Multidimensional Challenge of COVID-19, Including COVID-19 and HIV

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This activity is jointly provided by Physicians’ Research Network and the Medical Society of the State of New York.
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Disclosures for RTG: scientific advisory board for Merck
## Multidimensional Challenge of Treating COVID-19

| Clinical Manifestations | • Respiratory illness  
|                         | • Multisystem involvement  
|                         | • Thromboinflammation       |
| Stage and Severity      | • Early vs. late infection  
|                         | • Mild, moderate, severe, critical disease |
| Intervention            | • Antivirals                 
|                         | • Immunomodulators          
|                         | • Combination therapy       
|                         | • Rx complications: anticoagulation, ventilation |
Covid-19: Testing

• Diagnostic testing usually based on RT PCR of nasopharyngeal, nasal swab; saliva

• Antigen testing: less expensive, more rapid than PCR
  • Particularly helpful when rapid results critical to preventing transmission, eg congregate settings

• Serology usually + >=2 wks after sx onset
  • Not useful in dx of acute infection
  • Does not inform if someone is protected against infection


Covid-19: Isolation

- PCR may remain positive for weeks to months
  - Duration of infectivity $\leq 10$ d after sx onset in pts with mild-to-moderate disease
  - $< 15$-20 d in those with severe illness or immunocompromise

- Isolation can generally be discontinued 10 d after symptom onset and resolution of fever for at least 24 hours (without use of anti-pyretics) and improvement of other symptoms


Covid-19: Clinical Manifestations

Symptoms

• Fever, cough, sore throat, malaise, myalgias
• Gastrointestinal symptoms: anorexia, nausea, diarrhea
• Taste and smell disturbances: more common in women than men
• Shortness of breath develops in some people; median 5-8 days after symptom onset

Lab findings

• Lymphopenia
• Elevated D-dimer, LDH, CRP, ferritin, liver enzymes, interleukin-6

Gandhi RT, Lynch JB, del Rio C, NEJM, 2020
Covid-19: Radiographic Features

- Peripheral, bilateral ground glass opacities with or without consolidation
- Ground glass opacities may have rounded morphology

Courtesy of Dr. Brent Little (MGH Radiology)
Clinical Presentation in Adults: A Multi-System Disease

**Respiratory**
- Dyspnea
- Cough
- Hypoxemia
- Pulmonary infiltrates
- Pneumonia
- ARDS
- Pulmonary Embolus

**CNS/Neurological**
- Stroke
- Syncope
- Anosmia
- Dysgeusia

**Skin**
- “COVID toes”
- Vesicles, pustules
- Maculopapular rash
- Urticaria
- Livedo
- Emboli
- Kawasaki
  - Conjunctivitis
  - Rash

**Systemic**
- Neutrophilia
- Lymphopenia
- Thrombocytopenia
- Inflammation
- Viremia
- Coagulopathy
- Multisystem Inflammatory Syndrome

**Cardiovascular**
- Elevated CK, troponin
- Myocarditis
- MI
- Arrhythmia
- Cardiomyopathy
- Shock

**Renal**
- Elevated Creatinine

**Gastrointestinal**
- Nausea
- Diarrhea
- Loss of appetite
- Elevated liver function tests

*Slide courtesy of Dr. Jay Fishman, Mass General Hosp.*
Pernio/chilblains-like

Erythematous to violaceous macules, papules, and papulonodules, some with pseudovesiculation at tips of digits and soles of feet.

Slide courtesy of Dr. Daniela Kroshinsky (Mass General Hospital)
Cardiac Manifestations of COVID-19

• Acute cardiac injury: elevated troponin
• Heart failure, cardiogenic shock
• Myocarditis
• Arrhythmias
• Thrombosis
Thromboinflammation and Mortality

• Elevated inflammatory and coagulation biomarkers associated more severe disease and mortality
• Inflammatory response may lead to endothelial injury, coagulopathy
• Complications may include pulmonary emboli, myocardial infarction, disseminated intravascular coagulation

Zhou et al, Lancet 2020
Pathology of COVID-19

• Lungs from people who died of COVID-19 (n=7), influenza-related acute respiratory distress syndrome (n=7) and uninfected people (n=10)

• COVID-19 lungs showed:
  o endothelial injury
  o widespread thrombosis
  o alveolar capillary microthrombi
  o intussusceptive angiogenesis

Lymphocytic pneumonia with multifocal endothelialitis

Ackermann M et al, NEJM, 2020
## COVID-19 Spectrum

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic/</td>
<td>Positive test for SARS-CoV-2 but no symptoms</td>
</tr>
<tr>
<td>presymptomatic infection</td>
<td></td>
</tr>
<tr>
<td>Mild illness</td>
<td>Varied symptoms (e.g., fever, cough, sore throat, taste/smell disturbance) but no shortness of breath or abnormal imaging</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>( \text{SpO}_2 &gt; 94% ) &amp; lower respiratory disease (clinical or imaging findings)</td>
</tr>
<tr>
<td>Severe illness</td>
<td>( \text{SpO}_2 &lt; 94% ), ( \text{PaO}_2/\text{FiO}_2 &lt; 300 ), respiratory rate &gt; 30/ min, or lung infiltrates &gt; 50%</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Respiratory failure, shock, and/or multiorgan dysfunction</td>
</tr>
</tbody>
</table>

~80%  
~15%  
~5%  

## Risk Factors for Severe COVID-19

<table>
<thead>
<tr>
<th>Host</th>
<th>Severity</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
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<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
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<tr>
<td>Obesity (BMI of &gt;=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromised state from solid organ transplant</td>
<td>Possible risk factors include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other immunocompromised states</td>
</tr>
</tbody>
</table>

Disproportionate burden of COVID-19 among racial and ethnic minorities, Native Americans, the poor


Williamson EJ et al, Nature, 2020
Treatment Across the COVID-19 Spectrum

<table>
<thead>
<tr>
<th>Stage/Severity:</th>
<th>Asymptomatic/Presymptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ SARS-CoV-2 test but no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea</td>
<td>O₂ saturation &gt;=94%, lower respiratory tract disease</td>
<td>O₂ saturation &lt;94%, respiratory rate &gt;30/min; lung infiltrates &gt;50%</td>
<td>Respiratory failure, shock, multi-organ dysfunction/failure</td>
</tr>
<tr>
<td>Frequency:</td>
<td>?</td>
<td>80%</td>
<td>15%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Disease Pathogenesis:
- Viral replication
- Inflammation

Potential treatment:
- Antivirals
- Antibody therapy
- Decrease inflammation

Host Severity Interventions

Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020
SARS-CoV-2: Antiviral targets

- Viral entry: ACE2 and TMPRSS2: camostat
- Membrane fusion and endocytosis: hydroxychloroquine (HCQ)
- Viral protease: lopinavir/ritonavir
- RNA-dependent RNA polymerase: remdesivir, favipiravir
Case of Hydroxychloroquine (HCQ):
From single arm studies and observational cohorts

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philipp Gautret a,⁎, Jean-Christophe Lagier a,⁎, Lilian Lameille a,⁎, Philippe Tarara a,b,⁎, Van-Thuan Nguyen a,b,⁎, Line Meddeb a,⁎, Morgane Mailhe a,⁎, Barbara Doolier a,⁎, Johan Courjon a,b,⁎, Valérie Girodanello a,⁎, Vera Esteves Vieira a,⁎, Hervé Tisot Dupont a,b,⁎, Stéphane Honore a,⁎, Philippe Colson a,b,⁎, Eric Chabrière a,⁎, Bernard La Scola a,b,⁎, Jean-Marc Rolain a,b,⁎, Philippe Briouqui a,b,⁎, Didier Raoul a,b,⁎, Aït, Aït

Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data

Matthieu Mahé 9 ,⁎, Viet-Thi Tran 9 , Mathilde Rouquier 9 , Amélie Chabrol 9 , Romain Paule 9 , Constance Guillaud 9 , Élise Fais 9 , Raphaël Leguay 9 , Tali-Anna Swoboda 9 , François-Xavier Lesecq 9 , Frédéric Schlemmer 9 , Marie Matignon 9 , Méhdi Khelladi 9 , Elenor Cocks 9 , Benjamin Ferrer 9 , Caroline Mortes 9 , Paul Legendre 9 , Ruben Dang 9 , Yolanda Scholindre 9 , Jean-Michel Pawlotsky 9 , Marc Michel 9 , Elyscie Perego 9 , Nicolas Carlier 9 , Yves Rocher 9 , Victoire de Loze 9 , Céline Quyngthon 9 , Solène Kettaneh 9 , Philippe Manzana 9 , Luc Mouton 9 , Étienne Audefroy 9 , Philippe Ravaud 9 , Bertrand Godde 9 , Sébastien Carlier 9 , Nathalie Costesolle-Chalameau 9 ✉

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleis, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sabieszczuk, M.D., M.P.H., and Neil W. Schluger, M.D.
HCQ: To randomized controlled trials...

Preventive therapy: post-exposure prophylaxis

- SARS-CoV-2 Incidence

<table>
<thead>
<tr>
<th>Days Follow-up</th>
<th>HCQ</th>
<th>Control</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
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<td>5</td>
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<td>6</td>
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<td>7</td>
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<td>10</td>
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<td>11</td>
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<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Early Treatment

- Symptom Severity Score

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo</th>
<th>Hydroxychloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>14</td>
<td>0.05</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Hospitalized patients

- Statement from the Chief Investigators of the Randomised Evaluation of COVID-19 hydroxychloroquine (RECOVERY) Trial on hydroxychloroquine, 5 June 2020

No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19

Barnabas R et al, ID Week 2020, abst LB17; Skipper CP et al, Ann Int Med, 2020 RECOVERY Collaborative Group, NEJM 2020; Cavalcanti NEJM, 2020
The Case of Remdesivir (RDV)

- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- ACTT-1: hospitalized pts, lower respiratory tract infection randomized to 10-day RDV or placebo
  - Recovery more rapid with RDV than placebo (10 vs 15 d)
  - Mortality at 29 days: 11.4% RDV, 15.2% placebo (hazard ratio 0.73, 95% CI, 0.52-1.03).
  - Benefit of RDV clearest in those on supplemental oxygen but not intubated
- SIMPLE trial: in people with severe COVID-19 but not intubated: 5 days of RDV as good as 10 days
Remdesivir (RDV) in Moderate COVID-19

- 596 hospitalized patients with moderate COVID-19: pulmonary infiltrates, $O_2$ sat >94%
- Randomized to RDV 10-d, RDV 5-d, standard of care (SOC)
- Day 11:
  - RDV 10-day similar clinical status as SOC
  - RDV 5-day: better clinical status distribution as SOC but of “uncertain clinical importance”
- In hospitalized patients with moderate disease, reasonable to decide on RDV use on case-by-case basis
What about SOLIDARITY?

- WHO sponsored open label randomized trial
- >11,000 hospitalized patients in >30 countries
- Drugs: hydroxychloroquine, remdesivir, lopinavir/ritonavir, beta-interferon
- No study drug had definite effect on mortality: RDV group, death rate ratio: 0.95 (0.81-1.11)
- Solidarity did not assess time to recovery
- Open label design may have affected duration of hospitalization
- Meta-analysis of randomized RDV trials: Ratio of death rates
  - Lower risk groups (no ventilation): 0.80 (99% CI, 0.63, 1.01); higher risk groups 1.16 (99% CI 0.85-1.60)

https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1
Convalescent Plasma (CP)

• On August 23, FDA issued emergency use authorization for CP based on analysis of data from Mayo Clinic Expanded Access Program (EAP)

• Compared outcomes among patients who received CP with high titers of neutralizing antibodies (Ab) to outcomes in patients with low titers (Broad Institute assay)

• No difference in 7-day survival

• Post-hoc analyses by Mayo on ~3000 patients (out of ~35,000) suggested benefit of high titer plasma (Ortho-Clinical IgG assay) in patients who received CP within 3 days of diagnosis, who were not intubated, and were <80 yrs old

• Because of lack of comparison group and possibility of confounding, NIH COVID-19 Treatment Guidelines Panel (and FDA) conclude that CP should not be standard of care and that randomized trials should be completed

https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1; Pau A et al, Ann Int Med, 2020
Monoclonal Antibodies

• Monoclonal antibodies against SARS-CoV-2 being studied for treatment and prevention

• In outpatients with mild to moderate disease (n=452), participants randomized to received iv infusion of placebo or one of three doses of a neutralizing antibody directed against SARS-CoV-2 spike protein (LY-CoV555)

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Moherla, M.D., Valentina Stosor, M.D., Irmad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm. D., Dipak R. Patel, M.D., Ph.D., Paul Kleckotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators
LY-CoV555 (Bamlanivimab)

- At day 11, 2800 mg dose of antibody appeared to accelerate decline in viral load as compared to placebo
  - 3.4-fold lower in 2800 mg group than in the placebo group
  - Viral load decline did not differ significantly between other antibody doses and placebo
- In all 3 dose groups, there appeared to be a separation in virus level decay as compared to placebo

Figure 1: SARS-CoV-2 viral load change from baseline by visit.

Chen P et al, NEJM, 2020; https://www.fda.gov/media/143602/download
LY-CoV555 (Bamlanivimab)

- ED visit or hospitalization:
  - 1.6% in antibody group, 6.3% in placebo group
  - >65 year old, BMI >35: 4% in antibody group, 15% in placebo group
- Median time to symptom improvement: 6 days for participants who received bamlanivimab and 8 days for those who received placebo.
- Safety profile of bamlanivimab and placebo similar

<p>| Hospitalization/ED Visit: All Participants |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156</td>
<td>9</td>
<td>6%</td>
</tr>
<tr>
<td>700 mg</td>
<td>101</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>2800 mg</td>
<td>107</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>7000 mg</td>
<td>101</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Pooled antibody</td>
<td>309</td>
<td>5</td>
<td>2%</td>
</tr>
</tbody>
</table>

<p>| Hospitalization/ED Visit: Participants at Higher Risk of Hospitalization |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>69</td>
<td>7</td>
<td>10%</td>
</tr>
<tr>
<td>700 mg</td>
<td>46</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>2800 mg</td>
<td>46</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>7000 mg</td>
<td>44</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Pooled antibody</td>
<td>136</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>

Chen P et al, NEJM, 2020; https://www.fda.gov/media/143602/download
Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression

• Body mass index (BMI) ≥35
• Chronic kidney disease
• Diabetes
• Immunosuppressive disease or receiving immunosuppressive treatment
• ≥65 years of age
• ≥55 years of age AND have
  • cardiovascular disease, OR
  • hypertension, OR
  • chronic obstructive pulmonary disease/other chronic respiratory disease
• Criteria also listed for those who are 12 – 17 years of age

https://www.fda.gov/media/143602/download
LY-CoV555 in Hospitalized Patients

- LY-CoV555 sub-study of ACTIV-3 trial closed after data suggested a lack of clinical benefit for LY-CoV555 in a hospitalized population
Bamlanivimab: My Take

• Bamlanivimab shows promise but difficult to be certain as to magnitude of clinical benefit and which patients most likely to benefit
• More data from ongoing clinical trials needed; we continue to refer patients to those trials
• Bamlanivimab should not be used in patients hospitalized with COVID-19
• Awaiting data on monoclonal antibody combinations
• Logistical challenges in administering monoclonal antibodies to large number of people with mild to moderate COVID-19
Steroids: Case of Dexamethasone

- Controversy regarding use of steroids in viral pneumonia, acute respiratory distress syndrome
- Given hyperinflammatory state in COVID-19, steroids evaluated as potential intervention
- Open label, randomized trial among hospitalized patients in the UK: 2104 received dex, 4321 usual care

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Dex</th>
<th>Usual Care</th>
<th>RR mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>22.9%</td>
<td>25.7%</td>
<td><strong>0.83</strong> (0.75-0.93) p&lt;0.001</td>
</tr>
<tr>
<td>Ventilation/ECMO</td>
<td>29.3%</td>
<td>41.4%</td>
<td><strong>0.64</strong> (0.51–0.81)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>23.3%</td>
<td>26.2%</td>
<td><strong>0.82</strong> (0.72 – 0.94)</td>
</tr>
<tr>
<td>No oxygen</td>
<td>17.8%</td>
<td>14%</td>
<td><strong>1.19</strong> (0.91 – 1.55)</td>
</tr>
</tbody>
</table>

Conclusion: Dexamethasone associated with decreased mortality among those on supplemental oxygen or on mechanical ventilation/ECMO. No benefit in those not requiring oxygen.
### Anti-IL-6 Inhibitors

- Elevated interleukin-6 levels associated with worse clinical outcomes; may be part of cytokine storm that can occur in severe COVID-19
- Early non-randomized studies suggested possible benefit of IL-6 inhibition
# Anti-IL-6 Inhibitor: Tocilizumab

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</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td>PaO2:FiO2 &lt;150 ICU admission, death: RR, 1.05 (95% CI, 0.59 to 1.86)</td>
<td>Survival without NIV or MV by day 14: HR, 0.58 (90% CI, 0.33 to 1.00),</td>
<td>Clinical Status, 7-category scale: OR, 1.19 (95% CI, 0.81 to 1.76),</td>
<td>Death or MV, day 28: HR, 0.56 (95% CI, 0.32 to 0.97),</td>
<td>Intubation or death: HR 0.83 (95% CI 0.38 to 1.81)</td>
</tr>
<tr>
<td><strong>Mortality, tocilizumab vs comparator</strong></td>
<td>3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)</td>
<td>11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)</td>
<td>19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)</td>
<td>10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)</td>
<td>5.6% vs. 4.9%</td>
</tr>
</tbody>
</table>

Modified from Parr, JAMA, 2020
### Treatment Across the COVID-19 Spectrum

<table>
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<tr>
<td>+ SARS-CoV-2 test but no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, taste/smell changes; no dyspnea)</td>
<td>O₂ saturation ≥94%, lower respiratory tract disease</td>
<td>O₂ saturation &lt;94%, respiratory rate &gt;30/min; lung infiltrates &gt;50%</td>
<td>Respiratory failure, shock, multi-organ dysfunction/failure</td>
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<table>
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<th>Frequency:</th>
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<th>80%</th>
<th>15%</th>
<th>5%</th>
</tr>
</thead>
</table>

**Disease Pathogenesis:**
- Viral replication
- Inflammation

**Potential treatment:**
- Antivirals
- Antibody therapy
- Decrease inflammation

**Interventions:**
- Remdesivir
- Dexamethasone

**Note:**
- Most COVID-19 is mild whereas most trials have focused on moderate, severe or critical disease.
Treatment Across the COVID-19 Infection Spectrum

- **At Risk**
- **Exposed**
- **Infected**
- **Symptomatic**
- **Hospitalized**
- **Resp Failure**
- **Death**

**Interventions**:
- HCQ: RECOVERY, Hubei, NYP Study, UM ACTT1/2, Remdesivir Trials
- Favipiravir Trials
- IL-6 Inhibitors, Plasma, NO, Anticoagulation, Stem Cells, ACEI/ARBs, IFN, sirolimus, steroids, prazosin, ivermectin, Vit C, etc, etc

**Bang for the Buck?**
- HCQ Minnesota PEP Study
Multi-Dimensional Challenge of COVID-19

• COVID-19 prevention and treatment requires multidimensional approach, with understanding of the host, stage/severity of disease, and intervention

• Depending on host, stage/severity of disease, therapy may differ: antiviral therapy, immunomodulator, combinations (antiviral + immunomodulator)

• Lessons from HIV
  • Pressure to deploy interventions must be tempered by importance of finding out if a treatment works: our guide must be the science
  • Iterative process, building on advances until tipping point is achieved
COVID-19 and HIV

Is HIV a risk factor for severe COVID-19?

Do HIV medications have activity against SARS-CoV-2?

What is the impact of COVID-19 on HIV care and prevention?
Is HIV a risk factor for COVID-19? South Africa

- About 3.5 million active public sector adult patients; ~520,000 with HIV
- ~22,000 COVID-19 and not deceased; 625 COVID-19 deaths
- Adjusted hazard ratio for COVID-19 mortality for HIV: 2.14 (1.7, 2.7); irrespective of viral suppression/immunosuppression
- Cannot rule out residual confounding (eg socioeconomic status, obesity)

Associations with COVID-19 Death
Is HIV a risk factor for COVID-19? UK

- **ISARIC CCP-UK prospective cohort**
  - About 47,000 hospitalized patients with COVID; 123 with HIV
  - Overall mortality similar with and without HIV: 27 vs. 32%
  - In an adjusted analysis, mortality was higher among people with HIV (adjusted hazard ratio 1.52 to 1.92)

Is HIV a Risk Factor for Severe COVID-19? VA Study

- Veterans Aging Cohort Study
- Risk of severe COVID outcomes similar by HIV status

<table>
<thead>
<tr>
<th></th>
<th>PWH n=30,981</th>
<th>Uninfected n=76,745</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID+</td>
<td>253</td>
<td>504</td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>34%</td>
<td>35%</td>
<td>1.09 (0.85, 1.41)</td>
</tr>
<tr>
<td>ICU</td>
<td>14%</td>
<td>15%</td>
<td>1.08 (0.72, 1.62)</td>
</tr>
<tr>
<td>Death</td>
<td>9.5%</td>
<td>11.1%</td>
<td>1.08 (0.66, 1.75)</td>
</tr>
</tbody>
</table>

Park et al., AIDS 2020, Virtual Covid 2020
Risk for Severe Covid-19 in PWH Associated with lower CD4 Counts

- Multi center registry
  - N=286; 94% on ART; 57% hospitalized; 16% ICU; 9% mortality
  - Older age, lung disease, HTN, comorbidity burden: severe COVID-19 outcomes
  - CD4 <200: poorer COVID-19 outcomes

Dandachi, Clin Infect Dis., 2020
HIV and COVID-19: MGH Series

- Between March 3 and April 26, 2020, identified 36 people with HIV with confirmed COVID-19; another 11 with probable infection
- ~80% racial/ethnic minorities
- ~85% had non-HIV comorbidity: obesity, cardiovascular disease, etc.
COVID-19 and HIV

- Is HIV a risk factor for severe COVID-19?
- Do HIV medications have activity against SARS-CoV-2?
- What is the impact of COVID-19 on HIV care and prevention?
Does Lopinavir/ritonavir work against COVID-19?

- In vitro, LPV/r inhibits SARS-CoV protease; has been used off-label to treat people with COVID
- Randomized trial in China (n=199), LPV/r had no impact on clinical improvement, mortality
- RECOVERY: ~1600 patients randomized to LPV/r; ~3400 to usual care: no impact on mortality; mechanical ventilation progression, length of stay
- SOLIDARITY: no benefit of LPV/r
- Likely explanation: levels needed to inhibit SARS-CoV-2 not achieved in vivo

COVID-19 Among People with HIV on ART

- About 77,000 people with HIV receiving ART in clinics in Spain
- N=236 diagnosed with COVID-19, 151 hospitalized, 20 died
- Risk of COVID diagnosis and hospitalization lowest among those on TDF/FTC
- Hospitalization/10,000 people:
  - TDF/FTC: 10.5
  - TAF/FTC: 20.3
  - ABC/3TC: 23.4
  - Other regimens: 20
- Residual confounding? Groups may be different
COVID-19 and HIV

Is HIV a risk factor for severe COVID-19?

Do HIV medications have activity against SARS-CoV-2?

What is the impact of COVID-19 on HIV care and prevention?
Impact of COVID-19 on HIV Treatment and Prevention

• Survey of >13,500 LGBTI+ people in 138 countries:
  • 26% of PWH reported difficulty with access to ART refills
• Disruptions in PrEP care in the US
  • Especially among vulnerable subpopulations (young, non-white, Latinx, publicly insured) (Krakower D et al, AIDS 2020/Virtual Covid)

Final Thoughts

• Disproportionate impact on racial and ethnic minorities of COVID-19 and HIV highlight how disparities drive disparate infectious diseases → we must address structural forces to end intolerable inequities in health care access and outcomes for these “twin” epidemics.

• We cannot let the COVID-19 pandemic cause us to lose sight of how far we’ve come in our quest to end the HIV epidemic.

• Despite overwhelming need to respond to COVID-19, we must continue to move forcefully to end HIV epidemic here and around the world.
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Thank You for Your Attendance!
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