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

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Financial Relationships With Commercial Entities

Dr Gandhi has served as a consultant or advisor to Merck & Co, Inc. (Updated 08/08/20)

Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe the major clinical manifestations of COVID-19
▪ List considerations in treating a person with COVID-19
▪ Summarize current understanding of COVID-19 in people with HIV
Multidimensional Challenge of Treating COVID-19

<table>
<thead>
<tr>
<th>Host</th>
<th>Clinical manifestations</th>
<th>Risk factors for severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage and Severity</td>
<td>Early vs. late infection</td>
<td>Mild, moderate, severe, critical disease</td>
</tr>
<tr>
<td>Intervention</td>
<td>Antivirals</td>
<td>Immunomodulators</td>
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<tr>
<td></td>
<td>Combination therapy</td>
<td>Rx complications: anticoagulation, ventilation</td>
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</tbody>
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Covid-19: Transmission and Incubation Period

Transmission:
- Primarily through respiratory droplets
- Virus may be aerosolized and transmitted during certain activities (e.g., singing) or procedures (e.g., intubation or use of nebulizers)
  - Role of aerosols in transmission under active discussion
- Asymptomatic and pre-symptomatic people are infectious
  - May account for 40-50% of cases
  - High nasopharyngeal viral levels just before or soon after symptom onset

Incubation:
- Median 4-5 days
- 97.5% of those who develop symptoms will do so within 11.5 days

Covid-19: Clinical Manifestations

Symptoms
- Fever, cough, sore throat, malaise, myalgias
- Gastrointestinal symptoms: anorexia, nausea, diarrhea
- Taste and smell disturbances
- 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
Covid-19: Radiographic Features

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

Clinical Presentation in Adults: A Multi-System Disease

Pernio/chilblains-like

Erythematous to violaceous macules, papules, and papulonodules, some with pseudovesiculation at tips of digits and soles of feet.
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 with more severe disease and mortality
- Inflammatory response may lead to endothelial injury, coagulopathy
- Complications may include pulmonary emboli, myocardial infarction, disseminated intravascular coagulation

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:
  - endothelial injury
  - widespread thrombosis
  - alveolar capillary microthrombi
  - intussusceptive angiogenesis
- Lymphocytic pneumonia with multifocal endothelitis
**Risk Factors for Severe COVID-19**

- Older age
- Chronic obstructive pulmonary disease; severe asthma
- Cardiovascular disease
- Type 2 diabetes mellitus
- Obesity (BMI of >=30)
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid organ transplant

- Possible risk factors include:
  - Pregnancy
  - Other immunocompromised states, including HIV

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

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**Multidimensional Challenge of Treating COVID-19**

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<tr>
<th>Stage/Severity</th>
<th>Asymptomatic/Pre-symptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>?</td>
<td>60%</td>
<td>10%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Asymptomatic/Pre-symptomatic
- Mild Illness: Viral replication
- Moderate Illness: Inflammation
- Severe Illness: Inflammation
- Critical Illness: Inflammation

**Potential Treatment:**
- Antibiotics
- Antivirals
- Antibody therapy
- Decrease inflammation

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**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

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Case of HCQ: From single arm studies and observational cohorts ...

Post-exposure prophylaxis
Early Treatment
Hospitalized patients

HCQ: To randomized controlled trials...

The Case of Remdesivir (RDV)

- Nucleotide produg: inhibits viral RNA polymerase: chain terminator
- Macaques: reduced SARS CoV-2 levels in lung (not upper respiratory tract), ameliorated disease
- Preliminary analysis of ACTT randomized trial: recovery more rapid with RDV than placebo [11 vs 15 d]
  - Mortality at 14 days: 7.1% RDV, 11.9% placebo (hazard ratio 0.7, 95% CI 0.47 to 1.04).
  - 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

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Antibody Therapy

• Passive transfer of neutralizing Ab: convalescent plasma (CP), monoclonal antibodies (mAb)
• Open label randomized trial of CP in China: no benefit in overall population; suggested benefit in severe disease
• >20,000 people with COVID-19 in US: transfusion reactions <1%; low rate of other complications
• Ongoing prophylactic & therapeutic trials of CP, mAb

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 All participants</th>
<th>Dex</th>
<th>Usual Care</th>
<th>RR mortality</th>
</tr>
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<tbody>
<tr>
<td>All participants 21.6%</td>
<td>24.6%</td>
<td>0.83 (0.74 - 0.92)</td>
<td>p&lt;0.0007</td>
</tr>
<tr>
<td>Ventilation/ECMO 29%</td>
<td>40.7%</td>
<td>0.65 (0.45 - 0.91)</td>
<td></td>
</tr>
<tr>
<td>Oxygen only 21.5%</td>
<td>25%</td>
<td>0.8 (0.67 - 0.96)</td>
<td></td>
</tr>
<tr>
<td>No oxygen 17%</td>
<td>13%</td>
<td>1.22 (0.86 - 1.75)</td>
<td></td>
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</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.

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<tr>
<td>Frequency:</td>
<td>+ SARS-CoV2 test &amp; negative</td>
<td>HIF activation</td>
<td>Gi function impaired, fever, fatigue</td>
<td>Gi activation impaired, cytokine storm</td>
<td>Respiratory failure, shock, multi-organ dysfunction/Failure</td>
</tr>
<tr>
<td>Disease</td>
<td>Viral replication</td>
<td>Inflammation</td>
<td>Remodeling</td>
<td>Death</td>
<td>Antibody therapy</td>
</tr>
</tbody>
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NB: most COVID-19 is mild whereas most trials have focused on moderate, severe or critical disease
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?
Between March 3 and April 26, 2020, identified 36 people with HIV with confirmed COVID-19; another 11 with probable infection

- Nearly half (16/36) lived or worked in congregate setting
- ~85% had a non-HIV comorbidity: obesity, cardiovascular disease, etc.

Demographics and Comorbidities of Confirmed Cases

Disproportionate Burden Among Racial/Ethnic Minorities

77% of people with HIV and COVID-19 were non-Hispanic Blacks or Latinx

40% of people with HIV in MGH Clinic are Blacks or Latinx

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

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

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<tr>
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<th>PWH n=30,981</th>
<th>Uninfected n=76,745</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>COVID+</td>
<td>253</td>
<td>504</td>
<td>1.09 (0.85, 1.41)</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>
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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?

HIV and COVID-19

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-19
- 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
- Likely explanation: levels needed to inhibit SARS-CoV-2 likely not achieved in vivo
COVID-19 Among People with HIV on ART

- About 7,700 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

J del Amo et al, Ann Int Med, 2020

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Impact of COVID-19 on HIV Treatment and Prevention

- WHO survey: significant disruptions in access to HIV treatment because of COVID-19
- Survey of >13,500 LGBTI+ people in 138 countries:
  - Increased socioeconomic vulnerability
  - 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)

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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Question-and-Answer Session