

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

**Rajesh T. Gandhi, MD**  
Professor of Medicine  
Harvard University  
Boston, Massachusetts

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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)

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### 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

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### Multidimensional Challenge of Treating COVID-19



<b>Host</b>	<ul style="list-style-type: none"> <li>Clinical manifestations</li> <li>Risk factors for severe disease</li> </ul>
<b>Stage and Severity</b>	<ul style="list-style-type: none"> <li>Early vs. late infection</li> <li>Mild, moderate, severe, critical disease</li> </ul>
<b>Intervention</b>	<ul style="list-style-type: none"> <li>Antivirals</li> <li>Immunomodulators</li> <li>Combination therapy</li> <li>Rx complications: anticoagulation, ventilation</li> </ul>

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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

Host → Severity → Interventions

Gandhi RT, Lynch JB, del Rio C, NEJM, 2020

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### 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

Host → Severity → Interventions

Gandhi RT, Lynch JB, del Rio C, NEJM, 2020

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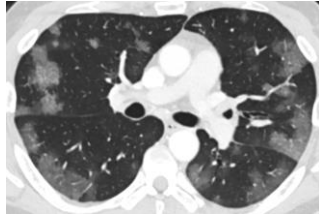
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## Covid-19: Radiographic Features

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



Courtesy of Dr. Brent Little (MGH Radiology)

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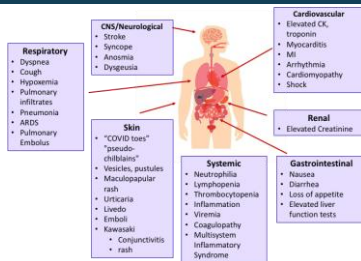
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## Clinical Presentation in Adults: A Multi-System Disease



Slide courtesy of Dr. Jay Fishman, Mass General Hosp.

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## 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)

Mazzotta F, Troccoli T. Acute acro-ischemia in the child at the time of COVID-19 (Monday case). <https://www.ajgpt.com/ajgptmondaycases>.

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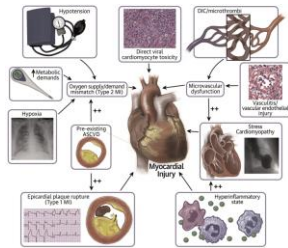
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## Cardiac Manifestations of COVID-19

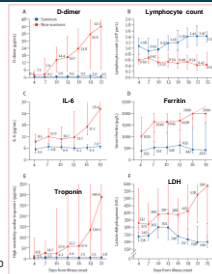
- Acute cardiac injury: elevated troponin
- Heart failure, cardiogenic shock
- Myocarditis
- Arrhythmias
- Thrombosis



Atri D et al JACC: Basic to Translational Science, 2020

## Thromboinflammation and Mortality

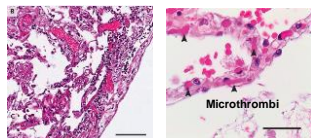
- Elevated inflammatory and coagulation biomarkers associated more severe disease and mortality
- Inflammatory response may lead to endothelial injury, coagulopathy
- Complications may include pulmonary emboli, myocardial infarction, disseminated intravascular coagulation



Zhou et al. Lancet 2020  
Bikdeli B et al JACC 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:
  - endothelial injury
  - widespread thrombosis
  - alveolar capillary microthrombi
  - intussusceptive angiogenesis



Lymphocytic pneumonia with multifocal endothelialitis

Ackermann M et al, NEJM, 2020

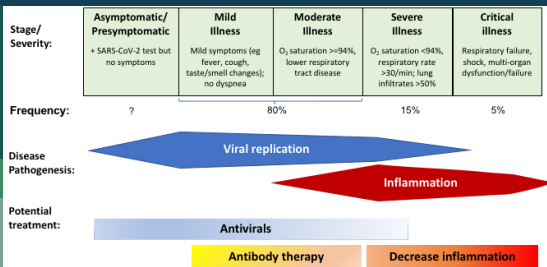
## Risk Factors for Severe COVID-19

- Older age
- Chronic obstructive pulmonary disease; severe asthma
- Cardiovascular disease
- Type 2 diabetes mellitus
- Obesity (BMI of  $\geq 30$ )
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid organ transplant
- Possible risk factors include:
  - Pregnancy
  - Other immuno-compromised states, including HIV
- Disproportionate burden of COVID-19 among racial and ethnic minorities, Native Americans, the poor

<https://www.cdc.gov/coronavirus/2019-ncov/need-ethnic-protection/evidence-table.html>  
Williamson EJ et al. Nature, 2020

Severity Interventions

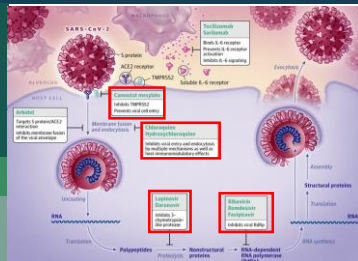
## Multidimensional Challenge of Treating COVID-19



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Gandhi R. CID, 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

Sanders et al JAMA 2020



Boost immune responses

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

Abraham J, Nature Reviews Immunology, 2020; Shen et al, JAMA 2020; Li JAMA 2020; Joyner M et al, Mayo Clin Proc, 2020

Severity

Interventions

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Decrease inflammation

Steroids: Case of Dexamethasone

RECOVERY

- 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

	Mortality	Dex	Usual Care	RR mortality
All participants	21.6%	24.6%	0.83 (0.74-0.92)	p=0.0007
Ventilation/ECMO	29%	40.7%	0.65 (0.45 - 0.88)	
Oxygen only	21.5%	25%	0.8 (0.67 - 0.96)	
No oxygen	17%	13%	1.22 (0.86 - 1.75)	

Conclusion: Dexamethasone associated with decreased mortality among those on supplemental oxygen or on mechanical ventilation/ECMO. No benefit in those not requiring oxygen.

<https://www.recoverytrial.org/>

Severity

Interventions

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Multidimensional Challenge of Treating COVID-19

Stage/Severity:	Asymptomatic/Presymptomatic	Mild illness	Moderate illness	Severe illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O <sub>2</sub> saturation >=94%; lower respiratory tract disease	O <sub>2</sub> saturation <94%; respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure
Frequency:	?	80%	15%	5%	
Disease Pathogenesis:	Viral replication				Inflammation
Potential treatment:	Antivirals		Remdesivir	Dexamethasone	Antibody therapy
			Decrease inflammation		

NB: most COVID-19 is mild whereas most trials have focused on moderate, severe or critical disease

Gandhi R

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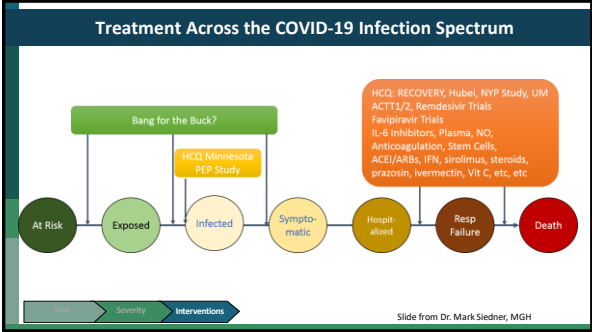
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### Multi-Dimensional Challenge of COVID-19

- 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

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### 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?**

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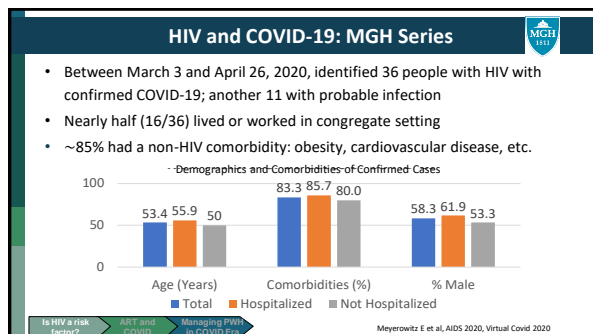
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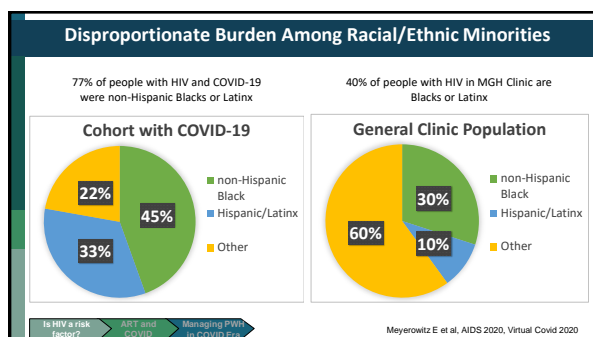
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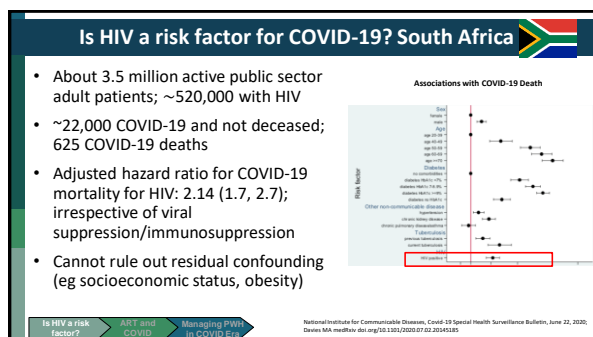
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## Is HIV a Risk Factor for Severe COVID-19? VA Study

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

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

Is HIV a risk factor? ART and COVID Managing PWH in COVID Era

Park et al., AIDS 2020, Virtual Covid 2020

## HIV and COVID-19

Is HIV a risk factor for severe COVID-19?

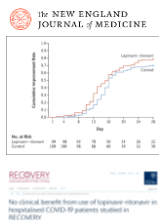
Do HIV medications have activity against SARS-CoV-2?

What is the impact of COVID-19 on HIV care?

Is HIV a risk factor? ART and COVID Managing PWH in COVID Era

## 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

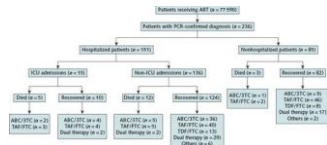


Cao B et al, NEJM, 2020; Schoergenhofer, Ann Int Med, 2020  
<https://www.clinicaltrials.gov/ct2/show/study?term=recovery&rank=1>

## 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



ART and COVID Managing PWH in COVID Era

J del Amo et al. Ann Int Med. 2020

## HIV and COVID-19

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?

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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) (Kraikower D et al, AIDS 2020/Virtual Covid)

<https://www.aids2020.org/aids-2020-virtual-opens-with-focus-on-impact-of-covid-19-on-global-hiv-response/>

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## 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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## Acknowledgments

- |                     |                            |
|---------------------|----------------------------|
| • Arthur Kim        | • Delaney Taylor           |
| • Mark Siedner      | • Malini and Kavish Gandhi |
| • Eric Meyerowitz   | • Efe Airewele             |
| • Rochelle Walensky | • Carlos del Rio           |
| • Virginia Triant   | • Rachel Bender Ignacio    |
| • Trip Gulick       |                            |

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**2020** Ryan White  
HIV/AIDS Program  
CLINICAL CONFERENCE

## Question-and-Answer Session

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