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Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: Lee N, Ison M, Dunning J. Early triple antiviral therapy for COVID-19. *Lancet* 2020; **396:** 1487–88.

Appendix

Table. Evidence and concerns on interferons, lopinavir-ritonavir and ribavirin for the treatment of coronavirus infections

Interferons	SARS-CoV1	non-randomized study: add-on interferon-α (n=9, median 8 days post-onset) *vs* corticosteroid-ribavirin alone, associated with improvements in pneumonia and oxygenation.[a,b] Practical challenge to administer in non-hospitalized patients.
	MERS-CoV	non-randomized study: interferon-α/b plus ribavirin (n=144, median 9 days post-onset) vs SOC, insignificant difference in clinical/virological outcomes.[c] Systemic review (8 clinical studies): no outcome benefit.[d]
Lopinavir-ritonavir	SARS-CoV1	non-randomized study: add-on lopinavir/ritonavir (n=75) *vs* corticosteroid-ribavirin alone, associated with reduced death/ARDS if given early (median 5.5 days from onset).[e,f]
	SARS-CoV2	randomized-controlled trial (n=199): lopinavir/ritonavir vs SOC, insignificant difference in clinical/virological outcomes. Trend towards clinical improvement if given <12 days from onset. Significant GI side-effects, with 14% discontinuation.[g] randomized-controlled trial: lopinavir/ritonavir (n=1616) vs SOC (n=3424) in hospitalized patients showed no clinical benefit.[h] Required therapeutic concentration likely unachievable with current dosing.[i]
Ribavirin	SARS-CoV1	systematic review (30 clinical studies): inconclusive benefit and possible harm (e.g. hemolytic anaemia). Required therapeutic concentration unachievable with current dosing. [b]
	MERS-CoV	systematic review (7 clinical studies): no outcome benefit and possible harm (e.g. hemolytic anaemia). Required therapeutic concentration unachievable with current dosing. [c,d]

SOC: standard of care (may include corticosteroids); interferons / lopinaivir-ritonavir (but not ribavirin) are candidates in the WHO 'Solidarity Trial': https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments ; and the UK 'Recovery Trial': http://www.isrctn.com/ISRCTN50189673

References:

(a) Loutfy MR, et al. *JAMA*. 2003;290(24):3222-8.

(b) Stockman LJ, et al. *PLoS Med*. 2006;3(9):e343.

(c) Arabi YM, et al. *Clin Infect Dis*. 2020;70(9):1837-1844.

(d) Kain T, et al. *Emerg Infect Dis.* 2020 Mar 26;26(6).

(e) Chu CM, et al. *Thorax*. 2004;59(3):252-6.

(f) Chan et al. *Hong Kong Med J* 2003;9(6):399-406.

(g) Cao B, et al. *N Engl J Med*.;382(19):1787-1799.

(h) RECOVERY Collaborative Group. Lancet. 2020:S0140-6736(20)32013-4.

(i) Schoergenhofer C, et al. Ann Intern Med 2020;M20-1550.