5U interferon-alpha 2b atomization inhalation BID OR LPV/r monotherapy (n=1) Day 3-6 after onset symptoms</td>
<td>Hypokalemia and GI adverse events after start LPV/r 3 discontinued LPV/r due to adverse events 2 deteriorated during LPV/r treatment LPV/r possibly beneficial for COVID-19 patients</td>
<td>N/A</td>
<td>[17]</td>
</tr>
</tbody>
</table>
Only data of HIV protease inhibitors are summarized in this table. Some studies also tested other compounds that are not added to this table.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Treatment Details</th>
<th>Outcome Details</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort study</td>
<td>200mg arbidol TID + 400/100mg LPV/r BID (n=16)</td>
<td>Day 7 nasopharyngeal swab negative 12/16 and 6/17 for combination and monotherapy respectively, and on day 14 15/16 and 9/17.</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>400/100mg LPV/r BID monotherapy (n=17)</td>
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<tr>
<td>Exploratory RCT (ELACOI) Mild/moderate clinical status COVID-19 (n=44)</td>
<td>400/100mg LPV/R BID 7-14 days (n=21)</td>
<td>No differences at baseline Positive to negative conversion: LPV/r: 8.5 days  Arbidol: 7 days  Control: 4 days  No difference in the rate of antipyresis, cough resolution, improvement on chest CT imaging  More adverse events in LPV/r group  More patients treated with LPV/r or arbidol deteriorated to severe/critical COVID-19</td>
<td>N/A</td>
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<td>200mg arbidol 100mg TID 7-14 days (n=16)</td>
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<td>Control (n=7)</td>
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<tr>
<td>Test: LPV/r + adjuvant therapy (n=42)</td>
<td>400/100mg LPV/r BID or 800/200mg LPV QD</td>
<td>Trend that body temperature decreased fasted in treatment group  Positive to negative conversion 7.8 days v 12.0 days (t vs c)</td>
<td>N/A</td>
</tr>
<tr>
<td>Control: adjuvant therapy (n=5)</td>
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<tr>
<td>Adjuvant therapy: interferon aerosol, arbidol, eucalyptol limonene, pinene, moxifloxacin, asmeton + oxygen support</td>
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</tbody>
</table>

Only data of HIV protease inhibitors are summarized in this table. Some studies also tested other compounds that are not added to this table.

/c: cobicistat
/r: ritonavir
BID: twice daily
CC<sub>50</sub>: half cytotoxic concentration
C_{\text{max}}: maximal plasma concentration
C_{\text{min}}: minimal plasma concentration
CoV: coronavirus
COVID-19: Corona virus disease 2019
DRV: darunavir
DTG: dolutegravir
EC_{50}: half maximum effective concentrations
EFV: efavirenz
IFNb: Interferon beta
LPV: lopinavir
MERS: Middle East Respiratory Syndrome
N/A: not applicable
QD: once daily
RBV: Ribavirin
RCT: Randomized controlled trial
SARS: severe acute respiratory syndrome
SI: Selectivity Index
TID: trice daily
Additional table 2: Overview of in vivo pharmacokinetic parameters in HIV-infected patients compared to in vitro antiviral activity against SARS-CoV-2.

<table>
<thead>
<tr>
<th>Protease inhibitor</th>
<th>Total plasma concentrations</th>
<th>Protein binding</th>
<th>Predicted unbound plasma concentrations</th>
<th>Intracellular/Plasma concentration ratio</th>
<th>in vitro EC$_{50}$</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>$C_{\text{min}}$ (mg/L)</td>
<td></td>
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<tr>
<td>400/100 mg lopinavir/ritonavir BID</td>
<td>9.8</td>
<td>5.5</td>
<td>98-99%</td>
<td>0.098-1.196</td>
<td>1.18</td>
<td>SARS-CoV: 4.0-10.74 mg/L (lopinavir + ribavirin: 1 mg/L)</td>
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<td></td>
<td>13.6 (6.2-24.3) mg/L</td>
<td></td>
<td></td>
<td>0.055-11</td>
<td></td>
<td>MERS-CoV: 5.03-7.29 mg/L SARS-CoV-2: 3.6 mg/L</td>
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<tr>
<td>800/100 mg darunavir/ritonavir QD</td>
<td>5.3</td>
<td>1.07</td>
<td>95%</td>
<td>0.266</td>
<td>0.22</td>
<td>SARS-CoV-2: 54.77-164.31 mg/L</td>
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</table>

± peripheral blood mononuclear cells (PBMCs) were used to determine the intracellular accumulation of the antivirals.

*pharmacokinetic parameter obtained intracellular.

BID: twice daily

$C_{\text{max}}$: maximal plasma concentration

$C_{\text{min}}$: minimal plasma concentration

CoV: coronavirus

COVID-19: Corona virus disease 2019

EC$_{50}$: half maximum effective concentrations
MERS: Middle East Respiratory Syndrome
QD: once daily
SARS: severe acute respiratory syndrome
TID: trice daily
References


