Lopinavir/ritonavir (Kaletra®)

A Review of Pertinent Drug Information for SARS-CoV-2

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Mechanism of Action – LPV/r

Protease inhibitors

- Antiviral agents for HIV
- Inhibition of HIV-1 protease → formation of **immature, noninfectious** viral particles

Lopinavir

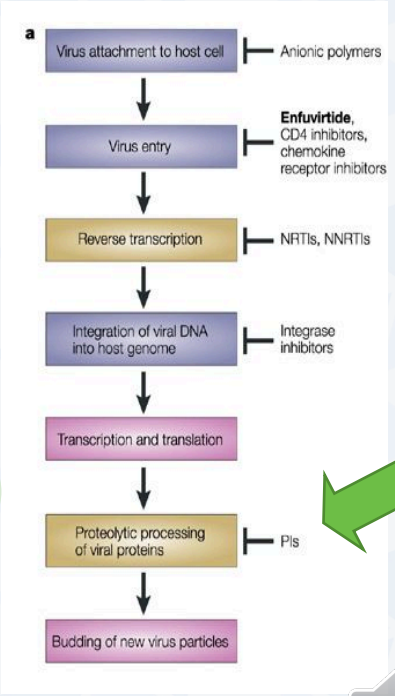
- **POTENTIAL INHIBITION** of Chymotrypsin-like protease (3CLpro) in SARS-CoV

Ritonavir

- CYP3A4 inhibitor
- **DECREASES metabolism = INCREASE serum levels**

Monitoring

- Lopinavir
  - **Peak**: 9.6µg/mL
  - **Trough**: 5.5µg/mL



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1.Infectious diseases. *Nat Rev Drug Discov* 3, S26–S32 (2004). https://doi.org/10.1038/nrd1409

2. Farkas J. COVID-19. The Internet Book of Critical Care. https://emcrit.org/ibcc/COVID19/#lopinavir/ritonavir_(KALETRA). Date Accessed March 14, 2020.

3. Totura AL. Expert Opin Drug Discov. 2019;14(4):397-412. https://doi.org/10.1080/17460441.2019.1581171

Dosing

- Similar to HIV therapy
- 400mg /100mg PO twice daily
- No renal adjustments
- Caution: hepatic impairment
- Crushing: may need increased doses

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Best BM, et al. J Acquir Immune Defic Syndr. 2011 Dec 1; 58(4): 385–391.
https://doi.org/10.1097/QAI.0b013e318232b057

Available Data – *in vitro* data in SARS-CoV-1

Molecular dynamics simulations: LPV/r may inhibit key enzyme

in vitro activity for LPV at 4µg/mL after 48h

Cytopathic inhibition seen at 1µg/mL when combined with ritonavir

EC_{50} values for LPV:

17.1-50µM; no activity with ritonavir

Binding site analysis: 1/2 of LPV left outside catalytic site --> poor efficacy

LPV/r may not have effect on replication of SARS-CoV

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1. Yao TT, et al. J Med Virol. 2020; 1-8. https://doi.org/10.1002/jmv.25729
2. De wilde AH, et al. Antimicrob Agents Chemother. 2014:58(8):4875-4884. https;//doi.org10.1128/AAC.03011-14

Available Data – *in vitro* data in MERS-CoV

Cytopathic inhibition seen with an EC_{50} of 8.0μM (SI = 3.1) when combined with ritonavir

89% inhibition observed at 12μM

Initial cytopathic effect assay: LPV not effective

EC_{50} values for LPV: 11.6μM (SI > 4.3); no significant enhancement with ritonavir

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EC_{50}: 50% effective inhibitory concentration; SI: selectivity index

1. Yao TT, et al. J Med Virol. 2020; 1-8. https://doi:10.1002/jmv.25729
2. De wilde AH, et al. Antimicrob Agents Chemother. 2014:58(8):4875-4884. https;//doi.org10.1128/AAC.03011-14
3. Chan JF, et al. J Infect. 2013;67(6):606-616. https://doi.org/10.1016/j.jinf.2013.09.029

Available Data – Animal Data in MERS-CoV

Untreated	Mycophenalate Mofetil	LPV/r	Interferon-β1b
• Increased respiratory rate, reduced movement • Loss of appetite, hypothermia • Higher mean clinical scores • **Extensive, multilobar hemorrhagic lung lesions and infiltrates**	• Increased respiratory rate • Reduced movement • Loss of appetite • Hypothermia • Higher mean clinical scores • **Extensive, multilobar hemorrhagic lung lesions and infiltrates** • **Highest mean viral loads in lung**	• No severe sx • Less weight reduction • **Improved mean clinical scores** • Less pulmonary infiltrates • **Lowest mean viral loads in lung**	• No severe sx • Less weight reduction • **Improved mean clinical scores** • Less pulmonary infiltrates • **Lower mean viral loads in lung**

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Chan JF, et al. J Infect Dis. 2015;212(12):1904-1913. https;//doi.org/10.1093/infdis/jiv392

Available Data – Animal Data in MERS-CoV

LPV	RTV	IFNb	RDV
• EC_{50} of 11.6 μM (SI>4.3) • LPV/r EC_{50} of 8.5 μM • Minimal effect when used as prophylaxis	• EC_{50} of 24.9 μM (SI>2)	• EC_{50} of 175 IU/mL (SI>16) • Activity not improved when combined w/ LPV/r • Minimal effect when used as prophylaxis	• EC_{50} of 0.09 μM (SI>100) • Diminished viral replication & disease • Reduced acute lung injury • Sustained when combined → pointing to monotherapy benefits

RTV: Ritonavir ; IFNb: Interferon beta; RDV: Remdisivir

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Sheahan TP, et al. Nat Commun.2020;11:222. https://doi.org/10.1038/s41467-019-13940-6 | www.nature.com/naturecommunications

Available Data – Human Data in SARS-CoV-1

Retrospective, matched cohort

Probable SARS

Ribavirin 2.4g PO LD, 1.2g PO q8h or 8mg/kg IV q8h X 14d

+ reducing regimen of steroids X 21d

PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 14d as *INITIAL THERAPY* (n=44)

PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 14d as *RESCUE THERAPY* (n=31)

- Sex
- Age (years)
- Co-morbidity
- Lactate dehydrogenase

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

Available Data – Initial vs. Rescue Therapy

Author Conclusions:

Early use but not rescue use of LPV/r was beneficial in reducing use of pulse corticosteroid therapy, intubation rates, and death. **No significant increases in ADEs.**

*synergism in rescue therapy not established by this study.

Table 3. Comparison of outcomes for the group given LPV/r as initial treatment and a matched cohort*

	LPV/r as initial treatment, n=44 Crude rate or mean (95% CI)	Matched cohort, n=634 Standardised rate or mean† (95% CI)	P value
Death rate (%)	2.3 (0-6.8)	15.6 (9.8-22.8)	<0.05
Intubation rate (%)	0	11.0 (7.7-15.3)	<0.05
Desaturation rate (SaO2≤95%) [%]	68.2 (52.3-81.8)	84.5 (74.4-95.2)	NS‡
Proportion requiring pulse methylprednisolone rescue (%)	27.3 (11.4-40.9)	55.4 (47.6-63.9)	<0.05
Mean pulse methylprednisolone dose (g)	1.6 (1.1-2.0)	3.0 (2.8-3.2)	<0.05

Table 4. Comparison of outcomes of the group given LPV/r as rescue treatment and a matched cohort*

	LPV/r as rescue, n=31 Crude rate or mean (95% CI)	Matched cohort, n=343 Standardised rate or mean† (95% CI)	P value
Death rate (%)	12.9 (0-25.8)	14.0 (5.2-26.3)	NS‡
Intubation rate (%)	9.7 (0-22.6)	18.1 (9.0-29.7)	NS
Desaturation rate (SaO2≤95%) [%]	93.5 (80.6-100)	92.1 (75.9-100)	NS
Mean pulse methylprednisolone dose (g)	3.8 (3.5-4.2)	3.0 (2.9-3.2)	<0.05

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

Available Data – Human Data in SARS

Open, non-randomized

Probable SARS

Ribavirin 4g PO LD, 1.2g PO q8h or 8mg/kg IV q8h X 14d

+ reducing regimen of steroids X 21d

Historical controls (n=111)

PLUS Lopinavir/ritonavir 400mg/100mg PO q12h X 14d (n=41)

1° Outcome	Historical Controls (n=111)	Treatment group (n=41)	P-value
Development of ARDS or death w/i 21d	32 (28.8%)	1 (2.4%)	<0.001
Death at day 21	7 (6.3%)	0 (0%)	
ARDS at day 21	25 (22.5%)	1 (2.4%)	

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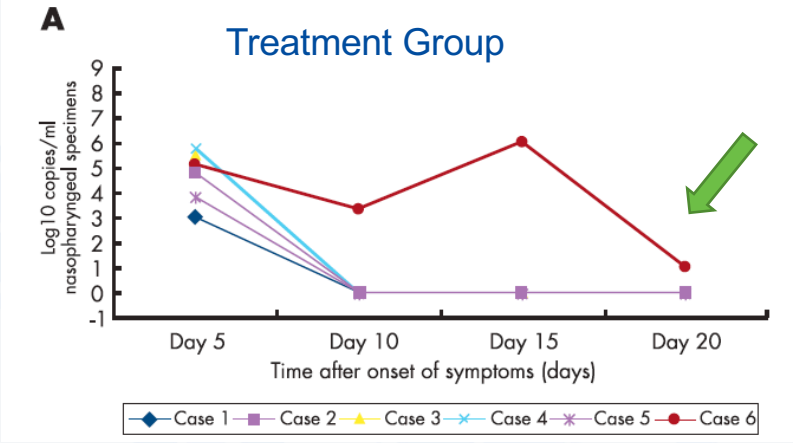
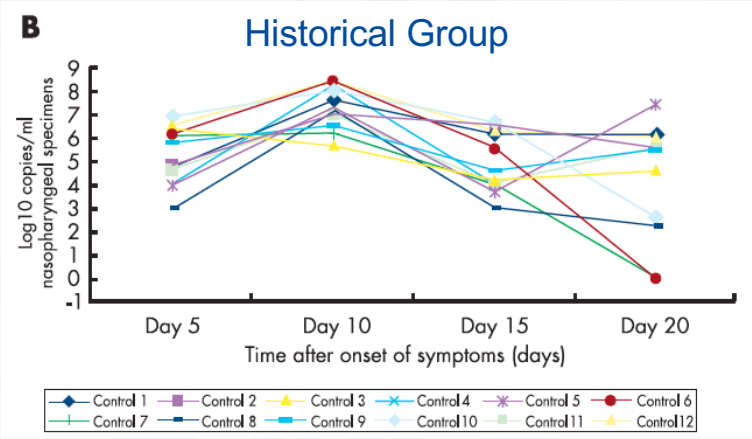
Chu CM et al. Thorax. 2004;59:252-256. https;//doi.org /10.1136/thorax.2003.012658

Change in viral load





Author Conclusions: When combined with ribavirin, lopinavir appears **considerably more effective**

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Chu CM et al. Thorax. 2004;59:252-256. https;//doi.org /10.1136/thorax.2003.012658

Available Data – Human Data in MERS

Retrospective, matched cohort

PEP in HCWs (n=43)

- Ribavirin 2g PO LD, 1.2g PO q8h X 4d, then 600mg PO q8h X 6-8d
  - *PLUS* Lopinavir/ritonavir 400mg/100mg PO q12h X 11-13d (n=22)
- Non-PEP (n=21)

Author Conclusions:
PEP therapy was associated with a **40% decrease** in the risk of infection. There were **no severe adverse events** during PEP therapy.

Outcome	PEP (n=22)	Non-PEP (n=21)	P-value
Subsequent MERS-CoV infection	0 (0%)	6 (28.6%)	P=0.009
Safety – ADEs (N/V/D)	21(95.5%)	0(0%)	
MERS-CoV rRTePCR (+)	0%	-	

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PEP: post-exposure prophylaxis; HCW: healthcare workers

Park SY et al. J Hosp Infect. 2019; 01(1):42-46. https://doi.org/10.1016/j.jhin.2018.09.005

Available Data – COVID-19 in China

Open-label, individually randomized

SARS-CoV-2 PCR(+) (n=199)

- Standard care PLUS LPV/r (400mg/100mg) PO q12h X14d (n=99)
- Standard Care (n=100)

Standard Care: Supplemental O_2, noninvasive and invasive ventilation, abx, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO)

1° Outcome	LPV/r (n=99)	Standard Care (n=100)	Difference
Time from illness onset to randomization, median days (IQR)	13 (11–17)	13 (10–16)	-
Time to clinical improvement, median days (IQR)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)
ITT 28d mortality, n (%)	19 (19.2)	25 (25.0)	−5.8 (−17.3 to 5.7)
mITT 28d mortality, n (%)	16 (16.7)	25 (25.0)	-8.3 (-19.6 to 3.0)
Time from randomization to d/c, median days (IQR)	12 (10 to 16)	14 (11 to 16)	1 (0 to 3)
Pts w/ clinical improvement at 14d, n (%)	45 (45.5)	30 (30.0)	15.5 (2.2 to 28.8)

Cao B, et al. NEJM, 2020. https://doi.org/10.1056/NEJMoa2001282

Available Data – COVID-19 in China

Author Conclusions:

LPV/r treatment added to standard txt was **not associated w/ clinical improvements or mortality in seriously ill patients** with COVID-19 vs. standard care alone. Decrease in viral loads over time **did not differ** between the two groups

*high overall mortality, numerical benefits in early txt group and post-hoc groups

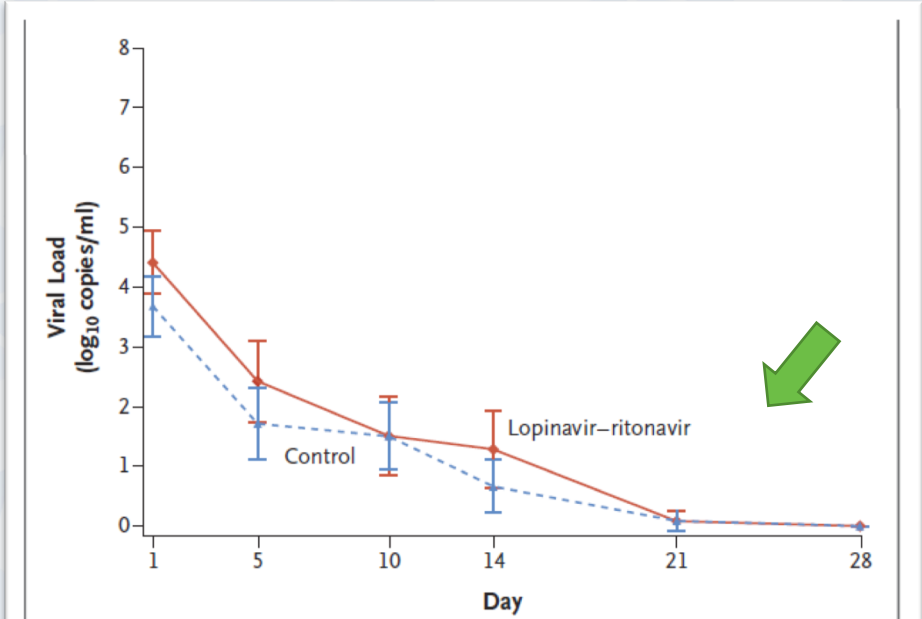

Figure 3. Mean Change from Baseline in SARS-CoV-2 Viral RNA Load by qPCR on Throat Swabs

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Cao B, et al. NEJM, 2020. https://doi.org/10.1056/NEJMoa2001282

Adverse Drug Reactions

Dermatologic	Endocrine/ Metabolic	Gastrointestinal	Hepatic
Respiratory	Cardiac	Central Nervous System	Hematologic

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Lexicomp® package insert. Lopinavir and Ritonavir. Accessed March 14, 2020.

Drug-Drug & Drug-Food Interactions

Drug-Drug

- **CYP3A4 inhibitor**
  - Other HIV and HCV agents
  - Antifungals
  - Amiodarone
  - Apixaban
  - Tacrolimus
  - Agents in psychiatric illness

Drug-Food

- Oral solution
  - High-fat meal can INCREASE levels
- Tablets
  - With or without food

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Lexicomp® package insert. Lopinavir and Ritonavir. Accessed March 14, 2020.

COVID-19?

Current Evidence	Conflicting Evidence in non-COVID pts	Treatment Guidelines: China	Special Populations	Safety profile - CONCERN
• No current reported study in U.S • NEJM 3/2020: no benefit in hospitalized adult pts • Lancet 5/2020: triple therapy	• Improvement in symptoms • Reduction in viral load	• LPV/r: recommended as antiviral regimen	• Pregnancy	• Diarrhea • Nausea • Asthenia • Anemia • Hyperbilirubinemia • Transaminitis

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Yao TT, et al. J Med Virol. 2020; 1-8. https://doi:10.1002/jmv.25729

(Update)Available Data – COVID-19 in China

SARS-CoV-2 PCR(+) (n=127)

- Combination Therapy (LPV/r 400mg/100mg PO q12h, ribavirin 400mg q12h PO, and INF-1b SQ) X14d (n=86)
- Control (LPV/r 400mg/100mg PO q12h) X 14d (n=40)

Phase 2, multicenter, open-label, randomized

Standard Care: Supplemental O_2, noninvasive and invasive ventilation, abx, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO)

Baseline Characteristics (*select*)	Combination (n = 86)	Control (n=40)
Hypertension	23 (27%)	13 (32%)
Hyperlipidemia	18 (21%)	11 (27%)
Fever	70 (81%)	32 (78%)
Cough	45 (52%)	23 (56%)
Sputum	29 (34%)	12 (32%)
Shortness of breath	7 (8%)	7 (17%)
Lymphocytes (1.06–3.61 × 10^9 per L)	1.0 (0.8–1.5)	1.3 (0.9–1.6)
LDH (143–280 U/L)	194.0 (159.8–249.0)	167.5 (142.0–200.0)
CRP	3.0 (2.0–9.2)	3.0 (1.5–7.2)
Abnormal CXR	64 (74%)	32 (78%)

NEWS2 – National Early Warning Score, 2nd version

Hung I, et al. Lancet, 2020. https://doi.org/10.1016/S0140-6736(20)31101-6

(Update)Available Data – COVID-19 in China

Outcomes	Combination (n = 86)	Control (n=40)	p-value
Time to negative RT-PCR in NP swab sample	7 (5-11)	12 (8-15)	0.0010
Time to NEWS2 of 0 sustained X 24h	4 (3-8)	8 (7-9)	<0.0001
Time to SOFA score of 0 sustained X 24h	3 (1-8)	8 (6.5-9.0)	0.041
Length of hospital stay	9 (7-13)	14.5 (9.3-16.0)	0.016
30-day mortality	0 (0)	0 (0)	1.00
Time to negative SARS-CoV-2 RT-PCR in all samples	8 (6-12)	13 (8-15)	0.0010
Serious adverse events	0 (0)	1 (2%)	0.15
Concomitant abx	4 (51%)	25 (61%)	0.33
O2 therapy	12 (14%)	5 (12%)	0.72
Non-invasive vent support	3 (3%)	2 (5%)	0.75
Vent support	0	1 (2%)	0.15

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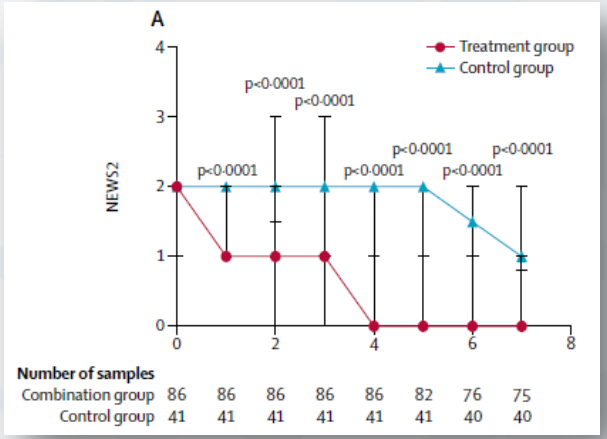
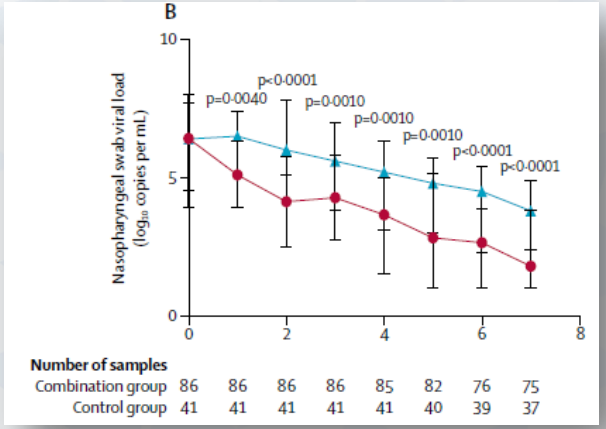
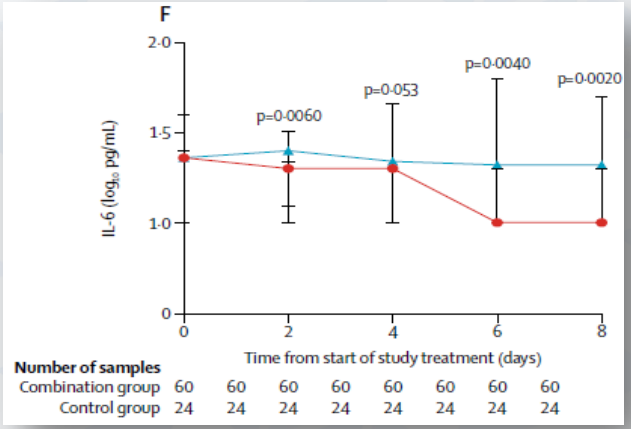
(Update)Available Data – COVID-19 in China







Author Conclusions:

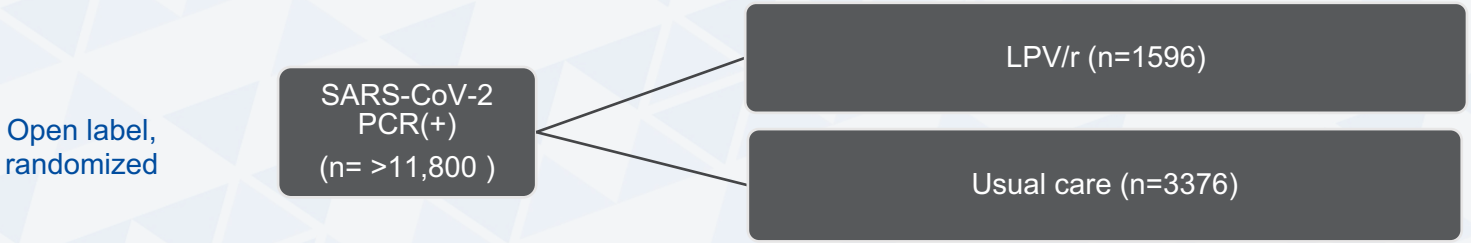
Early triple therapy w/ LPV/r, INF-1b, and ribavirin treatment **effectively suppressed viral load in all clinical specimens and IL-6**. Combination therapy was associated with **significantly shorter time to alleviation of symptom and shorter hospital stays**. Serious ADEs were **similar in both groups**, with minimal discontinuation.

Baseline characteristics, SOFA and NEWS2 scores were **not indicative of severe illness** and **may not have warranted admission** (if not required). There was **no statistically significant difference** in 30-d mortality, O2 requirement, and need for ventilatory support.

*ADEs and secondary abx were reported in almost half of pt population.

Hung I, et al. Lancet, 2020. https://doi.org/10.1016/S0140-6736(20)31101-6

(Update – 06/29/2020) RECOVERY Trial



- Patient randomized to either LPV/r, HCQ, Azithromycin, Convalescent plasma or Tocilizumab
- 4%: invasive mechanical ventilation when entering trial
- 70%: O2 alone
- 26%: no respiratory intervention.

Primary outcome: 28-d mortality

- 22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91- 1.18]; p=0.58
- **No beneficial effects in 28-d mortality, risk of progression to mechanical ventilation or length of hospital stay.**

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Horby P, et al. https://www.recoverytrial.net/files/lopinavir-ritonavir-recovery-statement-29062020_final.pdf

(Update – 12/06/2020) SOLIDARITY Trial

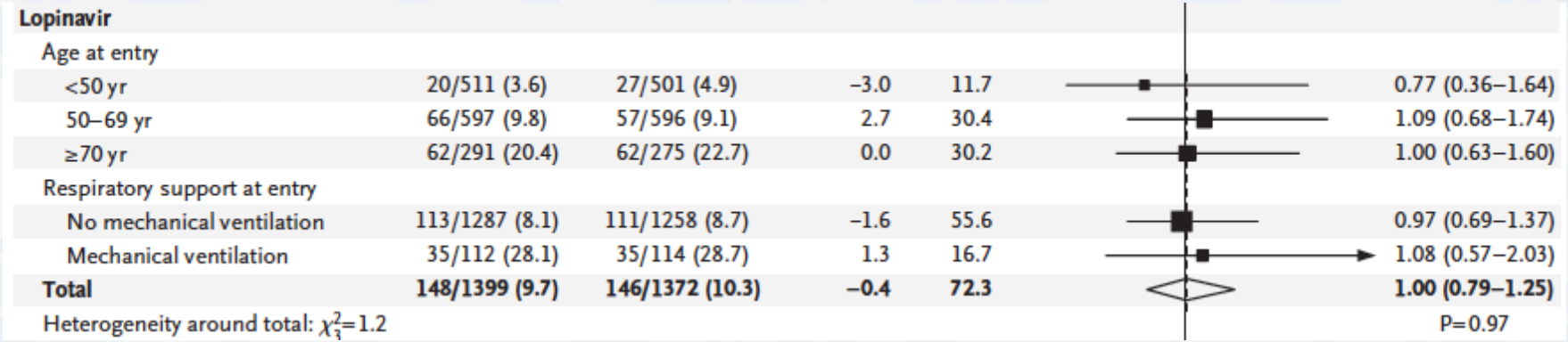
randomized

Hospitalized pts w/ severe COVID-19 illness (n=11,330)

- LPV/r (n=1411), LPV/r + INFb (651), HCQ (n=954), or RDV (n=2750)
- Standard Care (n=4088)

HCQ = hydroxychloroquine
RDV = Remdesivir

Figure 3. Rate Ratios for In-Hospital Death, Subdivided by Age and Respiratory Support at Trial Entry



Lopinavir					
Age at entry					
<50 yr	20/511 (3.6)	27/501 (4.9)	−3.0	11.7	0.77 (0.36–1.64)
50–69 yr	66/597 (9.8)	57/596 (9.1)	2.7	30.4	1.09 (0.68–1.74)
≥70 yr	62/291 (20.4)	62/275 (22.7)	0.0	30.2	1.00 (0.63–1.60)
Respiratory support at entry					
No mechanical ventilation	113/1287 (8.1)	111/1258 (8.7)	−1.6	55.6	0.97 (0.69–1.37)
Mechanical ventilation	35/112 (28.1)	35/114 (28.7)	1.3	16.7	1.08 (0.57–2.03)
Total	**148/1399 (9.7)**	**146/1372 (10.3)**	**−0.4**	**72.3**	**1.00 (0.79–1.25)**
Heterogeneity around total: χ^2_3=1.2					P=0.97

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Pan H, et al. NEJM 2020. https://doi.org/10.1056/NEJMoa2023184

(Update – 12/06/2020) SOLIDARITY Trial

Death occurred **in** 148 of 1399 patients receiving lopinavir and in 146 of 1372 receiving its control (rate ratio,1.00; **95% CI, 0.79 to 1.25; P = 0.97**), These data show that LPV/r **did not reduce mortality, initiation of ventilation or hospitalization duration** of hospitalized COVID-19 patients when compared to standard of care.

**does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19*

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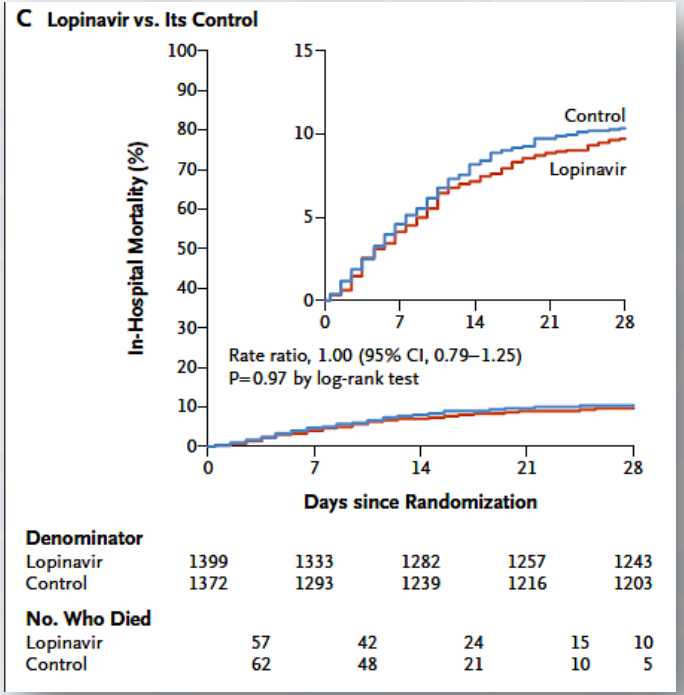
Figure 2. Effects of LPV/r on In-Hospital Mortality



Pan H, et al. NEJM 2020. https://doi.org/10.1056/NEJMoa2023184

Summary

- Evidence – **updated December 2020**
- Availability
- Single vs. multi-drug regimens?
  - Interferon
  - Ribavirin
- Safety Profile

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Lopinavir/ritonavir (Kaletra®)

A Review of Pertinent Drug Information for SARS-CoV-2

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