COVID-19 Update: Including the Intersection of HIV

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



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Disclosures: 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: 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

Host Severity Interventions

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

Covid-19: Radiographic Features

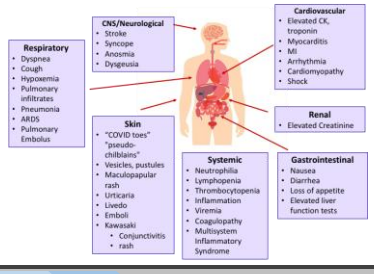
- Peripheral, bilateral ground glass opacities with or without consolidation
- Ground glass opacities may have rounded morphology



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.





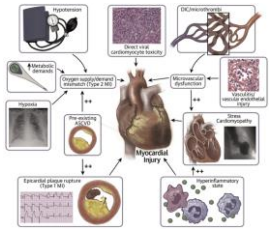
Slide courtesy of Dr. Daniela Kroshinsky (Mass General Hospital)

Host | Severity | Interventions

Mazzota F, Troccoli T. https://www.ejpd.com/en/mondayscase.

Cardiac Manifestations of COVID-19

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

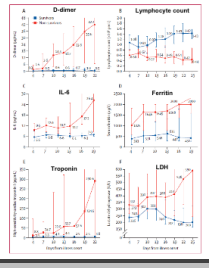


Host | Severity | Interventions

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



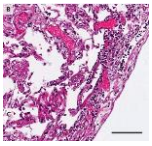
Host | Severity | Interventions

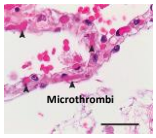
Zhou et al, Lancet 2020

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

COVID-19 Spectrum

	Stage	Characteristics
	Asymptomatic/ presymptomatic infection	▪ Positive test for SARS-CoV-2 but no symptoms
~80%	Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, taste/smell disturbance) but no shortness of breath or abnormal imaging
~80%	Moderate illness	▪ SpO_2 ≥94% & lower respiratory disease (clinical or imaging findings)
~15%	Severe illness	▪ SpO_2 < 94%, PaO_2/FiO_2 < 300, respiratory rate >30/min, or lung infiltrates > 50%
~5%	Critical illness	▪ Respiratory failure, shock, and/or multiorgan dysfunction

Host · Severity · Interventions

Wu Z et al, JAMA 2020; NIH COVID-19 Treatment Guidelines. Last updated June 11, 2020. www.covid19treatmentguidelines.nih.gov.

Risk Factors for Severe COVID-19

- Older age
- Chronic lung disease
- 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

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

Host · Severity · Interventions

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html
Williamson EJ et al, Nature, 2020

Treatment Across the COVID-19 Spectrum

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%

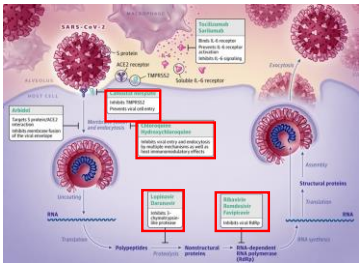
Disease Pathogenesis: Viral replication; Inflammation

Potential treatment: Antivirals; 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

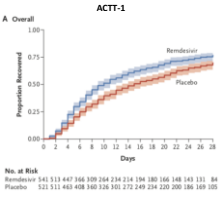
Host | Severity | Interventions

Sanders et al JAMA 2020

Antivirals

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



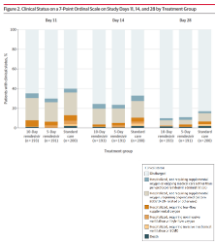
Host | Severity | Interventions

Beigel JH et al, NEJM 2020; Goldman JD et al, NEJM 2020

Antivirals

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



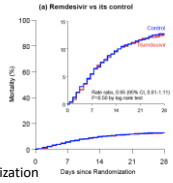
Host Severity **Interventions**

Spinner C et al, JAMA, 2020

Antivirals

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)



Host Severity **Interventions**

Boost immune responses

Convalescent Plasma (CP)

U.S. FOOD & DRUG ADMINISTRATION

COVID-19 Treatment Guidelines

- 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

Host Severity **Interventions**

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

Boost immune responses

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)


ORIGINAL ARTICLE

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

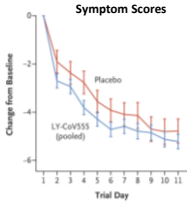
Host Severity **Interventions**

Chen P et al, NEJM, 2020

Boost immune responses

LY-CoV555 (Bamlanivimab)

- At day 11, intermediate dose of antibody appeared to accelerate decline in viral load
- COVID-19-related ED visit or hospitalization: 1.6% in antibody group, 6.3% in placebo group
  - In those >65 yo, BMI >35: 4% hospitalized in antibody group, 15% in placebo group
- Change in symptom score better in the antibody group than in placebo group



Host Severity **Interventions**

Chen P et al, NEJM, 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	22.9%	25.7%	**0.83** (0.75-0.93) **p<0.001**
Ventilation/ ECMO	29.3%	41.4%	**0.64** (0.51 – 0.81)
Oxygen only	23.3%	26.2%	**0.82** (0.72 – 0.94)
No oxygen	17.8%	14%	**1.19** (0.91 – 1.55)

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

Host Severity **Interventions**

RECOVERY Collaborative Group, NEJM, 2020

Decrease inflammation

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

Host Severity **Interventions**

https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-22-22-30-00
https://www.clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&cond=COVID-19&draw=2&rank=1
https://www.roche.com/investors/updates/inv-update-2020-07-29.htm

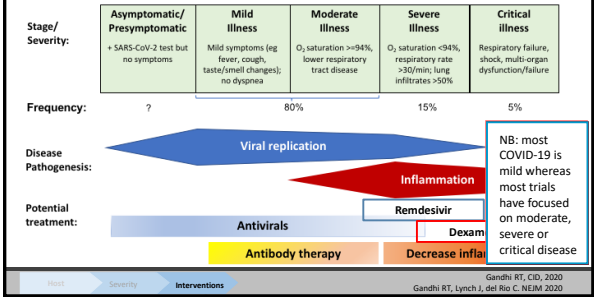
Decrease inflammation

Anti-IL-6 Inhibitor: Tocilizumab

Randomized Trial	Salvarani et al (RCT-TCZ-COVID-19) JAMA Int Med	Hermine et al (CORIMUNO-TOCI-1) JAMA Int Med	COVACTA Press release	EMPACTA Press release	Stone, BACC Bay, NEJM
Primary outcome	PaO2:FiO2 <150 ICU admission, death: RR, 1.05 (95% CI, 0.59 to 1.86)	Survival without NIV or MV by day 14: HR, 0.58 (90% CI, 0.33 to 1.00),	Clinical Status, 7-category scale: OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV, day 28: HR, 0.56 (95% CI, 0.32 to 0.97)	Intubation or death: HR 0.83 (95% CI 0.38 to 1.81)
Mortality, tocilizumab vs comparator	**3.3% vs 1.6%;** RR, 2.10 (95% CI, 0.20 to 22.6)	**11.1% vs 11.9%;** aHR, 0.92 (95% CI, 0.33 to 2.53)	**19.7% vs 19.4%;** ARD, 0.3% (95% CI, −7.6% to 8.2%)	**10.4% vs 8.6%;** ARD, 2.0% (95% CI, −5.2% to 7.8%)	**5.6% vs. 4.9%**

Modified from Parr, JAMA, 2020

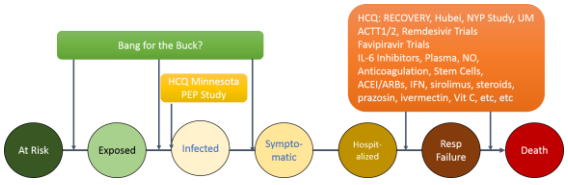
Treatment Across the COVID-19 Spectrum



Host Severity **Interventions**

Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Treatment Across the COVID-19 Infection Spectrum



Host Severity **Interventions**

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



Siedner M, Gandhi RT, Kim AY, JID, 2020

COVID-19 and HIV

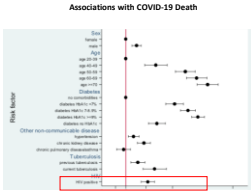
Is HIV a risk factor for severe COVID-19?

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)



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; Boulle A et al, CID, 2020

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)

Geretti AM, Stockdale A, Kelly S, et al. https://www.medrxiv.org/content/10.1101/2020.08.07.20170449v1. Geretti. HIV Glasgow 2020. Abstr O422.

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

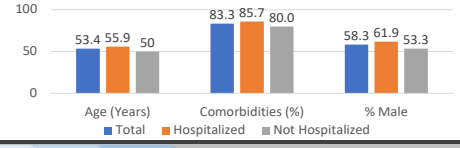
- Veterans Aging Cohort Study
- Risk of severe COVID outcomes similar by HIV status

	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)

Park et al., AIDS 2020, Virtual Covid 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.



Meyerowitz E et al, AIDS 2020, Virtual Covid 2020

COVID-19 and HIV

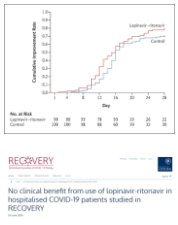
Is HIV a risk factor for severe COVID-19?

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
- Likely explanation: levels needed to inhibit SARS-CoV-2 not achieved in vivo



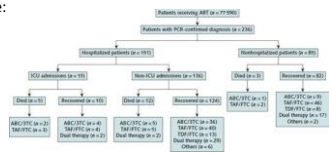
RECOVERY

No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY

Cao B et al, NEJM, 2020; RECOVERY Collaborative Group, Lancet, 2020
Schoergenhofer, Ann Int Med, 2020

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



Is HIV a risk factor? | ART and COVID | COVID and HIV Care

J del Amo et al, Ann Int Med, 2020

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)

Is HIV a risk factor? | ART and COVID | COVID and HIV Care

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

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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