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

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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

Slide 3 of X

Multidimensional Challenge of Treating COVID-19

Host/Clinical Manifestations	• Adults • Children • 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

Slide 4 of X

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

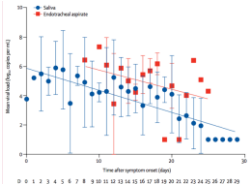
- Peripheral, bilateral ground glass opacities with or without consolidation
- Ground glass opacities may have rounded morphology

Host → Severity → Interventions

Courtesy of Dr. Brent Little (MGH Radiology)

Covid-19: Diagnosis

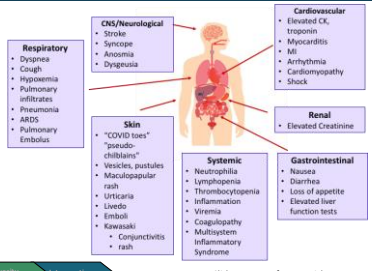
- PCR testing, most commonly of nasopharyngeal swab
- SARS-CoV-2 RNA levels peak just before symptom onset and remain detectable for ~3 weeks (occasionally months)
- Viral RNA may be detectable long after infectious virus is no longer culturable
- In several studies, virus no longer culturable after ~8-9 days of symptoms, at least in immunocompetent patients



Host | Severity | Interventions

To K, Lancet 2020; Arons NEJM 2020; Bullard CID 2020; Wolfel Nature 2020.

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.

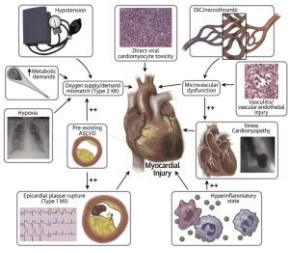
Slide courtesy of Dr. Daniela Kroshinsky (Mass General Hospital)

Host | Severity | Interventions

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

Cardiac Manifestations of COVID-19

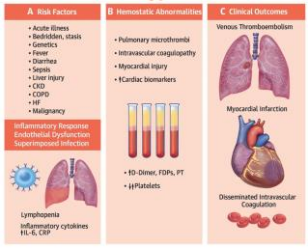
- Acute cardiac injury: elevated troponin
- Heart failure, cardiogenic shock
- Myocarditis
- Arrhythmias
- Thrombosis



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

Host | Severity | Interventions

Thromboinflammation and Hypercoagulability

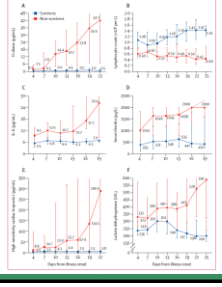


Bikdeli B et al JACC 2020

Host | Severity | Interventions

Thromboinflammation and Mortality

- Inflammatory biomarkers associated more severe disease and mortality
  - D-dimer
  - IL-6
  - CRP

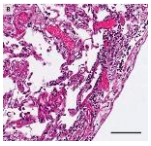


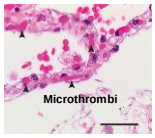
Zhou et al, Lancet 2020

Host | Severity | Interventions

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





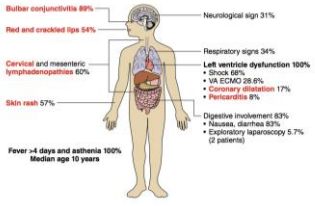
Lymphocytic pneumonia with multifocal endothelialitis

Ackermann M et al, NEJM, 2020

Host | Severity | Interventions

Host: Multisystem Inflammatory Syndrome in Children (MIS-C)

- Acute vasculitis with similarities to Kawasaki disease
- Fever, rash, conjunctivitis, gastrointestinal symptoms, shock and cardiac dysfunction
- Respiratory symptoms may be absent
- Children may have had recent SARS CoV-2 infection – MIS-C may represent a post-infectious hyper-inflammatory syndrome
- Cases have occurred in people in late teens, early 20s



Belhadjer Circulation 2020 https://doi.org/10.1161/CIRCULATIONAHA.120.048360; Jones Hospital Peds 2020 https://doi.org/10.1542/hpeds.2020-0123
Verdoni Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31103-X
Dufort EM et al NEJM, 2020 (https://doi.org/10.1056/NEJMoa2021756)
Feldstein LR et al JAMA, 2020 (https://doi.org/10.1056/NEJMoa2021680)

Host | Severity | Interventions

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

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

Host | Severity | Interventions

Risk Factors for Severe COVID-19

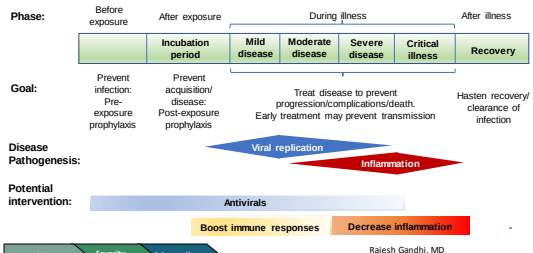
- Older age
- Chronic obstructive pulmonary disease; severe asthma
- Cardiovascular disease
- Type 2 diabetes mellitus
- Obesity (BMI of >=30)
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid organ transplant

- 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

Host | Severity | Interventions

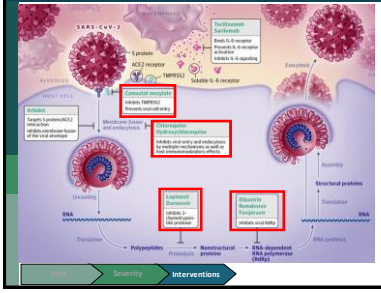
Goals of Treatment Across the COVID-19 Spectrum



Host | Severity | Interventions

Rajesh Gandhi, MD
Adapted from slide by Dr. Arthur Kim, Mass General Hosp

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

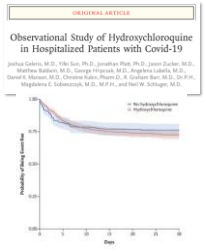
Sanders et al JAMA 2020

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

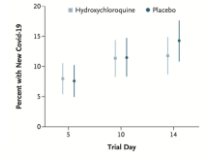

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Host | Severity | Interventions

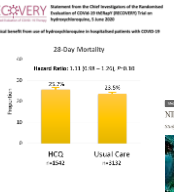
HCQ: To randomized controlled trials…

Post-exposure prophylaxis



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

Hospitalized patients



NIH halts clinical trial of hydroxychloroquine

Host | Severity | Interventions

Boulware D et al, NEJM 2020

https://www.recoverytrial.net/

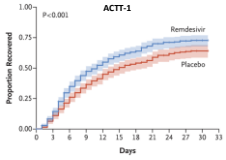
The Case of Remdesivir (RDV)

Antivirals

- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- Macaques: reduced SARS CoV-2 levels in lung (not upper respiratory tract), ameliorated disease


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

- 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



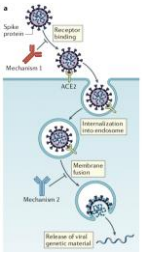
Host | Severity | Interventions

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



Host | 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

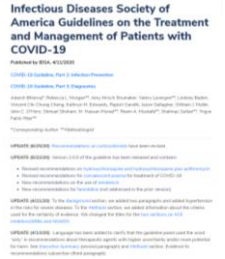
Mortality	Dex	Usual Care	RR mortality
All participants	21.6%	24.6%	**0.83** (0.74-0.92) **p=0.0007**
Ventilation/ ECMO	29%	40.7%	**0.65** (0.45 – 0.88)
Oxygen only	21.5%	25%	**0.8** (0.67 – 0.96)
No oxygen	17%	13%	**1.22** (0.86 – 1.75)

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

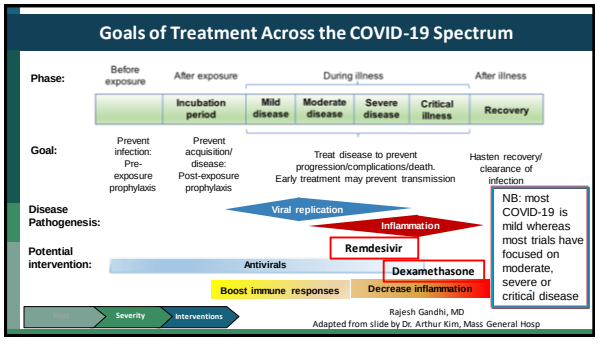
https://www.recoverytrial.net/

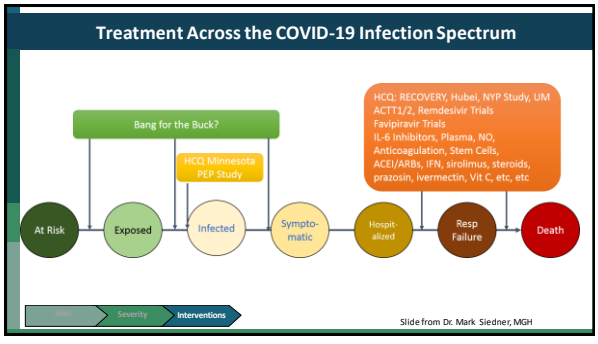
Host | Severity | Interventions

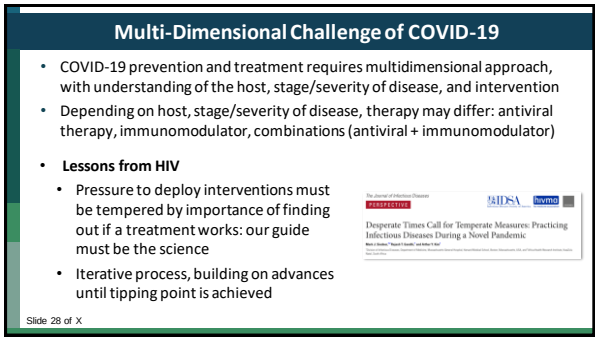
Treatment of COVID-19: Guidelines


Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Host | Severity | Interventions


Goals of Treatment Across the COVID-19 Spectrum
Phase:
Before exposure
After exposure
During illness
After illness
Incubation period
Mild disease
Moderate disease
Severe disease
Critical illness
Recovery
Goal:
Prevent infection: Pre-exposure prophylaxis
Prevent acquisition/ disease: Post-exposure prophylaxis
Treat disease to prevent progression/complications/death. Early treatment may prevent transmission
Hasten recovery/ clearance of infection
Disease Pathogenesis:
Viral replication
Inflammation
NB: most COVID-19 is mild whereas most trials have focused on moderate, severe or critical disease
Potential intervention:
Remdesivir
Antivirals
Dexamethasone
Boost immune responses
Decrease inflammation
Host
Severity
Interventions
Rajesh Gandhi, MD
Adapted from slide by Dr. Arthur Kim, Mass General Hosp


Treatment Across the COVID-19 Infection Spectrum
Bang for the Buck?
HCQ Minnesota PEP Study
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
At Risk
Exposed
Infected
Sympto-matic
Hospit-alized
Resp Failure
Death
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
PERSPECTIVE
IDSA
hivma
Desperate Times Call for Temperate Measures: Practicing Infectious Diseases During a Novel Pandemic
Slide 28 of X

COVID-19 and HIV

Is HIV a risk factor for severe COVID-19?

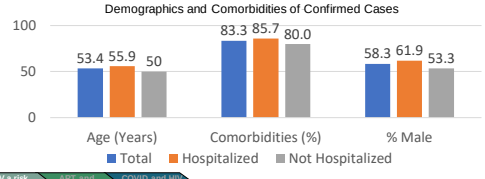
Do HIV medications have activity against SARS-CoV-2?

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

Slide 29 of X

HIV and COVID-19: MGH Series

- Between March 3 and April 26, 2020, systematically identified 36 people with HIV with confirmed COVID-19; another 11 with probable infection
- Almost 85% had a co-morbidity: obesity, cardiovascular disease, etc.



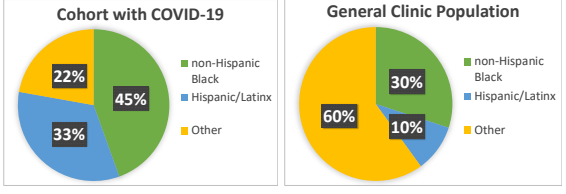
Is HIV a risk factor? | ART and COVID | COVID and HIV care

Meyerowitz E et al, AIDS 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

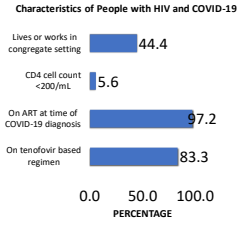


Is HIV a risk factor? | ART and COVID | COVID and HIV care

Meyerowitz E et al, AIDS 2020

Frequent Link to Congregate Settings

- Nearly half (16/36) lived or worked in congregate setting
- Only 2 had CD4 cell count <200
- All except one were on ART
- One person had newly diagnosed AIDS and cryptococccal meningitis

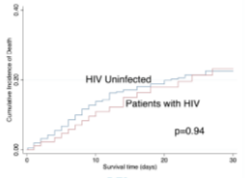


Meyerowitz E et al, AIDS 2020

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

Is HIV a Risk Factor for Severe COVID-19?

- Mt Sinai, NYC (March 12 to April 23, 2020)
- 88 PWH compared to 405 patients without HIV
- No difference in COVID-19 severity or mortality by HIV status
- Previous organ transplantation associated with death among those with HIV

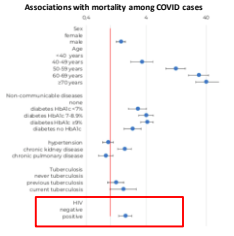


Sigel K et al, CID, 2020

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

HIV and COVID-19: South Africa

- About 3.5 million active public sector adult patients; ~535,000 with HIV
- ~12,500 COVID-19 and not deceased; 435 COVID-19 deaths
- Adjusted hazard ratio for death for HIV: 1.78 (1.38, 2.29); irrespective of viral suppression
- Cannot rule out residual confounding (eg socioeconomic status, obesity)



National Institute for Communicable Diseases, Covid-19 Special Health Surveillance Bulletin, June 22, 2020

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

HIV and COVID-19: "Twin" Pandemics?

- Non-HIV comorbidities common in people with HIV and COVID: these risk factors may play a dominant role in COVID-19 outcomes
- High rate of COVID-19 among racial and ethnic minorities: Structural factors and health care disparities drive "twin" epidemics of HIV and COVID-19
- High rate of COVID-19 among people with HIV who live or work in congregate settings → more must be done to protect vulnerable people in these settings
- Is HIV a risk factor for severe COVID-19? Additional data urgently needed but impact, if present, appears to be small

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

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?

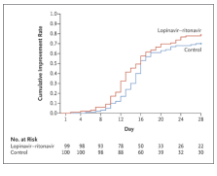
Is HIV a risk factor? | ART and COVID | COVID and HIV care

COVID-19 and HIV: The Question of LPV/r

- In vitro, LPV/r inhibits SARS-CoV protease
- LPV/r has been used as off-label treatment for people with COVID-19
- In an open label trial, 199 hospitalized patients with COVID-19 randomized to either 14 days of LPV/r or standard of care alone.
- No statistically significant difference was seen between the 2 groups in time to clinical improvement or mortality

The NEW ENGLAND JOURNAL of MEDICINE

March 18, 2020



Cao B et al, NEJM, 2020

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

RECOVERY: LPV/r vs. Usual Care

RECOVERY

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

- 1596 patients randomized to LPV/r; 3376 randomized to usual care
- 28-day mortality: 22.1% in LPV/r group, 21.3% in usual care group; relative risk 1.04 (95% CI 0.91 – 1.18, p=0.58)
- No evidence for beneficial effects on risk of progression to mechanical ventilation or length of hospital stay
- WHO's SOLIDARITY trial closed its LPV/r arm on July 4, 2020

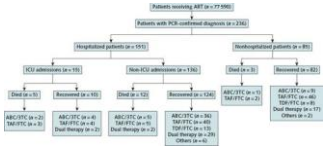
LPV/r Pharmacokinetics in People with COVID-19

- In vitro, half-maximal effective concentration (EC50) of LPV for SARS CoV-2: 16.4 micrograms/mL; EC50 for HIV much lower (0.07 micrograms/mL)
- Series of 8 patients with COVID-19 in Austria
  - Lopinavir/ritonavir 400/100 twice daily → measured trough levels
  - Unbound concentrations of LPV 60-120-fold lower than what is anticipated to inhibit SARS-CoV-2 protease

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



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

AIDS 2020 23RD INTERNATIONAL AIDS CONFERENCE 6–10 JULY 2020

- 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)

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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Question-and-Answer Session