

Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19 patients

The Liverpool Drug Interaction Group (based at the University of Liverpool, UK), in collaboration with the University Hospital of Basel (Switzerland) and Radboud UMC (Netherlands) (<http://www.covid19-druginteractions.org/>) is constantly updating a list of interactions for many comedication classes. This table is adapted from their valuable work and includes other drugs.

In light of pharmacological interaction, single cases management is mandatory.

Drugs reported (constantly updated): ATV, atazanavir; DRV/c, darunavir/cobicistat LPV/r, lopinavir/ritonavir; RDV, remdesivir/GS-5734; FAVI, favipiravir; CLQ, chloroquine; HCLQ, hydroxychloroquine; NITA, nitazoxanide; RBV, ribavirin; TCZ, tocilizumab; IFN-β-1a; interferon β-1a; OSV, oseltamivir.

| | ATV | *DRV/c ¹ | *LPV/r | RDV ² | FAVI | CLQ | HCLQ | NITA | RBV | TCZ ³ | IFN-β-1a ⁴ | OSV |
|-----------------|-----|---------------------|--------|------------------|------|-----|------|------|-----|------------------|-----------------------|-----|
| Brivaracetam | ↔ | ↔ | ↓ | ↔ | ↔ | ↑ | ↑ | ↔ | ↑ | ↔ | ↔ | ↔ |
| Carbamazepine | ↓↑ | ↓↑ | ↓↑ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↓ | ↔ | ↔ |
| Cannabidiol | ↔ | ↑ | ↑ | ↔ | ↔ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Cenobamate | ↓ | ↓ | ↓ | ↔ | ↔ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Clonazepam | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Clobazam | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Diazepam | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Eslicarbazepine | ↓♥ | ↓ | ↓♥ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Ethosuximide | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Felbamate | ↓ | ↓ | ↓ | ↔ | ↔ | ♥↓ | ♥↓ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Gabapentin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Lacosamide | ♥↔ | ↑ | ♥↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Lamotrigine | ↔ | ↑ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Levetiracetam | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Lorazepam | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Oxcarbazepine | ↓ | ↓ | ↓ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Perampanel | ↑ | ↓ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Phenytoin | ↓ | ↓ | ↓ | ↓ | ↔ | ↓ | ↓ | ↑ | ↔ | ↓ | ↔ | ↔ |
| Phenobarbital | ↓ | ↓ | ↓ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↓ | ↔ | ↔ |
| Pregabalin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Primidone | ↓ | ↓ | ↓ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↓ | ↔ | ↔ |
| Retigabine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Rufinamide | ↓ | ↓ | ↓ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Sulthiame | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Tiagabine | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Topiramate | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Valproic acid | ↔ | ↓ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Vigabatrin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Zonisamide | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

*Should not be administered without booster drug (ritonavir or cobicistat).

- ↑ Potential increased exposure of the co-medication;
- ↓ Potential decreased exposure of the co-medication;
- ↑↑ Potential increased exposure of COVID drug;
- ↓↓ Potential decreased exposure of COVID drug;
- ↔ No significant effect;
- ♥ One or both drugs may cause QT and/or PR prolongation.

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| | Drugs should not be co-administered. |
| | Potential interaction which may require a dose adjustment or close monitoring. |
| | Potential interaction likely to be of weak intensity. Additional acts/monitoring or dosage adjustment unlikely to be required. |
| | No clinically significant interaction expected. |

¹ Currently, the Johnson & Johnson, holder of Janssen Pharmaceutica owner of the drug **Darunavir**, highlighted the lack of evidence to support use of Darunavir-based treatments for SARS-CoV-2 (<https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus>).

² Some data on drug interactions of **Remdesivir** are not available yet.

³ An increase in IL-6, as well as other cytokines, can improve plasmatic concentration of administered drugs reducing hepatic metabolism (CYP-mediated), a treatment with **Tocilizumab** (anti-IL6R) could reduce plasmatic concentrations of other previous co-treatments due to hepatic metabolism normalization².

⁴ No studies have been performed yet in humans to assess drugs-interactions.

Notes:

- Ritonavir is a strong inhibitor of CYP 3A and 2D6 *per se*, independently to co-administered antiviral.
- Atazanavir can increase **midazolam** plasmatic concentration until 4-fold.
- Also refer to **SmPC** for further information.

1. Aitken, A. E., Richardson, T. A. & Morgan, E. T. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu. Rev. Pharmacol. Toxicol.* **46**, 123–149 (2006).

2. Kim, S., Östör, A. J. K. & Nisar, M. K. Interleukin-6 and cytochrome-P450, reason for concern? *Rheumatology International* **32**, 2601–2604 (2012).