CDC/IDSA COVID-19 Clinician Call

November 20, 2021

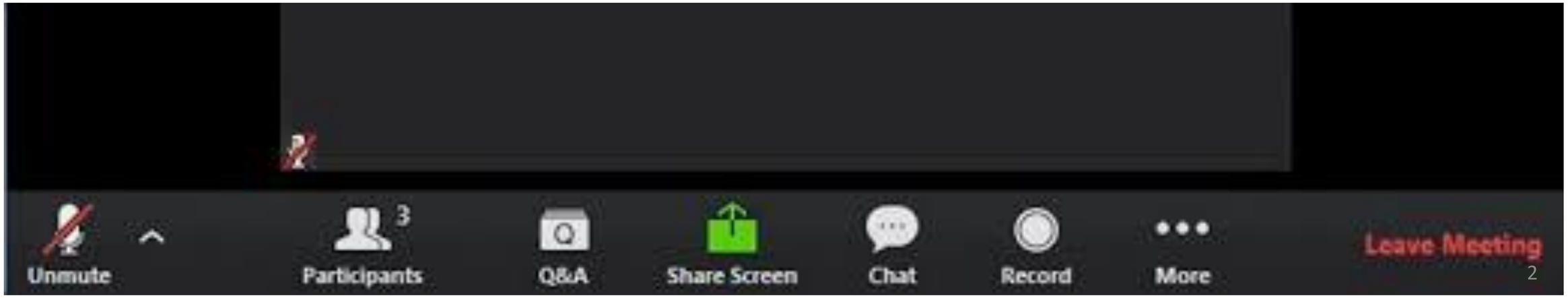
Welcome & Introductions

Dana Wollins, DrPH, MGC
Vice President, Clinical Affairs & Guidelines IDSA

- 79th in a series of weekly calls, initiated by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.

Question?
Use the “Q&A” Button

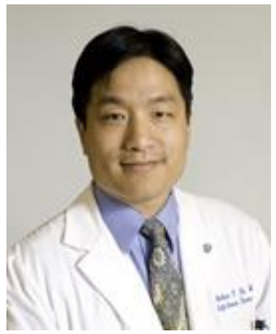
Comment?
Use the “Chat” Button



Updates on COVID-19 Treatment and Antibody-Based Prevention

Update on COVID-19 Therapeutics

Rajesh Gandhi, MD, FIDSA
Director, HIV Clinical Services and Education
Massachusetts General Hospital
Co-Director, Harvard Center for AIDS Research
Professor of Medicine, Harvard Medical School



Treatment of the Immunocompromised Patient: Case Presentation

Arthur Yu-Shin Kim, MD
Associate Professor of Medicine, Harvard Medical School
Associate Physician, Massachusetts General Hospital
Director, Viral Hepatitis Clinic, Division of Infectious Diseases
Massachusetts General Hospital

Oral Antivirals for COVID-19: Considerations for Use

Annie Luetkemeyer, MD
Professor of Medicine
Division of HIV, Infectious Diseases and Global Medicine
Zuckerberg San Francisco General Hospital
University of California San Francisco

Update on COVID-19 Therapeutics

Rajesh Gandhi, MD, FIDSA

Update on COVID-19 Therapeutics
(as of Nov 20, 2021 at 3 PM EST)

Rajesh T. Gandhi, MD

Massachusetts General Hospital

Harvard University Center for AIDS Research

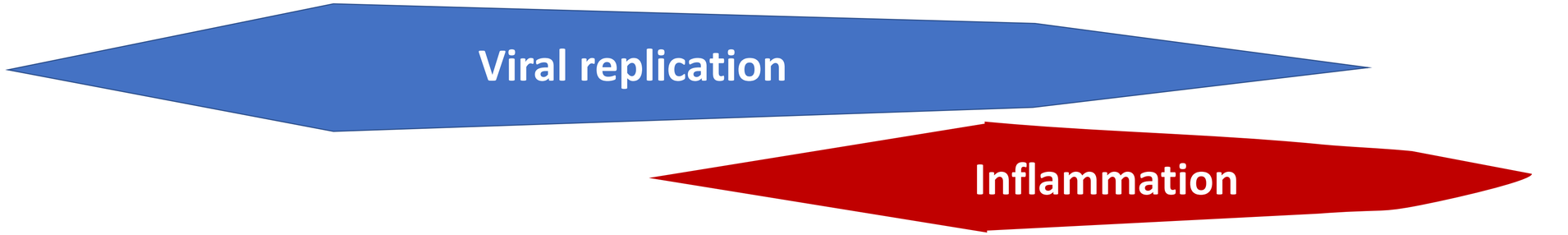
Disclosures (past 2 years):
Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels;
Recommendations in this talk are my own and not necessarily those of the Panels

Acknowledgments: Drs. Arthur Kim and Annie Luetkemeyer; Gregory Eschenauer, PharmD; Efe Airewele

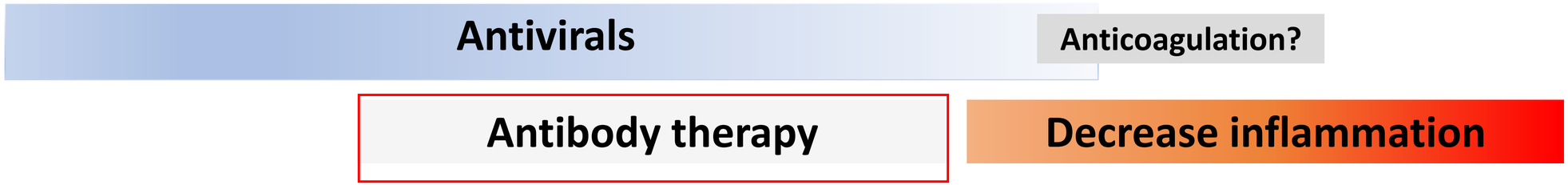
Treatment Across the COVID-19 Spectrum

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

Disease Pathogenesis:



Potential treatment:

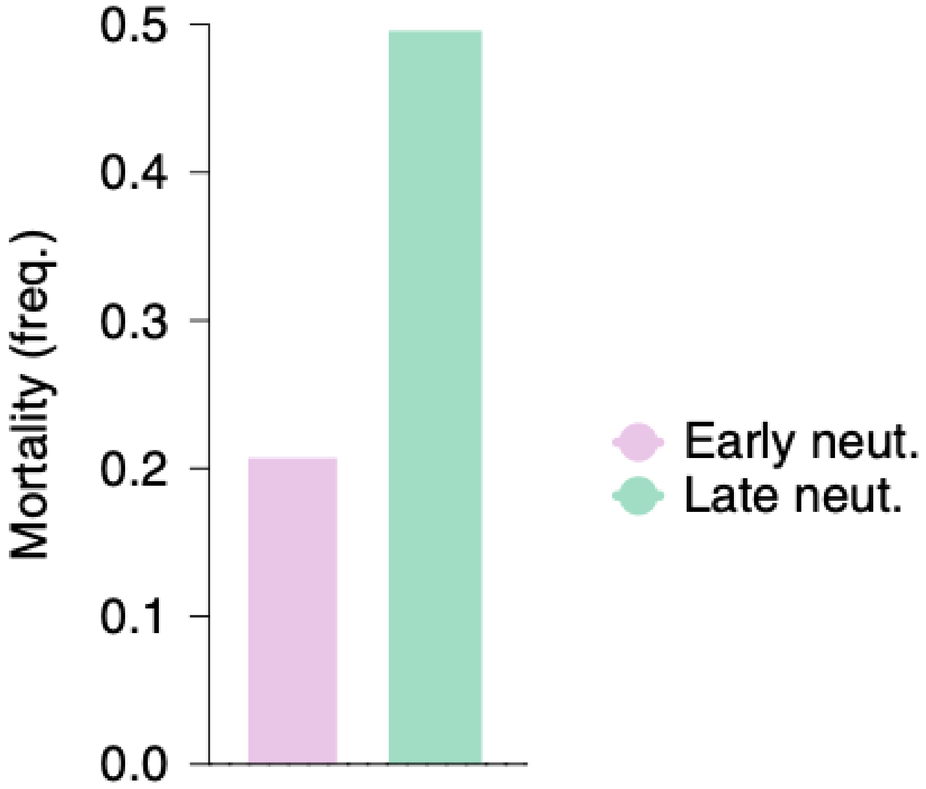


Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Anti-SARS-CoV-2 Monoclonal Antibodies for Treatment: Rationale

- Delayed production of neutralizing antibodies correlates with fatal COVID-19

- Would providing passive immunity through antibody therapy improve clinical outcomes?



Lucas C et al, Nat Med. 2021 May 5. doi: 10.1038/s41591-021-01355-0. PMID: 33953384.

Anti-SARS-CoV-2 Monoclonal Abs for Treatment

- Phase 3 placebo-controlled trials in non-hospitalized patients with mild to moderate COVID and ≥1 risk factor for severe disease

Antibody	% Reduction Hospitalization/Death
Bamlanivimab/etesevimab*	70%
Casirivimab/Imdevimab*	70%
Sotrovimab*	85%
BRII-196/BRII-198**	78%
Tixagevimab/Cilgivimab† (600 mg IM)	Sx ≤7 d: 50%; ≤3 d: 88%†
Regdanvimab††	72%††

*Authorized in US; **Interim analysis; †Reduction in severe COVID-19 or death in those with 3 d or less of symptoms; ††Approved in South Korea, authorized in European Union

Dougan M et al, NEJM, 2021; Weinreich et al., NEJM 2021; Gupta A et al, NEJM, 2021; Evering T et al, IDWeek 2021; https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-phiii-trial-positive-in-covid-outpatients.html; https://www.astrazeneca-us.com/content/az-us/media/press-releases/2021/new-analyses-of-two-AZD7442-COVID-19-Phase-III-trials-in-high-risk-populations-confirm-robust-efficacy-and-long-term-prevention.html; Ison MG et al, IDWeek 2021

Anti-SARS CoV-2 Antibodies for Prevention

Anti-SARS CoV-2 Monoclonal Abs for Post-Exposure Prophylaxis

- Casirivimab/imdevimab (subcutaneous or intravenous) and bamlanivimab/etesevimab (iv) authorized in individuals who are at high risk for progression to severe COVID and are:
  - Not fully vaccinated or not expected to mount adequate immune response to COVID vaccination (e.g., immunosuppressed individuals) AND
    - Have been exposed* to individual with COVID

      or

    - At high risk of exposure because of occurrence of COVID in same institutional setting (e.g., nursing home, prison)

*Within 6 feet for >=15 min, providing care at home, direct contact, exposed to respiratory droplets of infected person

PROVENT: Phase 3 Pre-exposure Prophylaxis Trial

IM Tixagevimab/cilgivimab (AZD7442) 300 mg vs. Placebo

Selection criteria
(N=5973 screened)

Key inclusion criteria:
- Adults age ≥18 years at increased risk for inadequate response to vaccination or SARS-CoV-2 infection
- Negative point-of-care SARS-CoV-2 serology test and unvaccinated at screening

Key exclusion criteria:
- History of laboratory-confirmed SARS-CoV-2 infection or positive SARS-CoV-2 result based on available data, history of SARS or MERS
- Prior vaccine or mAb/biologic for COVID-19

N=5197 Randomized and dosed

AZD7442
300 mg single dose (×2 IM injections of 1.5 mL each)
n=3460

Placebo (normal saline)
single dose (×2 IM injections of 1.5 mL each)
n=1737

Primary endpoints

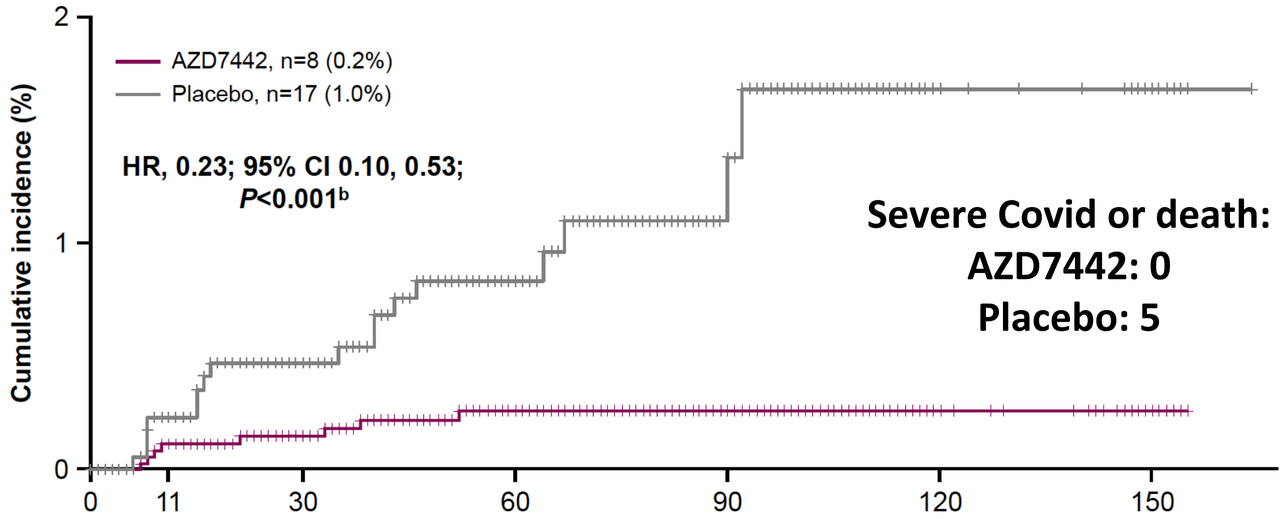
Efficacy endpoint:
SARS-CoV-2 RT-PCR–positive symptomatic illness prior to 183 days post dose (Full Pre-exposure Analysis Set)

Safety endpoint:
AEs through 457 days (15 months) post dose (Safety Analysis Set)

Who was in PROVENT (n=5172)?
- Age ≥60 yrs: 43%
- Obese: 41.7%. CVD: 8%; COPD 5%; CKD: 5%; Liver disease 4.6%
- Immunosuppressed: 3.8%

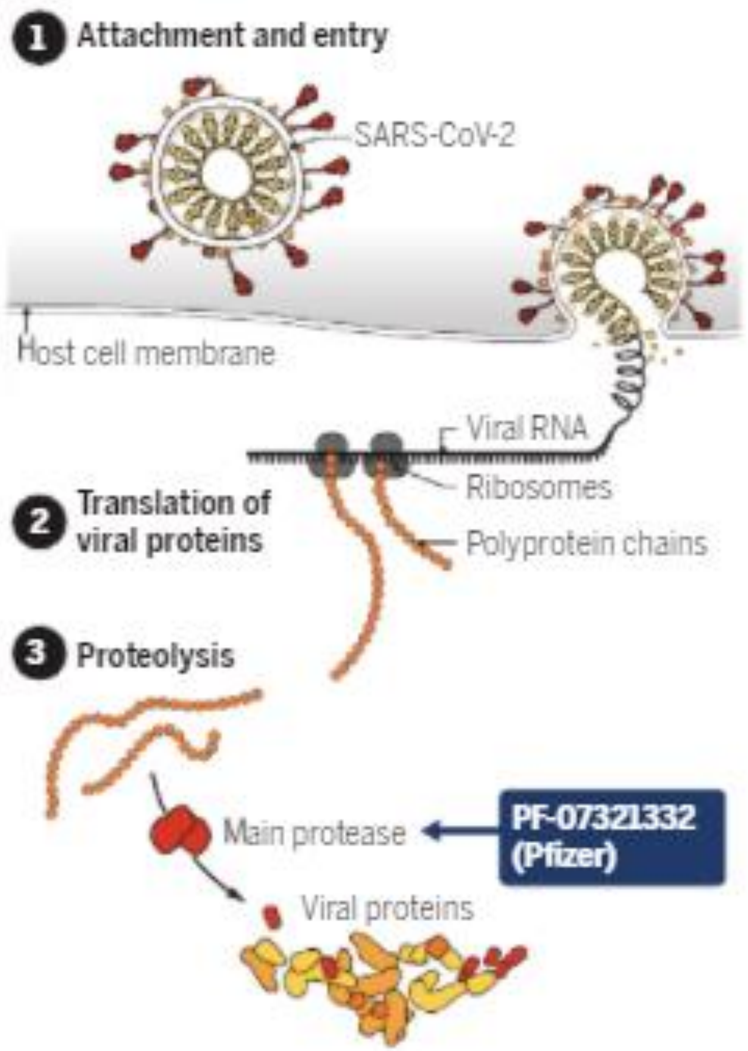
Symptomatic COVID-19: 77% Reduction

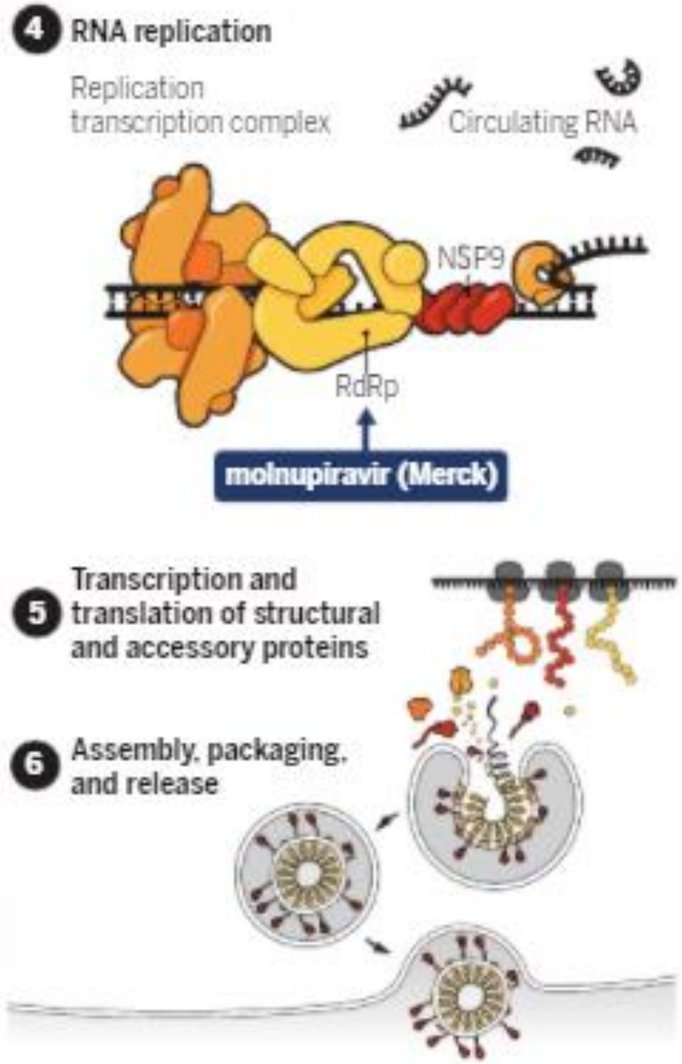
Updated Nov 18, 2021:
Median follow-up, 6 m (n=4991):
83% reduction



Levin M et al, IDWeek 2021, LB5
https://www.astrazeneca-us.com/content/az-us/media/press-releases/2021/new-analyses-of-two-AZD7442-COVID-19-Phase-III-trials-in-high-risk-populations-confirm-robust-efficacy-and-long-term-prevention.html

Small Molecule Inhibitors of SARS CoV-2 Replication

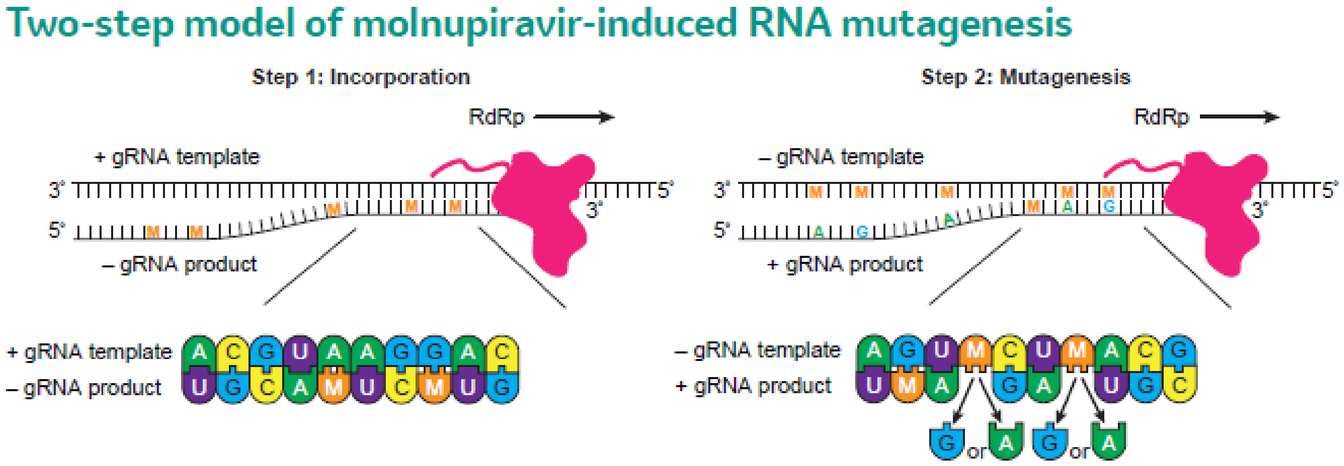




https://www.science.org/doi/epdf/10.1126/science.acx9605

Small Molecule Antiviral for SARS-CoV-2: Molnupiravir

- Oral ribonucleotide prodrug
- Converted into Beta-D-N4 hydroxycytidine (NHC)
- Inhibits SARS CoV-2 replication by inducing RNA mutagenesis (“viral error catastrophe”)



Adapted from Kabinger et al, 2021.

- Accumulation of multiple mutations beyond a tolerable threshold in the viral genome is known as viral error catastrophe, resulting in significant impairment or complete loss of viral replication

Strizki et al, IDWeek 2021, Abstract #511,

Molnupiravir

- **MoVE-In Trial:** hospitalized patients; stopped at interim evaluation because unlikely to demonstrate clinical benefit

- **MOVe-OUT Trial:**
  - Non-hospitalized adults, mild to moderate COVID-19
  - ≥1 risk factor for severe disease
  - Symptom onset within 5 days of study randomization
  - Molnupiravir 800 mg (four 200 mg pills) twice a day or placebo for 5 days
  - Interim analysis (n=775)

https://www.businesswire.com/news/home/20210415005258/en/Merck-and-Ridgeback-Biotherapeutics-Provide-Update-on-Progress-of-Clinical-Development-Program-for-Molnupiravir-an-Investigational-Oral-Therapeutic-for-the-Treatment-of-Mild-to-Moderate-COVID-19; https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

Molnupiravir (MOV)

- Who was in MOVe-OUT?
  - Median age 44 years
  - Age 60 years or older: 14%
  - Latin America (55%), Europe (23%), Africa (15%), US
  - Obesity (77%); diabetes (14%), active cancer (2%)
  - Symptom onset ≤3 d: 49%
  - Not vaccinated against COVID

	Hospitalization or death	% Reduction
MOV	**28/385 (7.3%)**	**48% (p=0.0012)**
Placebo	**53/377 (14%)**	

- Deaths: 0 (MOV), 8 (placebo)
- Appeared to be active against Gamma, Delta and Mu variants

https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio;
Johnson MG et al, ASTMH, Nov 17-21, 2021

Molnupiravir: Mutagenicity

Zhou et al, JID, 2021

- Hypoxanthine phosphoribosyltransferase gene mutation assay in CHO-K1 cells
- Cells exposed in vitro to dNHC for 32 days: evidence for mutagenesis

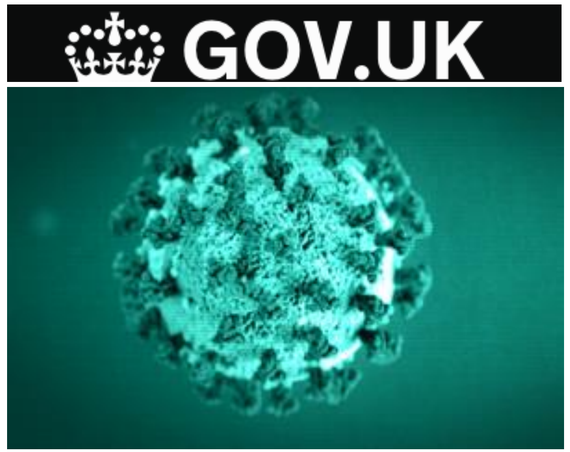
From UK Authorization:

- Positive in vitro bacterial reverse mutation assay (Ames test)
- In vivo rodent mutagenicity assays (Pig-a mutagenicity assay; Big Blue transgenic rodent assay): MOV did not induce increased mutation rate
- Negative for induction of chromosomal damage: in vitro micronucleus, in vivo rat micronucleus assays

Zhou S et al, JID, 2021; Troth S et al, JID, 2021; https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio;

Molnupiravir

- Authorized in UK for treatment of adults with mild-moderate COVID-19 who have at least 1 risk factor for developing severe illness
  - No renal, hepatic impairment dose adjustments; no drug interactions identified
  - Not recommended during pregnancy; women of child-bearing age should use contraception during treatment and for 4 days after last dose
  - Breast-feeding during treatment not recommended



- US FDA Advisory Meeting: Nov. 30, 2021

https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio

Small Molecule Antiviral for SARS-CoV-2: PF-07321332 (‘332)

- Oral SARS CoV-2-3CL protease inhibitor (given with ritonavir)
- Phase 2/3 EPIC trial in high-risk non-hospitalized patients
- Randomized to ‘332 (two 150 mg tablets)/ritonavir (one 100 mg tablet) twice daily or placebo for 5 days
- Interim analysis of patients treated within 3 days of symptom onset (n=774)

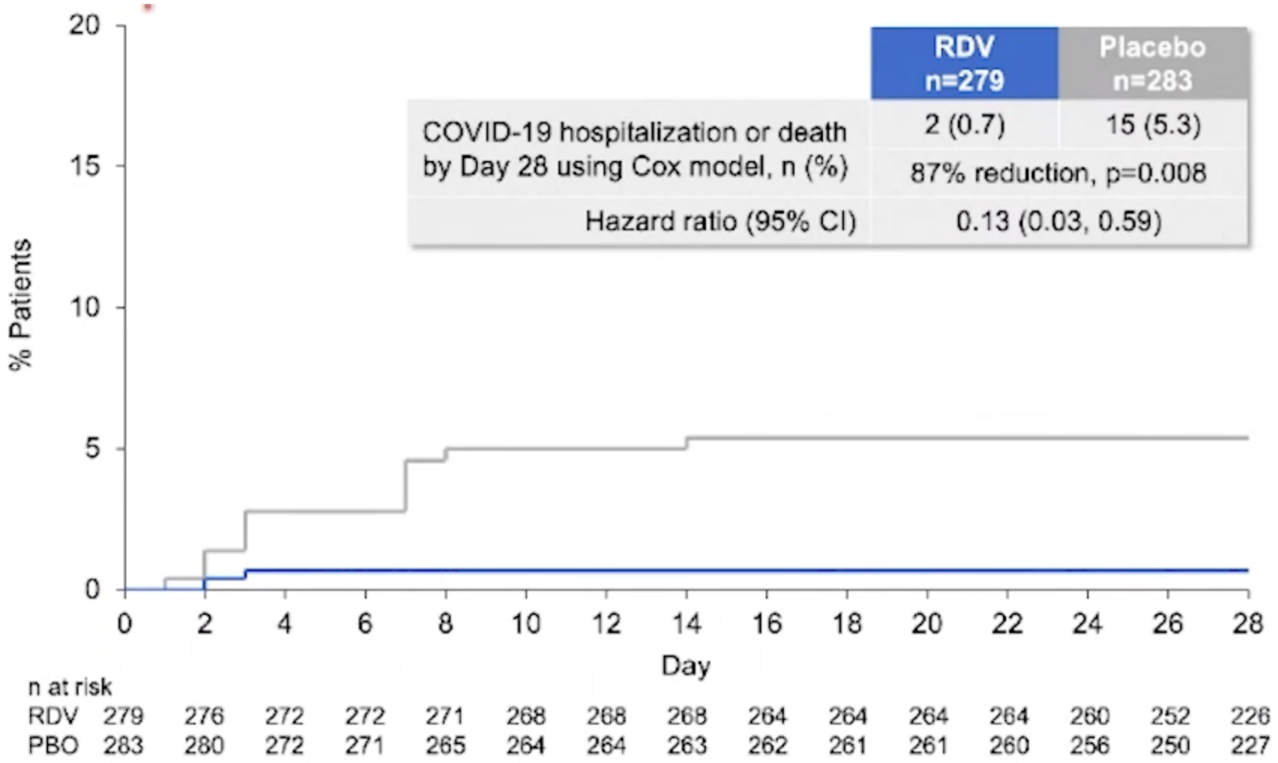
	Hospitalization or death	% Reduction
332/rtv	**3/389 (0.8%) 0 deaths**	**89% P<0.0001**
Placebo	**27/385 (7%) 7 deaths**	

- Similar reductions in hospitalization or death among people treated within 5 days of symptom onset (n=1219)
- Being evaluated: lower risk pts; vaccinees with risk factors; and as post-exposure prophylaxis

Owen DR et al, Science, 2021; https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

PINETREE: Remdesivir in Non-Hospitalized Individuals

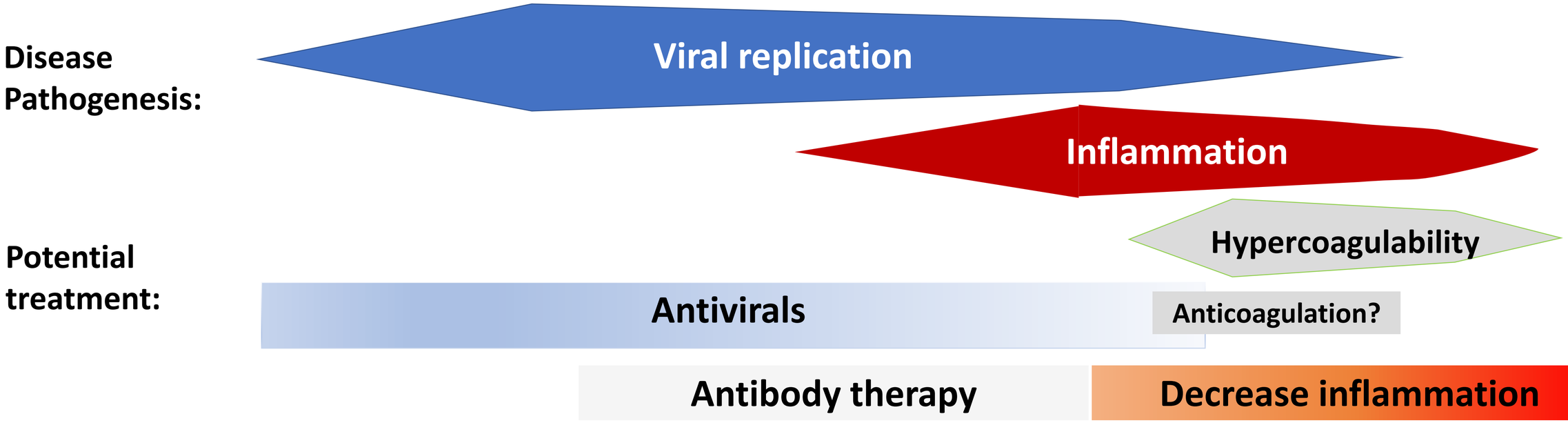
- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- Randomized trial (n=584):
  - High risk, symptoms <= 7 day
  - RDV IV x 3 days vs. placebo
- RDV: 87% reduction in hospitalization/death
  - No effect on NP SARS CoV-2 level



Hospitalized Patients with Severe or Critical COVID-19

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

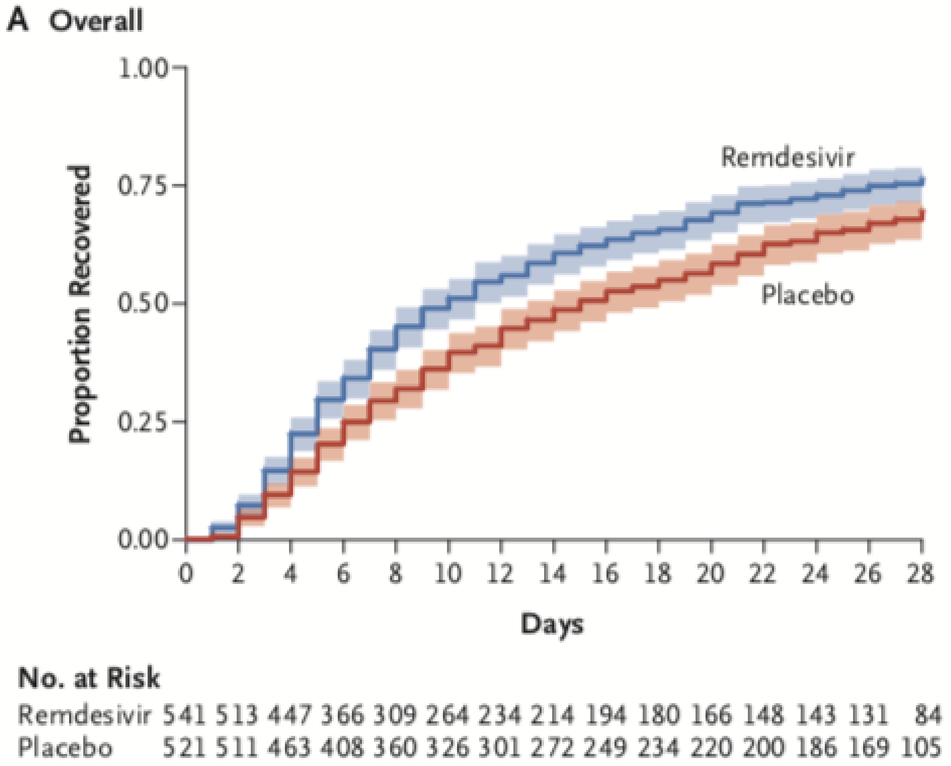


Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Remdesivir (RDV)

- ACTT-1: hospitalized pts, lower respiratory tract infection randomized to RDV or placebo
  - Clinical 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

ACTT-1: Time to Recovery

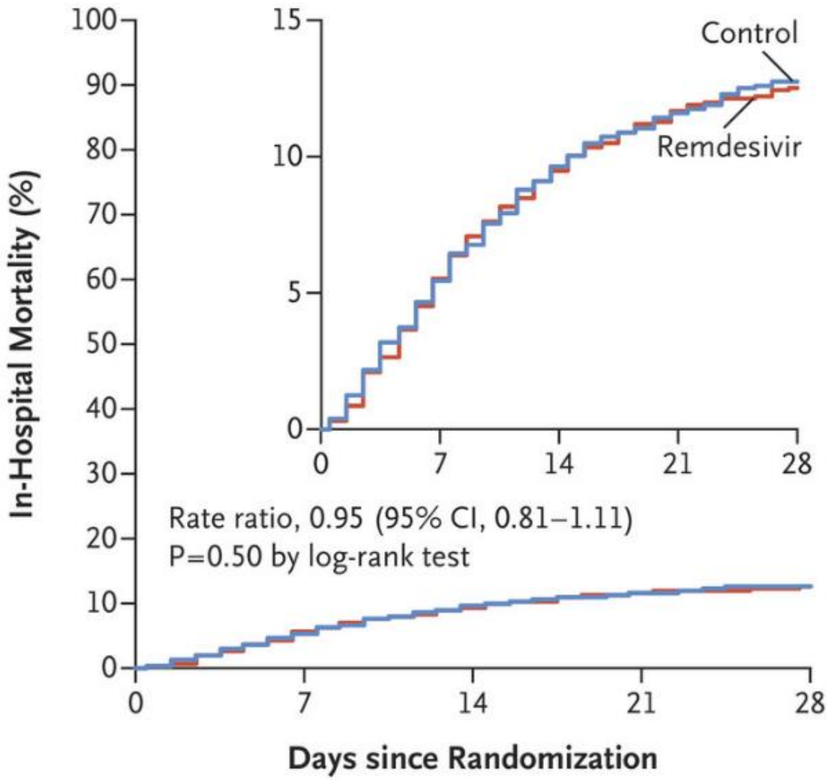


Beigel JH et al, NEJM 2020; Goldman JD et al, NEJM 2020

What about SOLIDARITY and DisCoVeRy?

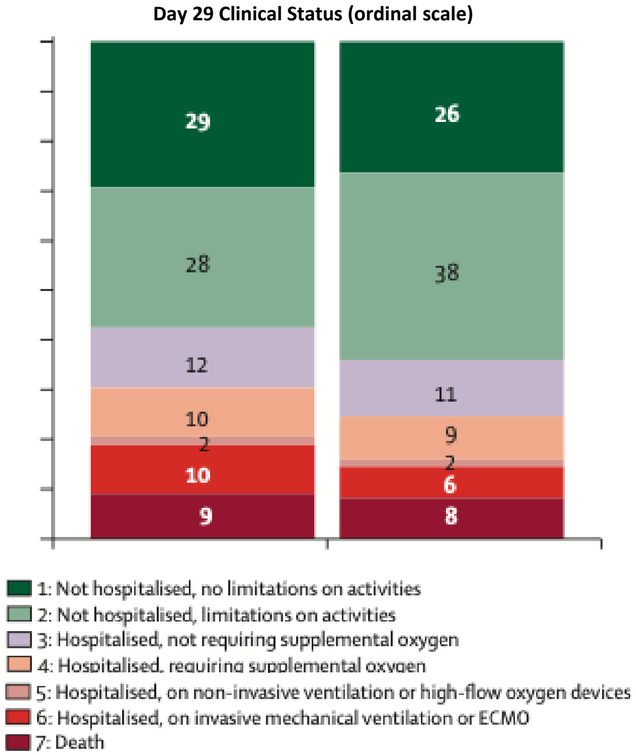
SOLIDARITY (WHO, >30 countries)

- Open label randomized trial
- No effect of RDV on mortality



DisCoVeRY (Europe)

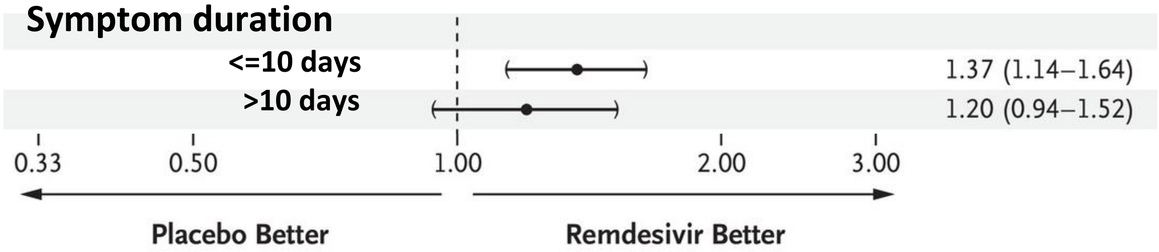
- Open label randomized trial
- >50% of participants also in SOLIDARITY
- Median symptom duration: 9 d
- No effect of RDV on clinical status or mortality



https://www.nejm.org/doi/full/10.1056/NEJMoa2023184; Ader F et al, Lancet, 2021

Where Does that Leave Remdesivir? My Take

- Early therapy more likely to confer benefit than later initiation
  - ACTT-1 Time to Recovery



  - PINETREE: RDV reduced hospitalization/death by 87% in high-risk non-hospitalized patients with symptoms <= 7 days

- RDV may have role in treating COVID-19 but benefit likely greatest if started early; if started when patient requiring increasing amounts of oxygen, combine with immunomodulation

Beigel JH et al, NEJM 2020; Hill J et al, IDWeek, 2021

Decrease inflammation

Immunomodulation

- Dexamethasone 6 mg/day: reduces mortality in hospitalized patients with COVID-19 who require oxygen
- Outcomes with 12 mg dexamethasone numerically better than with 6 mg but differences not statistically significant
- In hospitalized patients who do not require oxygen, dexamethasone may be harmful
- In patients with rapidly progressive COVID-19, hypoxemia and elevated inflammatory markers, adding tocilizumab (IL-6 blocker) or baricitinib (Jak inhibitor) to dexamethasone appears to be beneficial

RECOVERY Collaborative Group, NEJM, 2020; COVID Steroid 2 Trial Group, JAMA, 2021; REMAP-CAP, NEJM, 2021; RECOVERY Collaborative Group, Lancet, 2021; Marconi V et al, Lancet Resp Med, 2021

Areas of Uncertainty

Casirivimab/Imdevimab in Hospitalized Patients

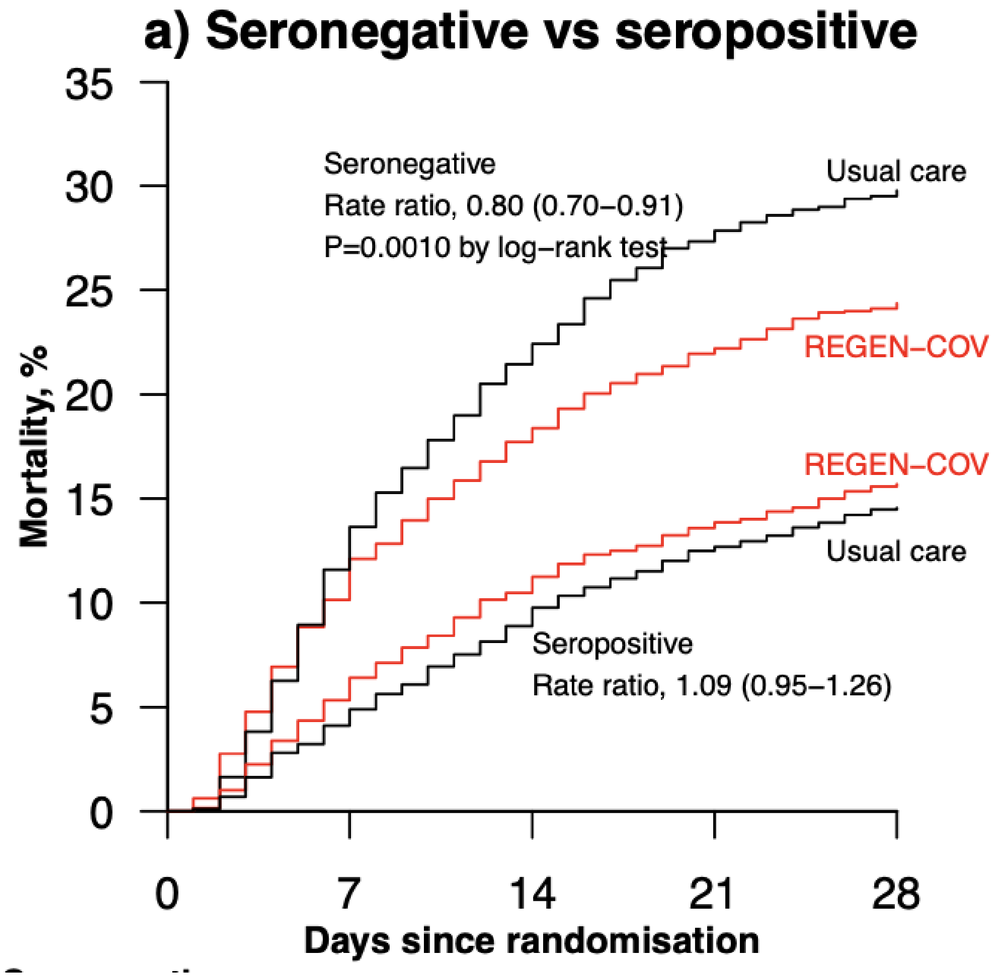
Hospitalized patients (n=9785) randomized to usual care with casirivimab 4,000 mg + imdevimab 4,000 mg IV or usual care alone (RECOVERY)

Results

- 28-day mortality: 20% vs. 21% (no difference)
- In those seronegative for anti-spike protein antibody, reduced mortality with casi/imdev: 24% vs. 30% (rate ratio 0.80)

Similar results in separate study of hospitalized patients on low-flow or no oxygen

We need rapid and reliable serology test to identify seronegative individuals



https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf;
Mylonakis E et al, IDWeek, 2021

Fluvoxamine: TOGETHER trial

- Placebo controlled randomized adaptive platform trial in Brazil
- Participants with risk factors for severe COVID-19 (n≈1500) and within 7 days from symptom onset
- Fluvoxamine 100 mg bid or placebo, 10 d
- Primary endpoint (composite of hospitalization or ED observation >6 hours): 11% (fluvoxamine) vs. 16% (placebo) (relative risk 0.68)

	Intention-to-treat analysis		
	N	n (%)	Relative risk (95% BCI)
Fluvoxamine	741	79 (11%)	0·68 (0·52–0·88)
Placebo	756	119 (16%)	1 (ref)

- No difference in hospitalizations (10% vs. 13%), duration of hospitalization, death (2% vs. 3%), viral clearance

Reis G et al, Lancet Global Health, 2021

Inhaled Steroids: Jury Still Out

- **Inhaled budesonide**
  - STOIC (n=146): open label randomized controlled trial
    - Decreased urgent care visits (including ED/hospitalization): 1 vs. 14%
  - PRINCIPLE (n=1856): open label randomized control trial
    - Improved time to recovery
    - Hospitalization/death: 6.8% vs. 8.8% (OR 0.75, 95% Bayesian CrI 0.55-1.03)
- **Ciclesonide** (30 days) (n=400): placebo controlled randomized clinical trial
  - Days to alleviation of symptoms: 19 days vs. 19 days
  - ED visit/hospitalization: 2/197 (1%) (ciclesonide) vs. 11/203 (5.4%) (placebo) (p=0.03)
  - Hospitalization/death: 3/197 (1.5%) vs. 7/203 (3.4%) (p=0.26, not significant)

Ramakrishnan S et al, Lancet Resp Med, 2021; Yu LM et al, Lancet, 2021; Clemency BM et al. Medrxiv 2021

COVID-19 Treatment Guidelines: What Not to Use and Areas of Uncertainty

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

Published by IDSA on 4/11/2020. Last updated, 12/2/2020

Adarsh Bhimraj*, Rebecca L. Morgan**, Amy Hirsch Shumaker, Valery Lavergne**, Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Rajesh Gandhi, Jason Gallagher, William J. Muller, John C. O'Horo, Shmuel Shoham, M. Hassan Murad**, Reem A. Mustafa**, Shahnaz Sultan**, Yngve Falck-Ytter**

Not recommended or suggested:

- Hydroxychloroquine
- Azithromycin
- Lopinavir/ritonavir
- Convalescent plasma in hospitalized patients (IDSA)

Insufficient data:

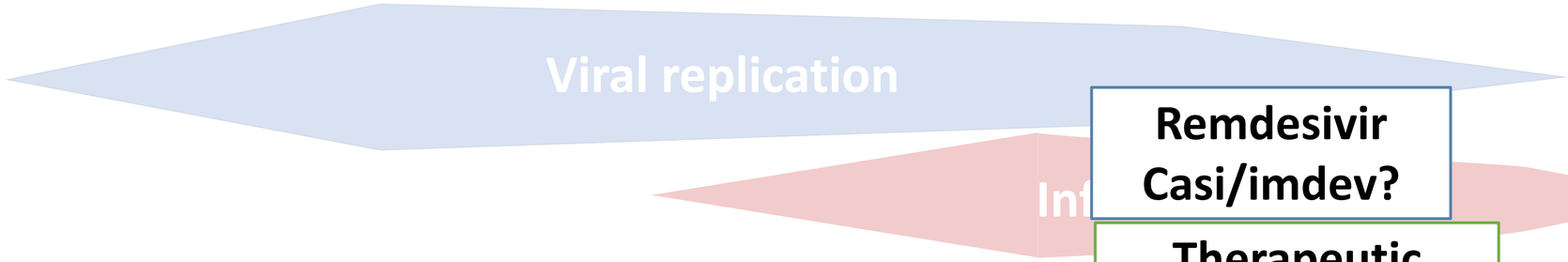
- Ivermectin
- Fluvoxamine
- Inhaled steroids
- Vitamin C, Zinc
- Colchicine

Prophylaxis and Treatment Across the COVID-19 Spectrum

Exposure	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (e.g., 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

Pre-exposure prophylaxis: COVID-19 VACCINES Tixagevimab/ Cilgavimab?

Post-exposure prophylaxis: Bam/Ete,Casi/Imdev (high risk, not fully vaccinated or immunosuppressed)



Remdesivir Casi/imdev?

Therapeutic anticoagulation?

Bam/Ete, Casi/Imdev or Sotrovimab (high risk outpatients with mild-mod COVID-19) Molnupiravir? '332?

Dexamethasone In some patients: IL-6 inhibitor or Jak inhibitor

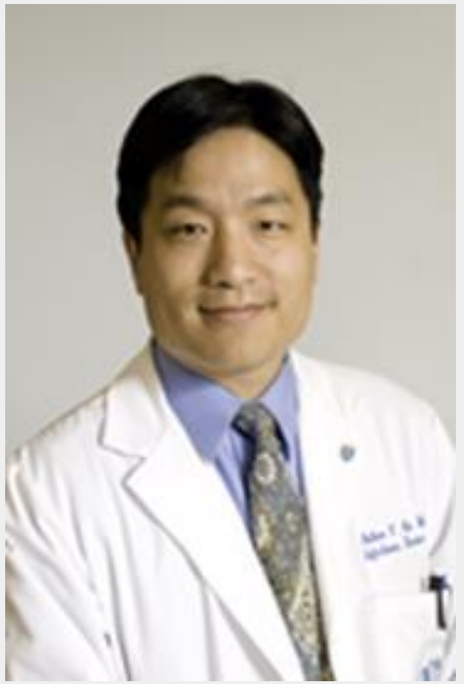
Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

COVID-19 Treatment: Final Thoughts

- Therapy for COVID-19 depends on host and severity of disease: not one-size fits all
- Antiviral therapy (including anti-SARS-CoV-2 monoclonal antibodies): greatest benefit early in disease when viral replication is active and, perhaps, in seronegative hospitalized patients
- Immunomodulators, including dexamethasone (and tocilizumab or baricitinib in select patients): greatest benefit later in course of disease when there is excess inflammation
- New therapies, including oral agents, needed (and are hopefully coming soon)

Treatment of the Immunocompromised Patient: Case Presentation

Arthur Yu-Shin Kim, MD



Case Presentation

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Disclosures, last 12 months (Updated 11/19/2021)

Research Funding:

National Institutes of Health

- **National Institute of Allergy and Infectious Diseases**
- **National Institute of Drug Abuse**

Patient-Centered Outcomes Research Institute

Industry support to myself/institution:

None

Scientific Advisory Board:

Data Monitoring Committee, Kintor Pharmaceuticals, ACTIV-6

Speaker's Bureau:

None

Royalties:

Uptodate

Disclaimer: Literature is vast and rapidly evolving

I will discuss the following off-label use in this presentation:

All treatments for COVID-19 except remdesivir (only approved medication)

Case Part 1

- 46 y/o man with history of living related kidney transplant
  - IgA nephropathy, kidney transplant performed 16 years ago
    - Maintained on sirolimus, prednisone 5 mg
    - Baseline Cr = 1.4 mg/dL
  - Post-transplant course complicated by gout, no infectious complications
  - Works as school administrator
- Since school opening, minimizes in-person meetings, wears masks
- Immunized with BNT162b2 (Pfizer) in February/March 2021
- Scheduled his 3rd dose
- November 2021: his wife, who is a kindergarten teacher, after known exposure tests positive with malaise, nasal congestion

Case Audience Response 1

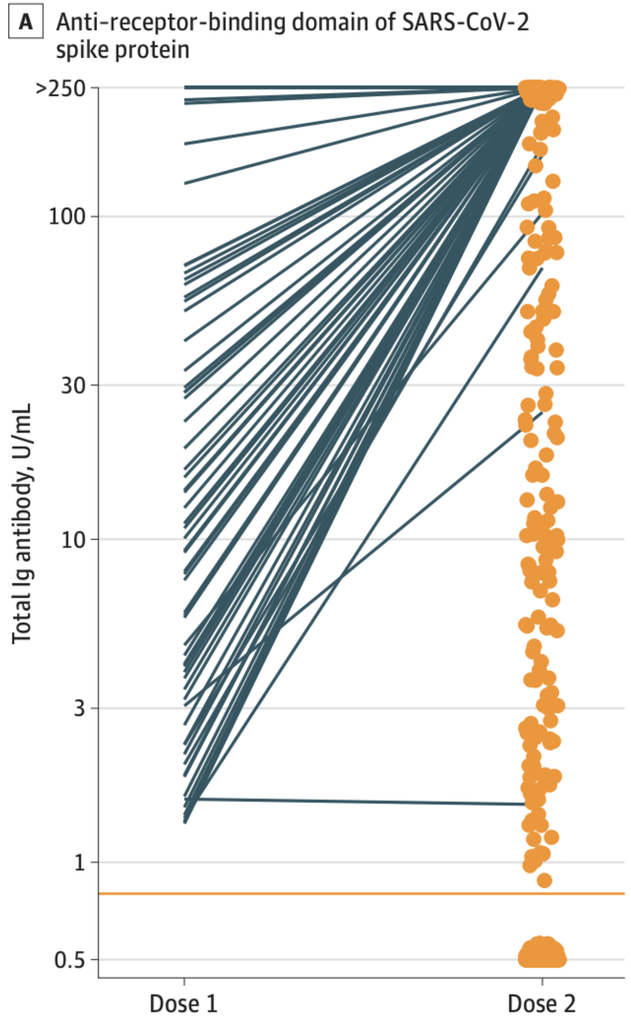
- 46 y/o man with history of living related kidney transplant on sirolimus, prednisone 5 mg, exposed to his wife with mild COVID-19.

- Tested d3 and d5 PCR negative after index case' symptom onset, asymptomatic

It is now d6 after her symptom onset. What is your next step?

A. Watchful waiting
B. Refer for monoclonal antibody administration for post-exposure prophylaxis
C. Arrange test for anti-spike antibodies; if negative give monoclonal antibody

Solid-organ transplant, vaccine-responses and risk of breakthrough COVID-19



- After mRNA vaccine administration, binding antibody responses are lower than in non-immunocompromised
  - A significant proportion do not have detectable antibodies
- 17 U.S. hospitals contributed outcomes from 18,215 fully vaccinated transplant recipients
  - 151 breakthrough infections, 87 hospitalizations
  - 14 deaths (mortality 9.3%)
  - Higher rate of infection and morbidity/mortality than general population

Boyarsky et al. JAMA 2021; Qin et al. Transplantation 2021

Case Part 2

- 46 y/o man with history of living related kidney transplant on sirolimus, prednisone 5 mg
- The patient did not contact provider and was not referred for mAbs
- Develops diarrhea, malaise, nasal congestion
- D3 of illness, Cr = 1.7 admitted for rehydration
- SARS-CoV-2 PCR positive, cycle threshold = 22
- Oxygen saturation 95-97%, CXR negative for infiltrates
- Mild leukopenia, absolute lymphocyte count 1000 cells / µl
- C-reactive protein 4.6 mg/dL

Case Audience Response #2

- 46 y/o man with history of living related kidney transplant on sirolimus, prednisone 5 mg with mild SARS-CoV-2, predominantly GI presentation

It is now D4 after his symptom onset and he is hospitalized.

What is your therapeutic priority?

A. Watchful waiting / supportive care
B. Increase dose of systemic corticosteroids to dexamethasone 6 mg
C. Fluvoxamine
D. Monoclonal antibodies
E. Remdesivir

Case Audience Response #2

- 46 y/o man with history of living related kidney transplant on sirolimus, prednisone 5 mg with mild SARS-CoV-2, predominantly GI presentation

It is now D4 after his symptom onset and he is hospitalized.

What is your therapeutic priority?

A. Watchful waiting / supportive care
B. Increase dose of systemic corticosteroids to dexamethasone 6 mg
C. Fluvoxamine
D. **Monoclonal antibodies**
E. Remdesivir

Questions

- *Is vaccination status relevant to treatment decisions?*
- *Can we generalize treatment data to the immunocompromised population?*

Are monoclonal antibodies effective in vaccinated populations?

- Randomized trials of mAbs recruited predominantly in the pre-vaccine era
- Observational data support use
  - Breakthrough cases in a cohort of 1396 persons
    - 7.7% required hospitalizations
    - Monoclonal antibody treatment associated with a significantly lower risk of hospitalization (OR 0.227, 95% CI 0.128-0.403)
    - Number needed to treat to prevent one hospitalization
      - Lowest-risk patients : 225
      - Highest-risk patients : 4

Bierle et al. Journal of Infectious Diseases 2021

Case Audience Response #3

- The patient is hospitalized for COVID-19 so cannot receive antibodies under the EUA. An emergency use investigational drug application is initiated. Meanwhile, his anti-spike antibody returns as positive.

What next?

A. Cancel monoclonal antibody, watchful waiting / supportive care
B. Proceed with monoclonal antibody administration
C. Remdesivir

Key take-home points

- Immunocompromised patients post vaccination have lower titers of antibodies and are at risk for severe breakthrough COVID-19 outcomes
  - Maintain social distancing, prioritize for 3rd dose / boosting
- Immunocompromised patients are prioritized candidates for available therapies, such as monoclonal antibodies
  - Treatment of outpatient COVID-19
  - Post-exposure prophylaxis with monoclonal antibodies
  - Future: Pre-exposure prophylaxis with monoclonal antibodies
- COVID-19 therapies should be deployed to the “right patient at the right time”

Oral Antivirals for COVID-19: Considerations for Use

Annie Luetkemeyer, MD

Oral antivirals for COVID-19

Considerations for use

CDC/IDSA Clinician Call

11/20/2021

ZUCKERBERG SAN FRANCISCO GENERAL Hospital and Trauma Center

Annie Luetkemeyer, MD
Professor of Medicine
@ANNIELUET
Division of HIV, Infectious Diseases and Global Medicine

Disclosures: Research grant support to UCSF from Astra-Zeneca, Merck & Gilead

Oral antiviral considerations

- **Impact of timing & disease severity**
- What role will monoclonals have when oral antivirals become available?
- Unanswered questions

Merck and Ridgeback Biotherapeutics Provide Update on Progress of Clinical Development Program for Molnupiravir, an Investigational Oral Therapeutic for the Treatment of Mild-to-Moderate COVID-19

Save

April 15, 2021 6:45 am ET

MOVE-IN study

- Phase 2 study of <u>hospitalized</u> patients <u>with symptoms x <10days</u>
- 200/400/800mg/Placebo x 5 days.
- Endpoint: sustained recovery through D29
- Stopped at interim evaluation "**unlikely to demonstrate clinical benefit**"

October 8, 2021
2:26 PM PDT
Last Updated a day ago

Healthcare & Pharmaceuticals

Two Indian drugmakers to end trials of generic Merck pill for moderate COVID-19

3 minute read

By Shivani Singh and Anuron Kumar Mitra, Neha Arora

- "Moderate" = 90-93% O2 sat
- Stopped for lack of efficacy in moderate COVID
- Reported to be effective in mild COVID (no data yet)

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Take Homes:

- Molunpiravir must be given VERY SOON after symptom onset: **≤ 5 days**
- Molnupiravir (at least as monotherapy) not effective once moderate/severe disease has developed

Oral antiviral considerations

- Impact of timing & disease severity
- **What role will monoclonals have when oral antivirals become available?**
- Remaining questions

	Monoclonal Abs	Molnupiravir	PF-07321332 (Paxlovid)
Efficacy	RR: 70-85% Absolute risk ≈ 5-10%-> 1%	RR 50% Absolute risk **14%** ->7%	RR 85-89% Absolute risk 6.7%-> 1%
Timing	EUA: Up to <u>10 days</u> from symptom onset • BRII data suggest no difference if ≤5d vs >5 from symptoms (11%→2%) Evering et al IDWeek 2021, LB2 *However:* • Still advisable to give as soon as possible: AZD TACKLE data showed improved efficacy when given sooner • Much clinical trial data limited to ≤ 5-7 days TACKLE, AZD press release 10/2021	Within <u>5 days</u> from symptom onset	
Route	• IV- programmatic burden • SC- easier programmatically but delayed absorption, no treatment data • IM- likely better than SC in terms of PK	Oral, BID	

	Monoclonal Abs	Molnupiravir	PF-07321332 (Paxlovid)
Priority populations	• **Highest** risk – immunosuppressed, elderly – mAbs preferred? • 6-10 days of symptoms • Expected drug interactions with '322 • GI side effects from COVID-19 *(Ritonavir-boosted PI can exacerbate)*	**MOST patients** meeting higher risk criteria as long as <u>within 5 days</u> of symptoms	
Populations to avoid	• Unable to come to an accessible site for treatment & monitoring	Avoid: • Pregnant women • Women trying to conceive	• On medications not compatible with PI or that cannot be held temporarily: PI/ritonavir: +++ interactions

Unanswered questions

- Role for combination therapy in highest risk?
- Emergent resistance with treatment failure ?
- Data in VACCINATED populations
  - Lower risk of hospitalization/death
  - Treatment still may impact transmission & symptom duration
- Distribution
  - Initial Allocation via HHS, similar to mAbs & remdesivir
  - Role of commercial pharmacies determined locally
- Limited initial supply:
  - 100,000 cases per day
  - ? 10% qualify as higher risk and within 5 days of diagnosis – treating ≥10K per day?

Q&A/Discussion

Today's Links

- Slide 1 - This webinar is being recorded and can be found with the slides online at https://www.idsociety.org/cliniciancalls
- Slide 8 - https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-phiii-trial-positive-in-covid-outpatients.html
- Slide 8 - https://www.astrazeneca-us.com/content/az-us/media/press-releases/2021/new-analyses-of-two-AZD7442-COVID-19-Phase-III-trials-in-high-risk-populations-confirm-robust-efficacy-and-long-term-prevention.html
- Slide 11 - https://www.astrazeneca-us.com/content/az-us/media/press-releases/2021/new-analyses-of-two-AZD7442-COVID-19-Phase-III-trials-in-high-risk-populations-confirm-robust-efficacy-and-long-term-prevention.html
- Slide 12 - https://www.science.org/doi/epdf/10.1126/science.acx9605
- Slide 14 - https://www.businesswire.com/news/home/20210415005258/en/Merck-and-Ridgeback-Biotherapeutics-Provide-Update-on-Progress-of-Clinical-Development-Program-for-Molnupiravir-an-Investigational-Oral-Therapeutic-for-the-Treatment-of-Mild-to-Moderate-COVID-19
- Slide 14 - https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

Slide 15 - https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio

- Slide 16 -https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio
- Slide 17 - https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio
- Slide 18 - Owen DR et al, Science, 2021; https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate
- Slide 23 - https://www.nejm.org/doi/full/10.1056/NEJMoa2023184

Today's Links Continued

- Slide 27 - https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf
- Slide 39 - https://jamanetwork.com/journals/jama/fullarticle/2779852
- Slide 39 - https://journals.lww.com/transplantjournal/Fulltext/2021/11000/Risk_of_Breakthrough_SARS_CoV_2_Infections_in.43.aspx
- Slide 43 - https://combatcovid.hhs.gov/
- Slide 45 - https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab570/6429422
- Slide 49 - https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1009766
- Slide 49 - https://www.nature.com/articles/s41591-021-01355-0
- Slide 51 - https://ard.bmj.com/content/79/7/859
- Slide 51 - https://www.nature.com/articles/s41584-020-00562-2
- Slide 52 - https://jamanetwork.com/journals/jama/fullarticle/2780870
- Slide 52 - https://www.nejm.org/doi/full/10.1056/NEJMoa2109682
- Slide 53 - https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/
- Slide 54 - https://www.nejm.org/doi/full/10.1056/NEJMoa2102685
- Slide 54 - https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced
- Slide 54 - https://www.nejm.org/doi/full/10.1056/NEJMoa2108163
- Slide 54 - https://www.nejm.org/doi/full/10.1056/NEJMoa2107934
- Slide 69 - https://www.idsociety.org/covid-19-real-time-learning-network/

CDC COVID-19 Vaccine Partner Update Call
Monday, November 22
11:00–11:45 AM ET

CDC will provide information following the Friday, 11/19 Advisory Committee on Immunization Practices (ACIP) meeting with time for questions and answers.

Connection Details:
Please click the link below to join the webinar: https://cdc.zoomgov.com/j/1610774405?pwd=UzN2M0YydlhkNGJQZGNFWEFCcjYxdz09; Passcode: rU*y2?x6
Or One tap mobile- US: +16692545252,,1610774405#,,,,*27815048# or +16468287666,,1610774405#,,,,*27815048#

Or Telephone-
Dial (for higher quality, dial a number based on your current location):
US: +1 669 254 5252 or +1 646 828 7666 or +1 669 216 1590 or +1 551 285 1373
Webinar ID: 161 077 4405
Passcode: 27815048
International numbers available: https://cdc.zoomgov.com/u/adw3IRbRPg

Or an H.323/SIP room system:
H.323: 161.199.138.10 (US West) or 161.199.136.10 (US East)
Meeting ID: 161 077 4405
Passcode: 27815048
SIP: 1610774405@sip.zoomgov.com
Passcode: 27815048

Please direct any questions to eocevent424@cdc.gov

White House - Public Health Community Appreciation Town Hall

Monday, November 22
12:00 – 1:00 PM ET

Federal, state, and local public health professionals have been leaders in responding to the COVID-19 pandemic since it first reached the U.S. This Thanksgiving season we express our sincere gratitude to the entire public health community.

Attendees will hear from the White House COVID-19 Response Team, HHS Secretary Xavier Becerra, and CDC Director Rochelle Walensky, as well as public health professionals from a variety of fields.

To Join:
https:/www.youtube.com/watch?v=RWCflZXeGIM

COVID-19 Real-Time Learning Network

Brought to you by CDC and IDSA

Real-Time Learning Network Needs your Feedback

Help shape future plans for the COVID-19 Real-Time Learning Network (RTLN).

Your responses to this short survey will ensure that the RTLN is useful for front-line clinicians.

https://www.surveymonkey.com/r/BFBJ5CK

Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID19

We want to hear from you!

Please complete the post-call survey.

Next Call

Saturday, Dec. 4th

A recording of this call will be posted at
www.idsociety.org/cliniciancalls

-- library of all past calls now available --

Contact Us:

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