

## antiviral and associated therapy - all results

| Treatment                          | Number of studies       | clinical deterioration                                 | clinical improvement                                                | deaths                                                 | viral clearance                                                     |
|------------------------------------|-------------------------|--------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------|
| chloroquine and derivatives        | 45 studies <sup>1</sup> | 1.04 [0.80 ; 1.35], 6 RCTs, I2=0% inconclusive result  | 1.07 [0.83 ; 1.39], 3 RCTs, I2=0% inconclusive result               | 1.07 [0.97 ; 1.18], 30 RCTs, I2=0% inconclusive result | 0.97 [0.73 ; 1.29], 3 RCTs, I2=0% inconclusive result               |
| ivermectin                         | 21 studies <sup>2</sup> | 0.66 [0.32 ; 1.34], 4 RCTs, I2=69% inconclusive result | 1.67 [1.05 ; 2.66], 3 RCTs, I2=0% moderate degree of certainty      | 0.66 [0.44 ; 1.00], 10 RCTs, I2=0% inconclusive result | 0.93 [0.78 ; 1.10], 2 RCTs, I2=0% inconclusive result               |
| favipiravir                        | 19 studies <sup>3</sup> | -                                                      | 1.65 [1.28 ; 2.13], 5 RCTs, I2=0% moderate degree of certainty      | 1.13 [0.76 ; 1.70], 7 RCTs, I2=0% inconclusive result  | 1.45 [0.98 ; 2.13], 8 RCTs, I2=64% inconclusive result              |
| remdesivir                         | 10 studies <sup>4</sup> | 0.95 [0.55 ; 1.64], 1 RCT, I2=0% inconclusive result   | 1.17 [0.92 ; 1.49], 5 RCTs, I2=71% demonstrated inconclusive result | 0.83 [0.67 ; 1.03], 7 RCTs, I2=15% inconclusive result | -                                                                   |
| hydroxychloroquine plus macrolides | 9 studies <sup>5</sup>  | 0.99 [0.57 ; 1.72], 1 RCT, I2=0% inconclusive result   | 0.81 [0.54 ; 1.22], 1 RCT, I2=0% inconclusive result                | 0.63 [0.20 ; 2.03], 3 RCTs, I2=0% inconclusive result  | -                                                                   |
| azithromycin                       | 8 studies <sup>6</sup>  | 1.07 [0.63 ; 1.82], 1 RCT, I2=0% inconclusive result   | 0.76 [0.56 ; 1.04], 2 RCTs, I2=0% inconclusive result               | 0.99 [0.79 ; 1.26], 5 RCTs, I2=28% inconclusive result | 715.00 [12.94 ; 39513.71], 1 study, I2=0% certainty unassessable    |
| lopinavir/ritonavir                | 8 studies <sup>7</sup>  | 3.69 [0.37 ; 36.57], 1 RCT, I2=0% inconclusive result  | 1.72 [0.98 ; 3.01], 3 RCTs, I2=64% inconclusive result              | 0.99 [0.89 ; 1.09], 8 RCTs, I2=0% inconclusive result  | 1.95 [0.73 ; 5.23], 3 RCTs, I2=72% demonstrated inconclusive result |
| sofosbuvir and daclatasvir         | 5 studies <sup>8</sup>  | -                                                      | -                                                                   | 1.11 [0.87 ; 1.40], 4 RCTs, I2=0% inconclusive result  | -                                                                   |
| umifenovir (arbidol)               | 5 studies <sup>9</sup>  | 0.86 [0.06 ; 11.36], 1 RCT, I2=0% inconclusive result  | -                                                                   | 1.00 [0.18 ; 5.59], 2 RCTs, I2=0% inconclusive result  | 2.80 [0.31 ; 25.53], 1 RCT, I2=0% inconclusive result               |
| bromhexine                         | 3 studies <sup>10</sup> | 0.48 [0.01 ; 27.44], 1 RCT, I2=0% inconclusive result  | -                                                                   | 0.09 [0.00 ; 1.68], 1 RCT, I2=0% inconclusive result   | -                                                                   |

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| Treatment                                                 | Number of studies       | clinical deterioration                                            | clinical improvement                                       | deaths                                                     | viral clearance                                               |
|-----------------------------------------------------------|-------------------------|-------------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------|
| nitazoxanide                                              | 3 studies <sup>11</sup> | 1.02 [0.29 ; 3.58], 1 RCT, I2=0%<br>inconclusive result           | 0.81 [0.52 ; 1.27], 1 RCT, I2=0%<br>inconclusive result    | 1.02 [0.02 ; 51.70], 1 RCT, I2=0%<br>inconclusive result   | -                                                             |
| doxycycline                                               | 2 studies <sup>12</sup> | 0.44 [0.24 ; 0.78], 2 RCTs, I2=0%<br>moderate degree of certainty | 1.89 [1.06 ; 3.38], 1 RCT, I2=0%<br>certainty unassessable | 0.39 [0.11 ; 1.42], 2 RCTs, I2=0%<br>inconclusive result   | -                                                             |
| sofosbuvir                                                | 2 studies <sup>13</sup> | -                                                                 | -                                                          | -                                                          | -                                                             |
| sofosbuvir and ledipasvir                                 | 2 studies <sup>14</sup> | -                                                                 | -                                                          | -                                                          | -                                                             |
| azvudine                                                  | 1 study <sup>15</sup>   | -                                                                 | -                                                          | 1.00 [0.02 ; 55.80], 1 RCT, I2=0%<br>inconclusive result   | 28.50 [1.27 ; 640.66], 1 RCT, I2=0%<br>certainty unassessable |
| baloxavir marboxil                                        | 1 study <sup>16</sup>   | -                                                                 | -                                                          | 1.00 [0.02 ; 55.80], 1 RCT, I2=0%<br>inconclusive result   | -                                                             |
| darunavir cobicistat                                      | 1 study <sup>17</sup>   | 2.07 [0.06 ; 66.79], 1 RCT, I2=0%<br>inconclusive result          | -                                                          | 1.00 [0.02 ; 53.89], 1 RCT, I2=0%<br>inconclusive result   | 0.82 [0.36 ; 1.87], 1 RCT, I2=0%<br>inconclusive result       |
| Emtricitabine/tenofovir plus colchicine plus rosuvastatin | 1 study <sup>18</sup>   | -                                                                 | -                                                          | 0.62 [0.33 ; 1.17], 1 RCT, I2=0%<br>inconclusive result    | -                                                             |
| Ensitrelvir (XOCOVA)                                      | 1 study <sup>19</sup>   | -                                                                 | -                                                          | -                                                          | -                                                             |
| favipiravir plus interferon                               | 1 study <sup>20</sup>   | -                                                                 | -                                                          | 0.83 [0.23 ; 2.96], 1 RCT, I2=0%<br>inconclusive result    | -                                                             |
| Lopinavir/ritonavir plus hydroxychloroquine               | 1 study <sup>21</sup>   | -                                                                 | 0.63 [0.37 ; 1.06], 1 RCT, I2=0%<br>inconclusive result    | 0.58 [0.36 ; 0.93], 1 RCT, I2=0%<br>certainty unassessable | -                                                             |
| lopinavir/ritonavir plus interferon $\beta$ -1a           | 1 study <sup>22</sup>   | -                                                                 | -                                                          | -                                                          | -                                                             |

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| Treatment                                             | Number of studies     | clinical deterioration | clinical improvement                                   | deaths                                               | viral clearance                                                      |
|-------------------------------------------------------|-----------------------|------------------------|--------------------------------------------------------|------------------------------------------------------|----------------------------------------------------------------------|
| lopinavir/ritonavir, ribavirin and interferon beta-1b | 1 study <sup>23</sup> | -                      | 3.92 [1.66; 9.24], 1 RCT, I2=0% certainty unassessable | 0.47 [0.01; 24.30], 1 RCT, I2=0% inconclusive result | 4.37 [1.86; 10.25], 1 RCT, I2=0% demonstrated certainty unassessable |
| niclosamide                                           | 1 study <sup>24</sup> | -                      | -                                                      | 1.00 [0.20; 5.12], 1 RCT, I2=0% inconclusive result  | -                                                                    |
| nirmatrelvir / ritonavir (Paxlovid)                   | 1 study <sup>25</sup> | -                      | -                                                      | -                                                    | -                                                                    |
| oseltamivir                                           | 1 study <sup>26</sup> | -                      | -                                                      | -                                                    | -                                                                    |
| tenofovir/emtricitabine                               | 1 study <sup>27</sup> | -                      | -                                                      | -                                                    | -                                                                    |
| zinc                                                  | 1 study <sup>28</sup> | -                      | -                                                      | 0.77 [0.11; 5.34], 1 RCT, I2=0% inconclusive result  | -                                                                    |

## Notes

<sup>1</sup>FACCT Trial, 2021 (NCT04392973); HYDRA (Hernandez-Cardenas, 2021 (NCT04315896); Abd-El Salam, 2020 (NCT04353336); ARCHAIC -hydroxychloroquine, 2020 (NL8490); CCAP-1, 2020 (NCT04345289); Chen, 2020 (NCT04384380); Chen, ChiCTR2000030054 - Chloroquine, 2020 (ChiCTR2000030054); ChiCTR2000030054-HCQ (Chen), 2020 (ChiCTR2000030054); Coalition Covid-19 Brazil I (Cavalcanti)-Hydroxychloroquine, 2020 (NCT04322123); Duke university HCQ, 2020 (NCT04335552); Duke University hydroxychloroquine/azithromycin, 2020 (NCT04335552); Gonzalez (HCQ), 2020 (NCT04391127); HAHPS, 2020 (NCT04329832); HC-nCoV (Shanghai), 2020 (NCT04261517); Huang, 2020 (ChiCTR2000029542); HYCOVID, 2020 (NCT04325893); Kamran, 2020 (NCT04491994); NCT04333654, 2020 (NCT04333654); NCT04342650, 2020 (NCT04342650); NO COVID-19 (Lyngbakken), 2020 (NCT04316377); OAHU-COVID19, 2020 (NCT04345692); ORCHID, 2020 (NCT04332991); PROTECT A, 2020 (NCT04338698); PROTECT B, 2020 (NCT04338698); RECOVERY, 2020 (NCT04381936); REMAP-CAP-HCQ, 2020 (NCT02735707); SOLIDARITY (WHO study) HCQ, 2020 (NCT04315948); Tang, 2020 (ChiCTR2000029868); TEACH, 2020 (NCT04369742); Zhaowei Chen, 2020 (ChiCTR2000029559); Arshad (HCQ), 2020 (); Belgian Collaborative Group on COVID-19, 2020 (); Chen *chloroquine*, 2020(); *Geleris*, 2020(); *Hu*

<sup>2</sup>I-TECH (Lim), 2022 (NCT04920942); Abd-El Salam, 2021 (NCT04403555); Babalola, 2021 (); Bukhari, 2021 (NCT04392713); Galan, 2021 (RBR-8h7q82); Kirti, 2021 (CTRI/2020/08/027225); RIVET-COV (Mohan) (12mg and 24mg), 2021 (CTRI/2020/06/026001); Ahmed, 2020 (); Chaccour, 2020 (NCT04390022); Chachar, 2020 (NCT04739410); Gonzalez (IVER), 2020 (NCT04391127); Hashim A, 2020 (NCT04591600); Krolewiecki, 2020 (NCT004381884); NCT04523831 (Mahmud), 2020 (NCT04523831); Okumuş, 2020 (NCT04646109); Shahbaznejad, 2020 (IRCT20111224008507N3); Glorial F, 2020 (NCT04343092); Camprubi, 2020 (); Espitia-Hernandez, 2020 (); Spoorthi, 2020 ()

<sup>3</sup>FACCT Trial, 2021 (NCT04392973); Holubar M, 2021 (NCT04346628); Shenoy S, 2021 (NCT04529499); Shinkai, 2021 (JapicCTI-205238); Solaymani-Dodaran, 2021 (IRCT20200318046812N1); AVIFA-VIR, 2020 (NCT04434248); Chang Chen et al., 2020 (ChiCTR2000030254); Dabbous HM, 2020 (NCT04349241); jRCTs041190120, 2020 (jRCTs041190120); Lou (FAVIPIRAVIR), 2020 (ChiCTR2000029544); NCT04310228-FAVI (Zhao), 2020 (ChiCTR2000030894); NCT04542694, 2020 (NCT04542694); Ruzhentsova T, 2020 (NCT04501783); Udwadia, 2020 (CTRI/2020/05/025114); Calik, 2020 (); Kocayigit H, 2020 (); Cai -FAVIPIRAVIR, 2020 (ChiCTR2000029600)

<sup>4</sup>Andreas (NOR-Solidarity), 2021 (NCT04321616); DisCoVeRy (remdesivir), 2021 (NCT04315948); Mahajan, 2021 (); Norwegian NOR study (remdesivir), 2021 (NCT04321616); CAP-China (Wang et al.), 2020 (NCT04257656); GS-US-540-5773 (Goldman), 2020 (NCT04292899); GS-US-540-5774, 10 days, 2020 (NCT04292730); GS-US-540-5774, 5 days, 2020 (NCT04292730); NIH NIAID ACTT-1, 2020

(NCT04280705); SOLIDARITY (remdesivir), 2020 (NCT04315948)

<sup>5</sup>ProPAC-COVID, 2021 (NCT04322396); Coalition Covid-19 Brazil I (Cavalcanti) - HCQ AZI, 2020 (NCT04322123); Duke university HCQ-AZI, 2020 (NCT04335552); Arshad (HCQ AZ), 2020 (); Davido, 2020 (NCT04453501); Lagier, 2020 (); Magagnoli (HC AZ), 2020 (); Rosenberg, 2020 (); Sbidian (HCQ plus AZI), 2020 ()

<sup>6</sup>Rashad A (AZI vs SoC), 2021 (); COALITION I Covid-19 Brazil (AZI, Cavalcanti), 2020 (NCT04322123); COALITION II Covid-19 Brazil (Furtado), 2020 (NCT04321278); RECOVERY (AZI, Horby), 2020 (NCT04381936); Sekhavati, 2020 (IRCT20200415047092N1); Rodriguez-Molinero, 2020 (); Rosenberg, 2020 (); Espitia-Hernandez, 2020 ()

<sup>7</sup>Ader (lopinavir/ritonavir), 2021 (NCT04315948); Cao, 2020 (ChiCTR2000029308); ELACOI (lopinavir/ritonavir), 2020 (NCT04252885); Nojomi, 2020 (IRCT20180725040596N2); RECOVERY, 2020 (NCT04381936); REMAP-CAP (lopinavir/ritonavir only), 2020 (NCT02735707); SOLIDARITY (lopi/rito), 2020 (NCT04315948); Chen<sub>i</sub>*opi, ito*, 2020()

<sup>8</sup>Mobarak (DISCOVER), 2021 (IRCT20200624047908N1); Mobarak S (DISCOVER), 2021 (IRCT20200624047908N); Sadeghi, 2020 (IRCT20200128046294N2); Yakoot, 2020 (DRKS00022203); Eslami, 2020 (IRCT20200324046850N2)

<sup>9</sup>ELACOI (Lopinavir/ritonavir), 2020 (NCT04252885); ELACOI (Standard of care), 2020 (NCT04252885); Nojomi, 2020 (IRCT20180725040596N2); Yethindra, 2020 (None); Chen<sub>a</sub>*rbidol*, 2020()

<sup>10</sup>Tolouian, 2021 (); Ansarin, 2020 (IRCT202003117046797N); Li T, 2020 (NCT04273763)

<sup>11</sup>Fontanesi, 2021 (NCT04348409); Silva, 2021 (NCT04463264); Rocco, 2020 (NCT04552483)

<sup>12</sup>Spoorthi, 2020 ()

<sup>13</sup>Alavi-moghaddam, 2021 (IRCT20200328046882N1); Sali, 2021 ()

<sup>14</sup>Elgohary, 2021 (NCT04530422); Nourian A, 2020 (IRCT20100228003449)

<sup>15</sup>Ren, 2020 (ChiCTR2000029853)

<sup>16</sup>Lou Y, 2020 (ChiCTR2000029544)

<sup>17</sup>Jun C, 2020 (NCT04252274)

<sup>18</sup>Gaitan-Duarte (Rosuvastatin plus colchicine plus emtricitabine/tenofovir), 2021 (NCT04359095)

<sup>19</sup>Mukae - Phase 2a, 2022 (jRCT2031210350)

<sup>20</sup>Khamis, 2020 ()

<sup>21</sup>REMAP-CAP (lopinavir/ritonavir plus hydroxychloroquine), 2020 (NCT02735707)

<sup>22</sup>Ader (lopinavir/ritonavir plus interferon), 2021 (NCT04315948)

<sup>23</sup>Hung et al., 2020 (NCT04276688)

<sup>24</sup>Abdulmir, 2021 (NCT04753619)

<sup>25</sup>EPIC-SR, 0 (NCT05011513)

<sup>26</sup>Chen<sub>o</sub>*seltamivir*, 2020()

<sup>27</sup>Gaitan-Duarte (Emtricitabine/Tenofovir), 2021 (NCT04359095)

<sup>28</sup>Patel, 2021 (ACTRN12620000454976)