2020 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

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)

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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

Host	• Clinical manifestations • Risk factors for severe disease
Stage and Severity	• Early vs. late infection • Mild, moderate, severe, critical disease
Intervention	• Antivirals • Immunomodulators • Combination therapy • Rx complications: anticoagulation, ventilation

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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

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

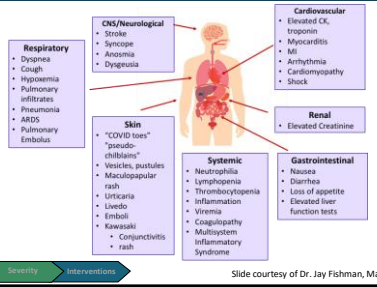
Covid-19: Radiographic Features

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

Host Severity Interventions

Courtesy of Dr. Brent Little (MGH Radiology)

Clinical Presentation in Adults: A Multi-System Disease



Host Severity Interventions

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.

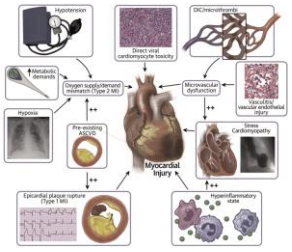
Slide courtesy of Dr. Daniela Kroshinsky (Mass General Hospital)

Host Severity Interventions

Mazzota F, Troccoli T. Acute acro-ischemia in the child at the time of COVID-19 (Mondays case). https://www.sjpd.com/en/mondayscase.

Cardiac Manifestations of COVID-19

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

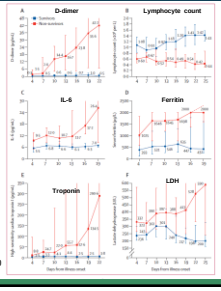


Host | Severity | Interventions

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

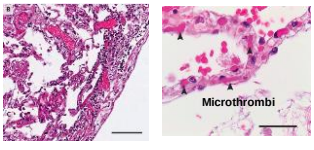


Host | Severity | Interventions

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

Host | Severity | Interventions

Ackermann M et al, NEJM, 2020

Risk Factors for Severe COVID-19

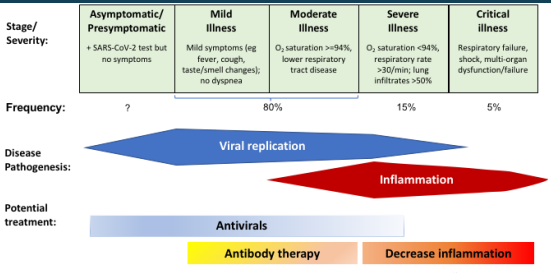
- Older age
- Chronic obstructive pulmonary disease; severe asthma
- Cardiovascular disease
- Type 2 diabetes mellitus
- Obesity (BMI of >=30)
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid organ transplant

- 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-extra-precautions/evidence-table.html
Williamson EJ et al, Nature, 2020

Severity | Interventions

Multidimensional Challenge of Treating COVID-19



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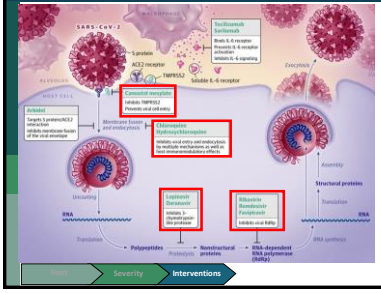
Gandhi R. CID, 2020

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

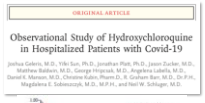
Severity | Interventions

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

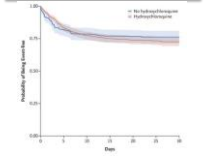

International Journal of Antimicrobial Agents

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


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


ORIGINAL ARTICLE

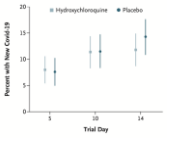
Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19



Host | Severity | Interventions

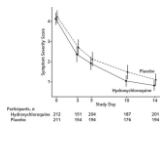
HCQ: To randomized controlled trials…

Post-exposure prophylaxis



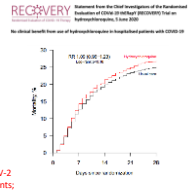
Limitations: most participants enrolled 3-4 days after exposure; only 2-3% had confirmed dx

Early Treatment



Limitations: lack of confirmed SARS-CoV-2 infection in large proportion of participants; endpoint changed to symptom severity score

Hospitalized patients



Host | Severity | Interventions

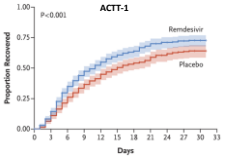
Boulware et al, NEJM 2020; Skipper CP et al, Ann Int Med, 2020
medRxiv 2020.07.15.20151852; doi: https://doi.org/10.1101/2020.07.15.20151852

Antivirals

The Case of Remdesivir (RDV)

- Nucleotide prodrug: 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


nature
Accelerated Article Preview
Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2



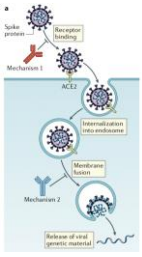
Host | Severity | Interventions

Williamson BN et al, Nature, 2020; Beigel JH et al, NEJM 2020; Goldman JD et al, NEJM 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



Test | Severity | Interventions

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

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.net/

Test | Severity | Interventions

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_2 saturation >=94%, lower respiratory tract disease	O_2 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; Dexa; Antibody therapy; Decrease inflan

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

Gandhi R

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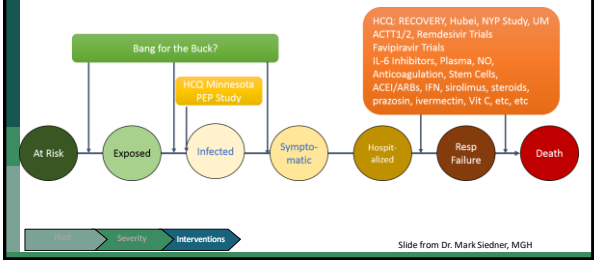
Treatment Across the COVID-19 Infection Spectrum



Slide from Dr. Mark Siedner, MGH

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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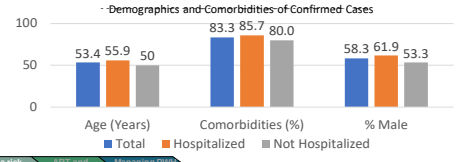
HIV and COVID-19: MGH Series

- Between March 3 and April 26, 2020, identified 36 people with HIV with confirmed COVID-19; another 11 with probable infection
- Nearly half (16/36) lived or worked in congregate setting
- ~85% had a non-HIV comorbidity: obesity, cardiovascular disease, etc.



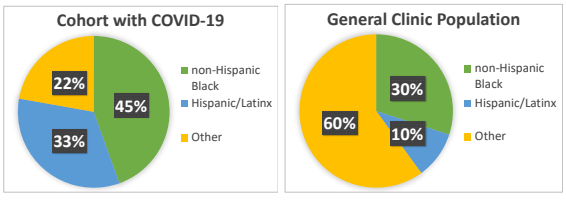
Is HIV a risk factor? | ART and COVID | Managing PWH in COVID Era

Meyerowitz E et al, AIDS 2020, Virtual Covid 2020

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

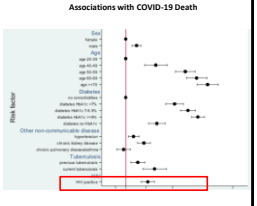


Is HIV a risk factor? | ART and COVID | Managing PWH in COVID Era

Meyerowitz E et al, AIDS 2020, Virtual Covid 2020

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? | ART and COVID | Managing PWH in COVID Era

National Institute for Communicable Diseases, Covid-19 Special Health Surveillance Bulletin, June 22, 2020; Davies MA medRxiv doi.org/10.1101/2020.07.02.20145185

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)
COVID+	253	504	
Hospitalized	34%	35%	1.09 (0.85, 1.41)
ICU	14%	15%	1.08 (0.72, 1.62)
Death	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?

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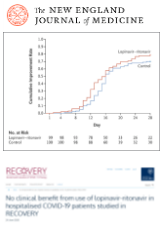
Is HIV a risk factor? | ART and COVID | Managing PWH in COVID Era

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

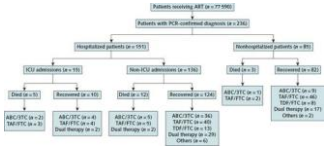


Is HIV a risk factor? | ART and COVID | Managing PWH in COVID Era

Cao B et al, NEJM, 2020; Schoergenhofer, Ann Int Med, 2020
https://www.clinicaltrialsarena.com/news/recovery-trial-lopinavir-ritonavir/

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



J del Amo et al, Ann Int Med, 2020

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

HIV and COVID-19

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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) (Krakower 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
- Mark Siedner
- Eric Meyerowitz
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- Carlos del Rio
- Rachel Bender Ignacio

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2020 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Question-and-Answer Session