

AMERICAN PUBLIC HEALTH ASSOCIATION

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RESPONDING TO COVID-19: A SCIENCE-BASED APPROACH

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WEBINAR #10: LEARNING TO TREAT COVID-19:
CLINICAL TRIALS AND DEVELOPING THERAPEUTICS
DURING A PANDEMIC

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WEDNESDAY
JUNE 24, 2020

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The webinar convened at 5:00 p.m.
Eastern Daylight Time, Carlos del Rio, MD,
Moderator, presiding.

PRESENT

CARLOS DEL RIO, MD, Distinguished Professor of Medicine; Professor of Global Health and Epidemiology, Emory Rollins School of Public Health; Executive Associate Dean, Emory at Grady; Co-Director, Emory Center for AIDS Research, Moderator

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RAJESH GANDHI, MD, Professor of Medicine, Harvard Medical School; Director of HIV Clinical Services and Education, Massachusetts General Hospital

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P-R-O-C-E-E-D-I-N-G-S

5:00 p.m.

DR. DEL RIO: Good evening, and welcome to the tenth webinar in the COVID-19 conversation series, brought to you by APHA and the National Academy of Medicine.

My name is Carlos Del Rio and today's webinar is entitled Learning to Treat COVID-19: Clinical Trials and Developing Therapeutics During a Pandemic.

Today's webinar has been approved for 1.5 continuing education credits for CHES, CME, CNE, and CPH. None of the speakers have any relevant financial relationships to disclose.

Please note that if you are wanting continuing education credits, you should have registered with your first and last name.

Everyone who wants credit must have their own registration and watch today's event in its entirety.

All the participants today will receive an email within a few days from

CPD@covid19conversations.com for information on claiming credit.

An online evaluation must be submitted by August 5, 2020 to receive continuing education credit. If you have any questions or topics you'd like us to address today or in future webinars, please enter them in the Q&A box or email us at APHA@APHA.org.

If you experience technical difficulties during the webinar, please enter your question in the Q&A box. Please pay attention to the chat for announcements about how to troubleshoot.

The webinar will be recorded and the recordings and transcript will be available on our website, www.covid19conversations.org. More information on the series and recordings of past webinars are available at that link.

I want to now use this opportunity to thank my Co-Chair in this webinar, Dr. Nicole Lurie, former Assistant Secretary for Preparedness and Response.

You can see in this slide the other members of the Expert Advisory Committee that have put this webinar series together.

Today's webinar will be focused on conversation on one of the most important and difficult issues relating to COVID-19.

Given that SARS-CoV is a novel agent, how do we find and evaluate treatments and develop treatment guidelines to lose morbidity and mortality during a pandemic?

We know that COVID-19 impacts different people in a different way. Some never experience symptoms while for some the fatality rate is inexplicably high.

As cases continue to rise and there are more than 9 million cases globally with more than 2 million in the U.S., and deaths globally now approaching 500,000, we know that a vaccine is still months away at best.

And therefore, there's a need to rapidly develop and deploy therapeutics and a real urgency to discover a silver bullet.

So, today we have an all-star cast of speakers who will help us understand the current state of the art on treatment as well as the challenges we face in trying to discover effective therapies while in the middle of a pandemic.

Today's speakers are well-known and accomplished clinical researchers who have a track record of discovery in HIV-AIDS and lead two of the major NIH-funded HIV clinical trials networks.

The infrastructure available for HIV networks have rapidly pivoted to conduct COVID-19 studies and will be critical in both treatment and prevention research.

I'd like now to introduce today's presenters. Dr. Judy Currier is a professor of medicine in the Department of Medicine at UCLA, where she serves also as the Chief of the Division of Infectious Diseases and is Associate Director for the UCLA Center for AIDS Research and Education.

Dr. Currier is trained in both

infectious disease and clinical epidemiology and her research interests include the treatment and prevention of complications of antiretroviral therapy, gender-related issues in HIV therapy, and the evaluation of antiretroviral treatment strategies in resource-limited settings.

Dr. Currier is the Principal Investigator for the AIDS Clinical Trials Group and the PI of the UCLA AIDS Prevention and Treatment clinical trials unit.

Dr. Rajesh Gandhi is a professor of medicine at Harvard Medical School and the Director of the HIV Clinical Services and Education at the Massachusetts General Hospital, where he is also the site leader for the MGH clinical research site of the ACTG.

He also is the Co-Director of the Harvard Center for AIDS Research. Dr. Gandhi is a Member of the NIH COVID Treatment Guidelines Panel and the Infectious Society of America COVID-19 Treatment Guidelines Panel.

He is also a Scientific Member of the

Department of Health and Human Services Panel for Antiretroviral Guidelines for Adults and Adolescents, and of the International AIDS Antiviral Society U.S.A. Panel and antiviral drugs for treatment and prevention of HIV.

Dr. Gandhi is Deputy Editor of the New England Journal of Medicine Journal Watch Infectious Disease.

Dr. Mike Cohen is a Yeargan-Bate Eminent Professor of Medicine, Microbiology and Immunology, and Epidemiology at the University of North Carolina.

In 2007, he was appointed Associate Vice Chancellor for Health Affairs. Dr. Cohen has served as Director of the UNC Division of Infectious Diseases, and since 1988 he has been the Associate Director of the UNC Center for AIDS Research.

Dr. Cohen's research focuses on the transmission and prevention of HIV and has an emphasis of co-infections.

Dr. Cohen is the Principal Investigator

of the multinational HIV Prevention Trials Network Study, HPTN 052, which demonstrated that antiretroviral treatment prevents the sexual transmission of HIV.

That work was recognized by Science Magazine as the breakthrough of the year in 2011.

He's a Co-PI of the HW Prevention Trials Network and a Member of the Institute of Medicine, the American Society for Clinical Investigation, and the American Association of Physicians.

Dr. Currier, over to you to kick off things.

DR. CURRIER: Thank you very much, Dr. Del Rio. It's really a pleasure to be here today.

I'm going to be starting us off by talking about some of the challenges of conducting therapeutic clinical trials in the midst of a pandemic.

And just to start by setting the stage, we find ourselves in the midst of this global pandemic with a disease that has a high mortality rate for people who are admitted to the hospital.

We have no known treatment and a limited understanding of how to manage the disease, at least initially.

We're dealing with a highly transmissible infection and we're also in a time, at least initially, where we had several medications that were available for other uses that appeared, at least in test tubes, that they might have activity against the SARS-CoV-2 virus.

So, these repurposed drugs are available and we need to figure out as quickly as possible which treatments are effective and safe. Next.

So, the three parts of my talk, I'm going to talk about randomized trials, what they are and why we need them, and what the alternatives might be.

And then I'll talk a bit about some of the implementation challenges to having these trials get the results we need and then some of the lessons that we've learned. Next.

So, randomized clinical trials are very

simply an experiment where a population of people who are living with a disease are identified and then they are randomized into two groups.

One group receives an experimental treatment and the other receives the standard of care or a placebo, and they're followed for outcomes in the hospitalized COVID-19 scenario for recovery and for mortality.

Next slide. And the beauty or the strength of the randomized trial is that people are randomized into these two groups and that will balance them out for a variety of characteristics that could impact their outcome. In the setting of a new disease, we don't know all of the factors that might be important in determining outcome and so assigning people at random will help provide this balance. Those are things like age or sex or the presence of other comorbidities, and so it's important that these be balanced into two groups. When the active treatment or experimental treatment and the control are blinded, it also provides an unbiased assessment

of the outcome.

So, for example, if you thought that a drug might have a certain toxicity and you knew a person was getting it, you might be more likely to ascertain that it was related.

Observational trials, on the other hand, are studies where people receive treatment and they're followed. And they're assigned really based on the clinician caring for them as to whether they might get one treatment or the other.

Now, these types of studies can yield some important information about the safety of agents in a particular population, but they really cannot replace a randomized trial, and especially in the setting when we're dealing with a new disease where we don't understand the natural history.

There's some people who get better without doing anything. We have to be careful not to ascribe an improvement to a treatment that was given to a particular patient.

Or sicker people might be more likely to be offered the treatment and they might have

a worse outcome, and we might say the treatment doesn't work, when in fact, it could have benefit in a randomized setting. Next.

So, at the beginning of the COVID pandemic, randomized trials were set up very quickly all over the world to try to evaluate some of the treatments that we thought might be helpful.

And initially, a lot of individual trials were set up, where people were being randomized to get an experimental treatment or the standard of care one after the other after the other.

And as you look at this, you can see that there's a lot of people getting placebos, each in their own trial. And you have to ask is there a way that we could do this more efficiently? Next slide.

So, adaptive platform trials have really come to the rescue in the setting of COVID-19.

There was a really nice review last

October by a consortium of adaptive trial people who do adaptive trials, and they're called the Adaptive Platform Trials Coalition.

This is an approach that was really pioneered in cancer and has been shown to be efficient. An adaptive trial is a trial of alternative treatment strategies that follow a single master protocol.

So, everybody is evaluated the same way. They can ask multiple questions on the effectiveness of interventions and the information that's generated during the trial can alter the subsequent operations in a pre-specified way.

These trials allow a single placebo arm to be shared across multiple treatments, which is much more efficient than the parallel randomized trials.

And importantly, they can adapt to new information that's learned about the disease during the conduct. Agents that are performing poorly can be dropped and new ones can be added.

They don't all have to be ready to start at the

same time.

Now, this approach was used during Ebola and there are several examples of adaptive platform trials in COVID, including RECOVERY, ISPY-2, REMAP COVID, and soon, two new trials under the ACTIV partnership.

And Dr. Gandhi will be talking more about what we've learned from specific trials in the next talk. Next.

So, this graphic just shows a very simplified version of what happens in an adaptive trial.

So, the people enroll and they might be stratified based on different characteristics, and they're randomized. Treatments come in at the bottom and they can come in at different times.

Outcomes are recorded, the data is updated, and then successful treatments continue and unsuccessful ones are terminated.

If a treatment in the beginning is shown to be effective, it can replace the standard of

care and continue on as new agents enter.

So, this is a much more efficient way to rapidly evaluate multiple different treatments simultaneously and reduce the number of people who would be exposed to the placebo group. Next slide.

Now, another important factor about how trials are done in COVID-19 is the fact that as we've learned about the disease, we see that there may be different stages of disease over the time course.

Initially, the viral response may be the most important and then later the host immune response may be important. And Dr. Gandhi will talk more about how this has impacted the actual evaluation of specific agents.

Next slide. So, I want to talk a little bit about what has been really challenging about implementing COVID trials, and I'll start with hospitalized patients.

Obviously, with a new disease the standard of care, for supportive care, evolves

rapidly as we learn to treat the disease, and that's a good thing.

But it's important if you're comparing outcomes to be able to adjust for changes over time in how people are treated. We've learned about how to position patients, how to use oxygen and others, how to manage fluids to improve patient outcomes.

Another logistical challenge is because this is a transmissible viral infection, patients are isolated in the hospital and we try to limit the number of times people go in and out of the room.

Importantly, this has also meant that no visitors are allowed and no family members are at the bedside.

These limitations in entering the room have also led to trying to limit the number of blood draws that are done and extra testing that can be done during the clinical trial, something that we're always trying to add to gather more information.

But we've had to really limit ourselves in many of these settings. We've had to adapt to doing informed consent remotely over the telephone or with the patient's legal authorized representative if they are on a ventilator.

This has created challenges in also making sure that other family members are involved in the discussion about participation in the trial.

Another really critical issue is that the systems are working at capacity during a surge and many of the people who would be leading and conducting clinical trials are pulled in multiple directions to provide direct patient care and to be involved in other activities in the hospital, making the conduct of trials each more challenging.

There were early on, and continue to be in some settings, limitations in the availability of personal protective equipment which reduces the number of times people can go in and out of the patient's room.

There's been a lack of availability of

actually the nasal swabs that are used to collect samples to measure the virus, and that's made it difficult to get all the measurements that people want.

And then importantly, there have been disparities in the location of where trials can be done.

On the one hand, many academic medical centers that have a lot of infrastructure and capacity have been bombarded with numerous trials to conduct, trying to decide how to prioritize one trial over the other.

Whereas in other settings with less infrastructure, there have been less opportunities for trials to be conducted. Next slide.

In the outpatient setting for early disease, this is an area where there have not been as many trials to date but where we really hope to see a lot more work coming in the near future.

But think about the fact that people are diagnosed with COVID and they're told you need

to stay home. They're unwilling to come to a site to participate in a trial.

So, investigators have gotten very creative and have developed trials where the entire study can be done remotely, where people can sign up online, have a consent done over the phone, and collect all their information remotely, where medication is shipped to their home.

And that can be good but it also may limit their connection to the trial site, and also it may limit the ability to get biologic outcomes.

So, for certain types of trials, this may be the way to go but for others where they're using new experimental medications that have not been tested in people, they really need to be in an observe setting to have that study visit conducted.

And where people see participants for trials has also been a challenge.

We see many parking lot or drive-through testing sites, some that now have

tents and other structures where people can be seen and evaluated safely in an isolation unit, like the isolation pod shown on the right side of the slide.

And then others have used mobile vans and other innovations to be able to go and see potential study participants at their home. Next slide.

The other implementation challenges are really the need to enroll population that are reflective of those who are experiencing the disease.

And this gets back to my earlier point about disparities in where trials are located.

There are populations who have been excluded from many of the early trials, including pregnant women and children.

And as we learn more about the disease, and particularly in pregnant women, we may find that it's critical -- we are finding that it's critical -- that we have therapeutic options for this population and need to find ways to include

them in these studies.

Bridging trials and compassionate use programs are filling the gap but this is an area where we certainly can do better. And then finally, coordination across industry, government, academia, and foundations is critical.

Next slide.

So, in April of this year the NIH announced the launch of a public-private partnership called Accelerating COVID-19 Therapeutic Interventions and Vaccines, or ACTIV, to develop this coordinated research and response.

And this has led to establishing a collaborative framework for both prioritizing therapeutic candidates and for accelerating vaccine evaluation.

It's also accelerating clinical trials of promising agents and leveraging many existing resources for clinical trials, and coordinating the regulatory process and leveraging assets amongst all partners. Next slide.

So, the groups that are involved are government partners including the FDA and NIH and BARDA and CDC, you can see them all on the slide, and then the industry partners.

And then importantly, nonprofit foundations. And working together, these groups are helping to really coordinate the response to developing therapeutic trials. Next slide.

So, what have we learned during COVID? Well, one thing we've learned for sure is that having a dedicated infrastructure for clinical trials at sites and people who are trained, investigators, at these sites really speeds up implementation of this work.

The rapid deployment of successful trials has been facilitated by the infrastructure built over the last 30 years for clinical research and other diseases, like HIV, cancer, heart disease, for example.

But the disparities in the location of these resources has, like many of things, been magnified by COVID-19.

We're learning that adaptive platform trials with well-defined outcomes and the ability to compare multiple strategies and learn as we go are yielding important results.

And we're seeing that necessity is the mother of invention and learning how to adapt to have more remote monitoring and simplified trials, and then ultimately, the really critical importance of the collaboration and coordination between multiple groups.

We're making a lot of progress and Dr. Gandhi will share some of the results of recent studies that inform our treatment guidelines. So, thank you.

DR. DEL RIO: Thank you, Judy, that was terrific. Raj, why don't you take it from here?

DR. GANDHI: Great, well, thanks for organizing this session. It's a pleasure to be here.

What I'm going to talk about in the next 15 to 20 minutes is what I'm terming the multidimensional challenge of treating COVID-19.

Next slide.

So, when we think of treating COVID-19, I think we need to think of it in three different dimensions.

I think we need to think of the host that we're treating, are they an adult, are they a child, and we are the risk factors for severe disease?

Second, we must pay attention to the stage and severity of disease. Is the person in front of us early in the course of infection, are they late?

Do they have mild, moderate, severe or even critical illness? And then finally, we need to talk about how are we going to intervene? Are we going to give an antiviral, are we going to modulate their immune system, or are we going to give a combination of therapies? And then in the critically ill patients, we need to think about how do we approach treatment of the complications?

Is anti-coagulation needed? Do they

need to be on a ventilator? Next slide.

So, in an adult SARS-CoV-2 infection is predominantly a respiratory illness with the hallmark being pneumonia. But SARS-CoV-2 in a very short time has been typified by causing multiple-organ disease.

It can cause neurologic complications, it can cause cutaneous complications, the heart can be affected, kidneys can fail, and a number of gastrointestinal manifestations can be evident, including hepatic dysfunction or liver dysfunction.

Systemically, SARS-CoV-2 infection can also cause a coagulopathy, and when we come back to that we'll highlight that further. Next slide.

So, here are some of the risk factors for severe COVID-19 in adults. I think what's agreed upon and is quite evident is that older age is a substantial risk factor, chronic lung disease, cardiovascular disease, diabetes, and obesity.

Those are well agreed upon and quite evident risk factors for having severe disease.

What's less certain is the role of immunosuppression, including advanced HIV.

We do know that immunosuppression and advanced HIV are risk factors for other complications and other respiratory viruses, such as influenza.

But we don't yet know if people with HIV, for example, are at increased risk for severe COVID-19.

The last point to make on this slide is there is a substantial and disproportionate burden of severe COVID-19 in racial and ethnic minorities, among the poor, and among Native Americans. Next slide.

What about COVID-19 in children? Here I think there's a somewhat unique manifestation, it's called the Multisystem Inflammatory Syndrome in Children, or MIS-C.

This is an acute vasculitis that has some of the features of Kawasaki Disease, which has been known about prior to the COVID-19 era.

Children with this, MIS-C, present with fever,

rash, they can have bulbar conjunctivitis, which is an eye finding.

They can have severe abdominal pain and it can progress to shock and cardiac dysfunction.

Now, as to how this happens, it's not clear.

Children may have had recent SARS-CoV-2 infection and in some instances this MISC may be a post-infectious, hyper inflammatory syndrome.

So, now let's talk about the spectrum of COVID-19. As Dr. Currier alluded to, you really need to know where your patient is in the course of their infection.

And we'll start with asymptomatic and pre-symptomatic infection. This is an individual who has a positive test, it's usually a PCR test for SARS-CoV-2 but has no symptoms.

Mild usually is characterized by respiratory complaints, things like cough, sore throat, as well as fever.

Interestingly, some patients will have taste or smell disturbances, but they're mild unless the patient has no shortness of breath and

has normal imaging, does not have an abnormal chest X-ray, does not have an abnormal chest CT.

Moderate illness is characterized by having normal oxygen saturations but there's now evidence of lower respiratory disease, either based on clinical criteria or based on radiographic or imaging findings.

Severe disease, at this point the patient has low oxygen saturations or has extensive lung infiltrates on imaging.

And then finally, critical illness is characterized by respiratory failure, shock, and/or multi-organ dysfunction.

Now, from early data in China we know that about 80 percent of people with COVID-19 will have mild or moderate illness.

About 15 percent of people will have severe illness, these are the people who are typically in the hospital.

And then about 5 percent of people with COVID-19 will have critical illness. So, you can see the majority of COVID-19 is mild or moderate.

Next slide.

So, the reason I wanted to frame the discussion in the context of the spectrum of COVID-19 is how you treat and what your goals are really depend on where you are in the spectrum.

So, the goals really, as I mentioned, depend on where you are. So, if the person is before exposure, the goals is to prevent infection.

This is pre-exposure prophylaxis, and we have some examples of that from the HIV world.

After exposure, during the incubation period, the goal of treatment is to prevent acquisition or to prevent disease, and this is known as post-exposure prophylaxis.

Once someone has the illness, the goal of treatment is to prevent progression, to prevent complications, and of course, to prevent death.

Early treatment may also prevent transmission to other individuals and we'll come

back to that near the end. And then finally, the goal in recovery is to hasten recovery and to clear the infection.

Now, the disease pathogenesis really lines up in some ways with where you are in the course of the COVID-19 spectrum.

We think that viral replication is predominant in mild to moderate disease, that's what driving mild to moderate disease. And there is growing evidence that inflammation is really the hallmark of severe and critical illness.

And then that leads you to what type of intervention you might contemplate.

So, early on in the course of this disease, we think that antivirals are going to be the mainstay of treatment, boosting the immune response may also be beneficial.

But then once people are more severely ill, once they're in critical illness for example, there, you're probably going to be wanting to decrease inflammation because at that point, you have an over exuberant immune response or hyper

inflammatory syndrome. Next slide.

So, let's talk a little bit about some of the antivirals targets. We're now going to go through some of the major interventions that have either been studied or will be studied. So, let's start with the virus lifecycle.

The virus enters the cell through the ACE2 and TMPRSS2 receptors. A drug called camostat is an example of an intervention that's being focused on, on that part of the virus lifecycle.

The virus then needs to go through membrane fusion and endocytosis, basically getting enveloped into the cell, and this is where hydroxychloroquine, a topic of a lot of discussion, is purported to work.

The SARS-CoV-2 virus has a protease which cleaves proteins and a repurposed drug from the HIV world, called lopinavir/ritonavir, is purported to work on that stage.

And the antiviral that we'll spend the most time on, for which there's the best evidence,

is working on the viral replication machinery, the RNA polymerase that allow the virus to make copies of itself.

And this is the drug remdesivir, as well as a drug that's further behind in development called favipiravir.

So, hydroxychloroquine.

Hydroxychloroquine has been the topic of a lot of discussion, of course, and I think Dr. Currier stated it well.

Early on, when I say early on, in March and thereabouts, what we started getting were single-arm studies as well as observational cohorts.

These are cohorts where people who are not randomized, where you're observing what happens and seeing if you can detect an effect of a drug.

And as Dr. Currier pointed out, those can come with substantial limitations because you never know in an observational study or a single-arm study if you're comparing apples to

apples, oranges to oranges.

You really need to have a randomized study.

And so during the month of June -- next slide -- we have begun to see randomized data. And this is the type of data we need to determine how to move forward.

So, we started with a randomized trial with a very innovative design looking at post-exposure prophylaxis. Can you prevent disease? And this showed no difference in a randomized trial between hydroxychloroquine and placebo. Now, this particular PEP trial, post-exposure prophylaxis trial, had some limitations. Most of the participants enrolled several days after exposure, three to four days after exposure. And the mean incubation time for SARS-CoV-2 is about four to five days.

And the other limitation of this particular trial is only two to three percent have confirmed diagnosis. The others were syndromically defined.

Hospitalized patients, it's the other end of the spectrum and two large studies have been conducted, randomized studies.

One is called the RECOVERY study, which we'll talk about again in a moment. This was done in the United Kingdom, and just about 10 or 12 days ago they announced their top-line results.

We're waiting for the data to follow but the top-line result is that 28-day mortality was no different in hospitalized patients who got hydroxychloroquine versus those that got usual care.

Even more recently, the National Institutes of Health halted a trial of hydroxychloroquine in hospitalized patients. That trial was called the ORCHID trial. This was just stopped over the weekend.

The top-line headline there is that the treatment of hydroxychloroquine was not found to be harmful but it also provided no benefit, and that's all we know so far. More to come on that front.

So, remdesivir. Remdesivir, as I mentioned, is an antiviral, it's a nucleotide prodrug. It works by inhibiting the viral RNA polymerase, that's what makes copies of the virus, and it works as a chain terminator.

Rhesus macaques are an animal model for SARS-CoV-2 infection and remdesivir has been found to reduce viral levels in the lung, interestingly not in the upper respiratory tract, and ameliorate disease in this animal model.

But what about humans? In the ACTT study, which is an NIH-funded study, a preliminary analysis of remdesivir versus placebo in over 1000 individuals with severe COVID infection, remdesivir was found to hasten recovery.

Recovery was more rapid with remdesivir than placebo by about 4 days, so 11 days versus 15 days.

Now, the preliminary mortality did not differ statistically, but there was certainly a trend towards lower mortality in the remdesivir group. About 7 percent versus about 12 percent.

And the benefit of remdesivir was clearest in those who were on oxygen supplementation but who were not yet intubated.

Now, I want to comment here that these are preliminary data.

Not all of the participants in the ACTT study had completed their 28 days of follow-up, so there will be more data to come and we will be all looking with great interest at how the final data set looks.

But this is what led to the emergency use authorization of remdesivir.

Another important trial was the SIMPLE trial, this was a manufacturer-sponsored study and what the SIMPLE trial did is it looked at people with severe COVID-19 who are not yet intubated.

And that's important, and compared five days of remdesivir to ten days of remdesivir, and what the SIMPLE trial found is that five days was as good as ten days for most people with COVID-19.

And that's important because this drug is in limited supply and so if you have severe COVID-19 but not yet intubated, this trial supports the use of five days of remdesivir for most of those people. Next slide.

The next category that I want to spend a moment on is boosting the immune response.

And Dr. Cohen will talk about this in more detail but I'll just set the frame here by saying passive transfer of neutralizing antibodies, for example convalescent plasma, plasma from someone who's recovered from COVID-19, or by isolating monoclonal antibodies against the virus is a promising way to approach the treatment of COVID-19.

We know that convalescent plasma is used to create other viral infections, such as Argentine hemorrhagic fever, and there's been some tantalizing data, although not definitive, for convalescent plasma in people with COVID-19.

Early on, again, just a few months ago, a case series of convalescent plasma in people with

COVID-19 showed improvement in radiographic findings as well as reduction of viral shedding.

And the more recent open-label randomized trial suggests that the benefit of convalescent plasma in people with severe COVID-19, but treatment was given quite late in the disease course, about 30 days after symptoms started.

And so it's not a definitive trial but it is at least suggestive.

What are the risks of convalescent plasma? Very few. There's been tens of thousands of people that have been given convalescent plasma now for COVID-19 and transfusion-related reactions are quite rare. There is a theoretic concern about antibody-dependent enhancement, that is antibodies making things worse, but there's not been evidence of that and this remains just a theoretic consideration, not something you'll see.

There are ongoing prophylactic and therapeutic trials of convalescent plasma, and as

you'll hear about in the next talk, of monoclonal antibodies as well.

So, most recently, and I'll give this as an example of how we can attack or decrease inflammation, there have been some promising data on the use of steroids, which are anti-inflammatories.

So, this is the case of dexamethasone.

So, there's been a long-standing controversy around the use of steroids in viral pneumonia and in acute respiratory distress syndrome. That's the complication of COVID-19.

Other things can cause ARDS or acute respiratory distress syndrome as well. But given that hyper inflammatory state in COVID-19, steroids have been evaluated as a potential intervention.

So, in the recovery trial that I mentioned earlier, this is an open-label trial.

It's randomized among hospitalized patients in the United Kingdom, and they reported just very recently that over 2100 people who were

randomized to dexamethasone were compared to a little over 4300 people who got usual care.

What are their findings? Well, as you can see in the box on your right, among all the participants in this particular part of the study, there was a 17 percent reduction in mortality.

So, the relative risk for mortality was 17 percent lower, 0.83, in the participants who got dexamethasone as compared to usual care.

This benefit was most evident in the sickest of the patients, those people who were on mechanical ventilation or who were on ECMO. There, there was a 35 percent reduction in the risk of mortality.

People who were a little bit less sick on oxygen but not yet on a ventilator also had about a 20 percent reduction in mortality, relative risk of 0.8.

Importantly, and this is important, the people who were hospitalized but were not on oxygen did not have the benefit of dexamethasone. In fact, they could not exclude harm.

The relative risk of mortality was 1.22, it was not significantly -- it did not show significance in terms of harm but they could not exclude harm.

So, what are the conclusions from this?

More data is needed, this is available really just as a pre-print at this point and we need to see all the details.

But so far, it look like dexamethasone is associated with decreased mortality among those on supplemental oxygen or those who are mechanically ventilated or on ECMO.

But there's no benefit in those who are not requiring oxygen, people who are less ill.

Next slide. So, my last intervention slide is here. What about the complications of COVID-19 beyond the ones that I've already mentioned.

We know that SARS-CoV-2 infection can cause an inflammatory state but it also can cause a pro-thrombotic state. What does that mean? It can cause people to be more prone to develop blood

clots.

And as a result, thromboembolic disease, clotting disorders, have been reported in people who COVID-19, particularly in those with critical illness. So, why might that be?

Well, people with severe COVID-19 have a number of other risk factors for having hypercoagulability, or having a clotting disorder.

They have an acute illness, they're often bedridden, they have a number of end organs that are affected, and those all place them at risk for clotting.

In addition to the inflammatory response, an over-exuberant inflammatory response can also cause damage to the lining of the blood vessels, and endothelial dysfunction. And that can also predispose to clotting.

In addition, there are a number of clotting disorders.

People can have high D-dimers, they can have low or excess platelets, and when we look at

pathology from people with severe COVID-19, they can have microthrombi, small clots in their lungs, even in their heart and other organs.

And finally, in terms of clinical outcomes, they can have pulmonary emboli, clots in their lungs, they can have heart attacks or myocardial infarction.

And based on recognizing these complications, it's now recommended that hospitalized patients should receive prophylactic or preventive therapy to try to prevent blood clots.

What is not known, and there are a number of ongoing as well as upcoming trials that should be giving higher doses of anti-coagulation or blood thinners, intermediate doses or even full doses, and that is the topic of a number of ongoing as well as upcoming trials.

So, let's return now to the goals of treatment across the COVID-19 spectrum. I think you can see that remdesivir and dexamethasone have data supporting their use in moderate to severe

disease.

More data will come for remdesivir, we'll see in the near future I think around moderate disease. And we've seen some data, more to come on dexamethasone.

But here I want to make one point that Dr. Currier also alluded to. Most of the trials to date in the first phase COVID-19 trials have been in severe disease, people in the hospital.

But as I said at the beginning, 80 percent plus of people with COVID-19 have mild disease.

So, if you go to the next slide, I think most of those trials, some of which I've alluded to, are really in this hospitalized respiratory failure part of the spectrum.

What I think we'll see in the next phase of COVID trials are earlier trials. Can we get a bigger bang for our buck by treating earlier, treating people who are just exposed, treating people who are early in the disease course?

And will that have the benefit of not

only preventing progression but could we actually prevent acquisition or transmission to others?

Our next speaker has taught us that HIV treatment results in HIV prevention. We need to see if we can do the same for SARS-CoV-2.

So, my last slide leaves us with some final thoughts. COVID-19 treatment really requires a multi-dimensional approach.

We need to understand the host, we need to understand the stage and severity of the disease, and we absolutely need to understand the intervention.

Depending on the host, stage, and severity of the disease, the optimal intervention may actually differ. In some instances, we might want to be applying antiviral therapy.

In other instances, we might want to modulate the immune system. And I don't doubt there's also going to be important studies about trying to do both, trying to do combinations of antivirals, trying to combine antivirals in immunomodulators.

And the NIH ACTT 2 study is doing just that, it's going to be looking at remdesivir with an immunomodulator.

I also want to conclude by saying we can really learn a number of lessons from our experience with HIV. Many of the speakers on this call all have a firm foot in the door of the HIV world.

Some of the lessons that I got from HIV, the pressure to deploy interventions really has to be tempered by the importance of finding out if a treatment really works.

We learned that in HIV and the same is certainly true in COVID-19. Our guide has to be the science. It's also going to be an iterative process.

We've got to build on some of the advances that we have early on. Until we get to get to that tipping point, in HIV it was 1996 when a number of things came together to the point that now we have very highly effective treatment for HIV.

And then last, just as with HIV, it is critical, absolutely critical, to address the disparities and inequities revealed by these findings. So, with that, I will conclude and I look forward to the further dialog.

DR. DEL RIO: Thank you, Raj, that was terrific. Mike, you want to take the lead now?

DR. COHEN: Thanks. Well, thank you for inviting me this afternoon. I'm going to now transition to kind of trying to look forward. And the next slide, please.

This slide is adapted, or stolen from the active collaboration that Dr. Currier talked about. And I like it, because it identifies the kind of four areas that we can look forward to in terms of improved treatment of COVID-19.

Antivirals, which I'll talk about a little bit, host-targeted immunomodulators, you just heard about dexamethasone, only a couple of days old in its presentation, symptomatic and supportive care, oxygen as a drug, and positioning people on respirators in the most appropriate

position to do well, and neutralizing antibodies as for treatment and prevention.

This afternoon I'm going to focus on, just as examples, antivirals and neutralizing antibodies. I guess I should have looked at the questions. There's a lot of questions about treatments.

And I would note that as of today there are 2,282 trials focused on COVID-19 treatment, or COVID-19. And 1,522 treatment trials.

So, there's no shortage of interest in trying to move forward in this field. Now, totally independent of the active collaboration that's underway, I just want to talk about the development of some agents that I believe hold promise, but that are examples of where we might go. And show the next slide, please.

So, Raj very nicely emphasized the idea that the best thing that could happen to us would be someone develops symptomatic SARS-CoV-2, or COVID-19. They go to a physician. The test is positive. They receive a pill that interrupts the

progression of disease.

This has to be one of our highest priorities. Investigators at many universities work together to examine the possibility that an oral antiviral agent called EID-2801 might successfully inhibit the replication of SARS-CoV-2 in a test tube. That in fact proved to be true.

Workers at Emory, investigators at Emory went on to develop an oral version of this drug. Next slide, please.

And then they took it to mice. And I just want to focus on the circles on the right-hand side.

So, they've gone from the idea that they have an agent that inhibits replication of the virus in a test tube potently. And in this case much more potently than remdesivir.

And then they take it to a mouse. And they show, if you look on the far-right upper-hand corner, you see virus lung fighters.

The gray is a control. You see if the drug is given 12 hours after exposure to

SARS-CoV-2, you inhibit replication of the virus.

And if you look at the lower section, you look at lung damage, you see that in the gray bar, you see lots of lung damage. And you see if you give the drug before exposure to SARS-CoV-2 or after exposure to SARS-CoV-2, you can prevent lung damage.

So now we see, whoa, here's a drug that possibly might be developed going forward. Let's go to the next slide.

And just to show the kind of repetitiveness with which the field is moving, this drug has already gone into phase two trials. I chose a trial being done at my own university, the University of North Carolina, by Dr. Fischer and others.

It's a randomized, double-blind controlled trial to look at the safety, tolerability and efficacy of this drug, EID-2801.

And what's important here is again, getting back to what Dr. Gandhi mentioned, the end point of the trial is to show that in people with early

infection, you can demonstrate antiviral activity.

So, people come to an outpatient clinic. They're not sick enough to be hospitalized. They're within four days of the onset of symptoms.

You can recover SARS-CoV-2 from the nose with a nasal swab. And you're giving this pill in order to demonstrate you can stop the replication of the virus.

And then, I guess more than theoretically, that might be a pill that could stop the replication of the disease. I anticipate there will be other antivirals developed.

This is just an example of one antiviral in early phase therapies that it proves at this point safe. And is now looking for its earliest moments of efficacy. Next slide, please.

So, I want to move -- so that's one category, antivirals. Let's move to an alternative strategy, using antibodies to prevent infection and progression of disease.

Now again, Dr. Gandhi talked about

convalescent plasma that could be harvested from people who have been infected. And some people have titers of antibodies that are so substantial that there's a belief that if they're -- that if the antibody -- if the plasma is infused, it would inhibit the progression of the disease, stop the progression of the disease.

You can take that, the blood from those people. And from that blood, you can isolate on the far right, upper left, sorry, far left, upper left-hand corner.

You can isolate B-cells that make immunoglobulins from people who are recovering from SARS-CoV-2 infection. And some of those B-cells will end up making very potent antibodies.

And you can take a single B-cell, and from that single B-cell, you can make what's called a monoclonal antibody, directed at the SARS spike protein-binding sites, shown in the next slide, the second slide to the right.

And so you now have a B-cell making potent antibody. And you show that the antibody,

you can show exactly where the antibody might bind, or you try to bind it and -- and then in a test tube, again, you show neutralization.

And then let's take the antibody to a mouse and see whether it will prevent a mouse from getting infected. Next slide, please.

In last week's issue of Science, there were five articles looking at monoclonal antibodies, trying to look at how they work, where they strike the virus.

And in this paper by Dr. Burton's group, they show really excellent effect of a neutralizing antibody to protect a small animal. Next slide.

In this case it was a hamster, I believe.

And so, in this paper, if you -- just look at the right. I just want to show you the circle. You just see a very nice correlation between the concentration of antibody, and the amount of weight loss of the small animal.

A small animal exposed to SARS-CoV-2 loses weight. In this case, as I said, a Syrian hamster.

And they're showing that as they give a higher concentration of antibodies, they can then prevent weight loss. Implying that they're preventing progression of disease.

So, now we're operating at very fast speed. Let's go to humans. Next slide.

Let's think about using monoclonal antibodies in humans. And we have a couple of applications we consider, prevention and treatment.

What advantages do monoclonal antibodies offer us? Well, a vaccine takes time to work, to force the development of antibodies.

But, when you give a monoclonal antibody, you get immediate protection.

It might be appropriate for somebody who knows they've been recently exposed to a person with COVID-19, who's not vaccinated, so we make a vaccine. Or, in a high risk setting, such as healthcare workers at the beginning of the epidemic.

It can be provided to people unlikely

to respond to a vaccine or allergic to a vaccine.

A monoclonal antibody might not only allow prevention of infection, it might also stop the replication of the virus once it tries to take hold, and therefore block progression of disease.

And lastly, if we can show that monoclonal antibodies work to prevent SARS-CoV-2, the concentration of antibodies required, will give us a target of titer required for a vaccine.

That is how much antibodies should a vaccine elicit in order to be successful.

It will also give us molecular targets for vaccines. We'll see where these antibodies bind.

Who might you give monoclonal antibodies to? People living in long term care facilities, especially skilled nursing homes. Both residents and attendants, because this has been a place that suffered greatly with the SARS epidemic.

High incident work places such as meat packing plants. Again, another place where the

epidemic has hit very hard.

Contacts of an index case. So, you're living in a household where someone you live with acquires COVID-19. The chance you might acquire it in the same household, is between 10 and 30 percent.

So, we have a lot of spaces where monoclonal antibodies might prove very appropriate for prevention and treatment. Remember, environment will drive the exposure to the virus that we're trying to prevent. And biological factors will control the progression of the disease as Dr. Gandhi noted.

Are monoclonal antibodies a potential solution? And where are we with the development of monoclonal antibodies? We go from the science papers I showed you forward. Next slide, please.

So, here we have five, six companies, I'm sorry. Or five companies who are already making monoclonal antibodies for use in humans.

Eli Lilly has already made antibodies. They put the first in human antibody, in one of

their antibodies in hospitalized patients for treatment in May. They put a second antibody in hospitalized patients in June.

Regeneron has a cocktail of monoclonal antibodies. And they put the first in human, for treatment of hospitalized patients in June.

VIR, another company, has an excellent monoclonal antibody. And they're getting ready for human trials.

AstraZeneca, has a cocktail of monoclonal antibodies. And they're getting ready for human trials. And BMS, working with Rockefeller, intends to make monoclonal antibodies in the fall.

For the most part, the technologies that I've described to you are how these antibodies are made. Identifying patients recovering, and then harvesting B-cells that would make very potent antibodies.

There are, however, other technologies at work. And Regeneron uses their own unique technology to make monoclonal antibodies. So,

it's a very exciting field. Next slide. And the antibodies exist.

So, let's talk about how we might deploy antibodies right now. So, a third of all Coronavirus deaths, only about, I think, 11 percent of all the cases of Coronavirus are in skilled nursing homes.

But 35 percent of the deaths are in nursing homes. And you can understand that because this is a very vulnerable population, with many comorbidities. Next slide, please.

And this is a map of the United States that's showing you nursing homes that have patients or attendants, people living there or attendants, who've acquired SARS-CoV-2. And you can see this is nationally distributed. And in general, if there's one case of SARS-CoV-2, there have been many cases of SARS-CoV-2.

Now, of course the nursing homes and long term care facilities and adult living facilities that have been affected by this, and meat packing plants and other risky situations,

they've done everything possible to prevent infection already through the standard of care.

Next slide, please.

But, one idea might be to take one or more of the monoclonals that are available, and think about using it in the very near future in the skilled nursing home. And this would be a randomized controlled trial.

And you could imagine if you had either attendants or other people in the skilled nursing home who had a SARS-CoV-2 infection, you might then provide antibodies to determine very quickly whether you can prevent infection or prevent disease.

So, if you gave them -- and monoclonal antibodies can last a long time. And they can be given in IV or subQ.

So, you can imagine an infusion of a monoclonal antibody that would last a month might be used to try to prevent infection in somebody who has not been infected, or in somebody who's got asymptomatic infection, or pre-symptomatic

infection. You might, that same monoclonal antibody might prevent progression of disease.

Now, these kinds of studies, randomized to a placebo, and the monoclonal antibody, can be done pretty efficiently and pretty quickly compared to some other research. And you can use nasal swab PCR recovery as an end point.

By studying whether the virus is replicating or not, week after week after week for just a few weeks, you can determine whether you've been successful or not. You can also, of course, look daily for signs and symptoms of COVID-19 to see if you've clinically stopped the progression of the disease.

Now, in addition, it's possible when you give a monoclonal antibody that you'll affect the process of seroconversion. That is, using antibodies to prove someone's infected.

So, it's going to be important to look at this phenomenon as well, as you progress with these antibodies. Next slide, please.

In addition, when you're studying these

monoclonal antibodies, you can do a lot more science in this kind of environment. You can look at the amount of virus in the nose and the saliva, and whether the monoclonal antibody decreases the amount relative to a control group.

You can look at the duration of shedding on a daily or weekly basis. Have you reduced the amount of shedding?

And this gets at the treatment as prevention idea. If these antivirals or monoclonals are successful in the trials that we anticipate, they might stop replication of the virus so the next person will not be infected.

You can use a test called subgenomic RNA as an alternative to measuring viral replication. There's some correlation between this kind of a PCR amplified fragment and replication competence.

In some settings you can even take material from the nose and see whether it can grow.

That's call replication competence. Hard to do, but an important phenomenon.

And you can measure seroconversion, realizing that an antibody could delay or disrupt seroconversion as I've already said. Next slide.

So, I want to point out that as we go forward, we're trying to, through many means, work as a collaborative team around the United States and around the world to try and develop treatment and prevention for SARS-CoV-2. This is moving at an incredible pace relative to HIV.

This, we've only known of this virus, or worked against it for six months. And as we go forward, one thing we're looking a lot is at the NIAID sites, I happen to work as a National Institute of Allergy and Infectious Disease investigator, we're looking at where our sites are.

And where the incidents of SARS-CoV-2 is, where it's getting bigger.

We can look at nursing homes and meat packing plants, and lots of other facilities. And direct our energies to the places where we can get answers for treatment and prevention most quickly.

Next slide, please.

Now, I just want to end as Carlos and Dr. Gandhi said, all of us have worked a lot, we're kind of repurposed HIV investigators. Although all of us have been, you know, thrown into the middle of COVID.

And one thing we learned from HIV, but that has got to be very true for COVID, is the notion of combination prevention. There is no real magic bullet in my mind.

The first thing that happens with a new pathogen is we look for preventability of avoiding getting the infection, or avoiding the progression of the disease. And in this case, the behavior changes that have proven to be incredibly important, are masks and more masks, and masks, and social distance, and hand hygiene. And we know this works.

And we've had trouble with messaging to get the maximal benefit of this in the United States and in some other countries. But we know that we have a behavior change that has proven very effective.

The next stage in combination and prevention is the development of antiviral agents, or -- in this case I presented two kinds of agents that could be developed. One kind of agent would be an antiviral drug, and I used an example of one.

Another kind of agent would be monoclonal antibodies that would serve as antiviral drugs, as an antiviral drug. And I showed you that many are already in development and soon will be available.

And so we would anticipate that those drugs, if they work, would cause incredible relief, because they would help us to have a tool that was immediately available for prevention, and also immediately available to stop the progression of disease.

And I'll just reiterate kind of fantasy, but it's not really a fantasy, that you can go to a physician. And he would know that he could test you for COVID. And he would have a drug that would stop the progression of disease.

That would be, I think, an incredible

positive event. Much like Raj's slide that showed interruption at the earliest phase of the disease.

And lastly, you heard in an earlier series of webinars, two different series, about vaccine development. And the last and almost, and certainly most important prevention tool for us, is vaccine development.

And as we said earlier, at least seven vaccines are going to clinical trials. They take large numbers of subjects. They take a little longer. But, they obviously provide us tremendous power, scientific power to deal with the COVID epidemic.

So, I think what I would say is, there is no magic, one magic bullet. All three of these things have to be developed concomitantly.

We can't really give up one of these prevention activities, or treatment activities for the other. We need our new normal to embrace combination prevention.

It's a thing we learned from HIV. And I think that lesson has got to be true for

SARS-CoV-2 as well. So, next slide, please.

It just says thank you, from me. So, thank you, Carlos.

DR. DEL RIO: Thank you, Mike. That was terrific. We're going to proceed with the question and answer session.

And we have a lot of questions. But, I'm going to try to summarize some of them. And I will start with you, Judy.

There's questions, can you please discuss the unique issues surrounding patient consent to a randomized trial when so much is unknown? When the consequences could be dire, and when there really is no animal studies, or have been truncated in using this.

So, what is the risk/benefit ratio, and how do you deal with that with patients?

DR. CURRIER: Thank you, Carlos. I think it's really critically important to share as much information as available about what's known of the risks and benefits of any treatment that's being studied.

And that people make as informed decision as possible. And I think that we are dealing with very limited information for some of these interventions.

And particularly, you know, I think in the earlier stages of disease, where a lot of people are going to get better if you do nothing. Trying to really understand, you know, what their individual risk might be, and then what is known about the treatment.

But, that's why it's really important to have a conversation about this. And even if it's done over Zoom or on the phone, it's important to spell out what's known, and share those uncertainties in making a decision.

DR. DEL RIO: Thank you. For Dr. Gandhi, Raj, this is for you. Can you talk a little bit about what some of the immune interventions that are being considered?

And what do you think, what do we know about the immune response to the infection and how to modify it?

DR. GANDHI: Yeah, that's a great question. It's a very expansive question. There's a lot to it.

So, there are many different immune modulators that are being investigated. So, steroids is one of our older immune modulators.

Steroids work by affecting lymphocytes, which are one of the arms of the immune system. And we've used them for many, many decades for a lot of autoimmune diseases or rheumatologic diseases, diseases that involve immune dysregulation or over-exuberant immune response.

But there are many more sophisticated immune modulators, things that target certain cytokines. Things that cytokines are things that are targeted, ways that the immune system responds.

So, one of them, for example, is an interleukin-6 antibody. That has been studied, and is being studied in COVID-19. Interleukin-6 antibodies are also used by our rheumatology colleagues to treat autoimmune diseases.

There's another class of drugs called

JAK inhibitors, which are used sometimes by oncologists, as well as other fields of medicine.

So, there's a kind of panoply of different immune modulators.

The question is, how do you target the immune system and prevent the immune damage, while also not interfering with the clearance of the virus?

That's the critical point in all of, in many of our minds, which is the immune system is a double-edged sword. If you -- you need the immune system to clear the virus. But, if it's over-exuberant, you want to dampen down that inflammation.

And so that's the balance that people are trying to achieve in COVID-19. I would say that it's really only these randomized trials that are going to give us the answer. Just as with antivirals, if you give anti-inflammatories without a comparator group, you can get seriously misled.

As Dr. Currier said at the outset, most

people with COVID-19 are going to get better, including most people in the hospital with COVID-19. And so unless you have a comparison group, you just don't know if your intervention is doing what you meant it to do.

There are randomized trials, for example, at our institution of interleukin-6 antibodies, as well as at other institutions. And then the JAK inhibitors is another area of active investigation, alongside many others. That's just a taste of what we're, what people are doing.

DR. DEL RIO: Thank you. Mike, there's a question that I would like you to give a few comments about.

Somebody says, early in the course of HIV, of the HIV epidemic, clinical trials faced many of the barriers of location, underserved populations, et cetera, that we are talking about.

The community program for clinical research phrase was established to address that.

Should we do the same in COVID-19?

DR. COHEN: That's a great question.

And the answer is unequivocally, yes. COVID-19, as everyone on the call realizes, has not been fairly distributed in the United States.

It's certainly affected minority communities much more heavily, for a variety of reasons. Much of it having to do with density of populations.

And in the trials that are being planned, there's tremendous attention, both vaccine trials and treatment trials, attention to equity, in terms of who's involved in the trials.

And then for the trials that are being developed, at least the ones that I'm involved with, there are community working groups already underway, trying to represent the communities that would potentially benefit from -- take the risk of the trials, and benefit from trials.

So, this is, has been an absolute from the very beginning of the consideration.

DR. DEL RIO: Thank you. Dr. Currier, can you provide details on how to ensure the participation, again, staying with underserved

populations. I mean, particularly the African-American populations have, there's a history of abuses, like Tuskegee.

How do we build trust? What lessons do we have from HIV that we can apply to COVID?

DR. CURRIER: Thank you. I think it's a really important issue. And I think it has to start, you know, with just broad education about the disease early on.

And there was a question I saw in the chat about who should be the messenger? Who should be -- where should people get their information about COVID?

And I think that really varies by age group and population who the trusted sources are.

And I think we need to do more in sort of in the public health arena in terms of helping people understand the disease and what we're -- what the therapeutic options are, so that clinical trials, you know, are something that will be considered.

Another, just related to that, is this, you know, sort of practical issue, too, that

oftentimes if a patient's in the hospital and they're on a ventilator, it's their family who's asked, or their legal authorized representative to help make the decision about trials. And that's a lot of pressure to put on a family member.

And so, I think having just more general information about the disease, and the approaches to treatment, will help people feel more comfortable making those choices.

DR. DEL RIO: Thank you. Raj, given that cardiovascular disease is a major risk, and what you talked about, you know, thrombosis, is there any data emerging suggesting an effective, you know, efficacy of aspirin or anti-platelet drugs, or for example, also statins in improving outcomes for people with COVID?

DR. GANDHI: Yeah. That's a fantastic question. So, the thrombosis and COVID is still being sorted out as to what the mechanism is.

But, I can say that in the MISC, the Multisystem Inflammatory Syndrome in Children, which is an inflammatory condition, we think, and

got some similarities to Kawasaki, things like aspirin has been used for Kawasaki. And I think there's similar kinds of approaches for MISC that are being explored.

In fact, the American College of Rheumatology just in recent days have been giving some guidance around that.

In terms of other interventions for the thrombosis, I think the intensity of anticoagulation still needs to be determined. Even though thrombosis or clotting is one aspect, we've also seen bleeding as well.

So, early on, many of the series reported a very high rate of thrombosis or clotting. But there's also been recent data of bleeding complications.

So, getting the balance right, just as I said with inflammation, is also true for coagulation. And I do think these trials are going to be the only way to answer that question.

Carlos, I feel like there may have been another aspect beyond the aspirin. Was there

something else there?

DR. DEL RIO: Yeah. About the statins.

DR. GANDHI: Yes, statins. Thank you. Okay. So, statins, theoretically, there are reasons to think that statins could have a beneficial effect in COVID-19.

But, we don't have the data to support their use, kind of widespread use, unless there's another indication for statins.

What I would say about statins is the following: if a person is on a statin for another indication, they should absolutely continue that drug. Getting COVID-19 is not the time to be stopping their statin.

As to whether someone should be started on a statin for COVID-19, we don't know yet. But that's the kind of question that we need to answer.

An important trial also out of HIV world, is the REPRIEVE trial. The REPRIEVE trial is a randomized trial involving many thousands of people around the world that looks at giving a

statin versus not giving a statin.

And I think the important data and people in REPRIEVE who acquire COVID-19 to understand if the statins are having a beneficial effect. Those data are being collected.

So, right now, if you're on a statin, continue it. If you've got a reason for it, don't stop it. If you're not on a statin, that's where we need to study it.

DR. DEL RIO: Yeah. Very good point about REPRIEVE. Dr. Cohen, what do you, can you tell us a little bit about the duration of protection with monoclonal antibody therapy.

Do you think we're going to have to have regular infusions of these antibodies?

DR. COHEN: Great question. The antibodies that are currently available for the most part, last about a month.

And their current usage is, for example, a single time in a household where there's an infection, or early for treatment, as I've already said, in an outpatient setting.

If we don't -- if a vaccine proves to be, for whatever reason a vaccine does not prove to be effective for the elderly, as sometimes happens for vaccines, you can envision then that monoclonals might be required to protect that population.

However, we can modify the FC receptor of the monoclonal, and make it last six months or longer. The VIR Company has already done that.

They've modified their monoclonal to make it more appropriate for infrequent usage.

So, I think there's a lot of technical advances that exist that would allow these drugs to realize a pretty big potential in this space in the future.

DR. DEL RIO: Thank you. Dr. Currier, as you look at clinical trials, do you think we're going to get to the point that we would be doing clinical trials and enrolling into clinical studies asymptomatic patients?

DR. CURRIER: I think that the asymptomatic people early in the course of

infection, I think that they, you know, the main issue is really understanding the natural history of that. And whether there are some who are initially asymptomatic or pre-symptomatic that are going to progress to a symptomatic phase.

And that that maybe a group where you would want to intervene. We also need to understand whether, what the risk of transmission from asymptomatic people to others in the community are.

And understand sort of the viral load of that. And I think that's an area where we really need to understand more about the natural history and how we might intervene.

So yes, I think there's interest. But, I think that it's a poorly defined group in terms of what their natural history is.

DR. DEL RIO: Raj, could you tell us a little bit about, you know, sort of the way to interpret clinical trials, and randomized clinical trials?

For example, in recovery in the U.K.,

the use of ICU was pretty different then what it is here in the U.S. There very few patients, there were 80 who were intubated.

What caution should we exercise in the U.S. where our ICU population is considerably older? Do you use the same rec -- would you then apply the same recommendations for dexamethasone given that the circumstances are very different?

DR. GANDHI: Yeah. That's a great question. As the person asking the question observed, the mortality in the U.K. is quite high.

And it may reflect the fact that the overall mortality in the U.K. is not just in the trial, but outside of the trial, was quite high.

So, these, the recovery trial was done in the NHS, the National Health Service. And the overall mortality was probably in the 25 percent range. Which is, depending on where you are, and what the institution is, we have seen that kind of mortality in the U.S., but not in all places.

So, for example, our mortality in our critically ill patients is about 15 percent.

There's a lot of variability around the country.

What I would say is that, it is also true that there are differences in the United States and the U.K. in terms of who gets intubated.

As the questioner observed, very few people over the age of 80 actually were in the mechanically ventilated group.

I think there was only 16 people, 1-6, who were in the mechanically ventilated group, that were over the age of 80. And that's different then in the United States.

That being said, my own opinion, and we'll know more as we get more data, is that the signal was so strong in mechanically ventilated patients that I think it is reasonable to apply some of those findings from the U.K. to our own population.

We're going to need to monitor people.

There are well-known side effects of dexamethasone. But, I think those are things we have familiarity with, and we'll need to manage them carefully.

But the mortality benefit was not small. And it is, even though there maybe complications, those are things that are balanced out, I think, by the benefits.

So yes, the bottom line is there's differences in the location. But, I think the principal is there in terms of the mortality benefit with dexamethasone.

More to come. Invite us back in a month or two, and we can give you more. Or have a whole session on this. I think this is well deserving of kind of an in-depth discussion of the dexamethasone thing.

DR. DEL RIO: Thank you, Raj. Mike, I want to ask you one question, because I think it's a good opportunity to dispel what I see here as a problem, a myth.

One of the questions that comes says, the U.S. government is cutting funding for treatment and research to focus predominantly on vaccines. What will be the impact of this decision on the research that you are discussing today?

DR. COHEN: Well, you know, the funding that's being made available for COVID research writ large, is a lot. Vaccine trials are very expensive.

So, I think as people see one source of funding, BARDA for example, really moving toward preparing for a vaccine, it's certainly something that's essential. I don't think it is necessarily going to compromise research in other areas to the extent that I think fear has blossomed.

I think that there's tremendous interest in all the fields of research that we've just talked about. And I've not seen evidence, maybe you have. I've not seen evidence of fields cut off or compromised at this moment in time.

As we move -- remember, we are moving, it's worth talking, we are going to test vaccines this summer. We are going to test monoclonal antibodies this summer for treatment and prevention.

So, this has moved very fast. And so, you know, we have to deploy the funds in order to

move this forward at this speed. I don't believe it will compromise other areas.

DR. DEL RIO: Thank you. Dr. Currier, you know, there is a question here about, could the new treatment options cause the virus to continue to mutate, and cause a continual need to develop new treatments?

Or could drugs we develop to prevent the virus from mutating? I mean, a lot of people ask and talk about questions about mutation.

So, given the experience in HIV, what can you tell us.

DR. CURRIER: Yeah. I can start and Dr. Cohen may want to comment specifically about escape, about viral escape and the setting of a monoclonal antibody. I think this is something that we worry about when you don't completely turn off viral replication that virions to our preexisting resistance could emerge.

I think it's too early to tell whether that's going to happen with COVID. There may be some natural evolution of the virus over time as

it enters into different populations.

But it's going to be something that we have to look for in people who are treated with immune-based therapies. And possibly antiviral drugs as well. Those would have the same potential risks.

But to date, we haven't really seen evidence of that. But Dr. Cohen may want to comment more.

DR. COHEN: Can I just add one thing here?

DR. DEL RIO: Certainly.

DR. COHEN: Just -- no, I think this is a really great question. We know, but HIV has much less fidelity than SARS-CoV-2.

So, for every trial that I'm aware that's being done, escape mutants are being studied. So, for example, as we see in the hospital now, monoclonal is being used whether in singles or in combinations.

Viruses that are recovered, are looked for for mutation to see whether they've escaped,

as we've studied so aggressively in HIV. The current belief is, or the current theory is, we don't know.

And the thing to do is not to bury your head in the sand, sequence everything you can recover. Just as Judy said.

DR. GANDHI: I'll just add that some of my best friends are HIV virologists. And they tell me that compared to HIV, as Dr. Cohen was saying, we see less mutations in SARS-CoV-2.

But, until we do these studies, until we do the sequencing, we just don't know.

DR. DEL RIO: Well Raj, here's a question for you. With over two thousand COVID trials and many coming online every day, how does the research community stay on top of the evolving science?

About designing research based on new findings, and coordinating research efforts across government, institutions, industry, foundations, how do we avoid duplicating research in such a rapid fire environment?

DR. GANDHI: Yeah. That's a really

important point that's being made. I will tell you from my own personal experience early on when Boston was being hit very, very hard, we had few trials at the beginning. And then the trials ramped up quickly.

But, by the time we had many, many trials in place, the numbers of patients began to go down. So, there's also the issue of how do you match up the trials with, you know, places where the incidence is the highest?

And how do you make sure you don't open too many trials, and then not have patients that you can make sure you get an answer?

So, I think that is going to be challenging. In terms of how do you coordinate and synthesize information, based on the treatment front, that's what the role of the guidelines committees are trying to take on.

The NIH guidelines committee, the Infectious Disease Society of America, they're trying to take the data that's coming out at a rapid pace, synthesize it, because a busy clinician is

not going to be able to keep track of every single trial.

Synthesize it and say, what is today's standard of care, or next month's standard of care? And that's a living document. That's changing on a weekly -- a monthly if not weekly basis.

And so, I think there's the role of the guidelines for standard of care. But then we need to go beyond standard of care.

And coordination of trials is a critical one. I think that's well worth discussing.

But, you know, I think there's many aspects to this, one is standard of care. And then how do you build trials? The trials can be formed by standard of care.

One point of discussion is if dexamethasone is shown to have a mortality benefit, then we need to rethink for hospitalized patients, how do we, what is the comparator group? Can you do a non-dexamethasone group? And that's being discussed right now.

DR. DEL RIO: Yeah. I mean, I think

that's really interesting and really important to see how for example, ACTT 2 was modified very quickly as a result of their own remdesivir trials.

DR. GANDHI: Yeah.

DR. DEL RIO: And went from a four arm trial to a two arm trial as a result. And the placebo was removed from the remdesivir arm. And then remdesivir became the standard of care.

DR. GANDHI: That's a perfect example.

That happened in real time. Essentially as soon as the remdesivir data became available, the trials evolved. They changed to reflect that new reality.

DR. DEL RIO: Well one question, last question for all of you, which is, could each one of you comment on the merits or lack of, of prescribing antibiotics to protect against secondary infection in COVID-19?

DR. GANDHI: Maybe I'll start. So, it's interesting, in China as well as in the United States, the rate of secondary infections, bacterial infections, was relatively low.

That's been our experience. And I think that's been generally the case. So, I think although super-infections and bacterial infections on top of COVID-19 can certainly happen, they're not extremely common.

So, I think one has to have a really strong clinical suspicion if there is a suspicion that there's a second infection, empiric antibiotics should be started. That is, antibiotics while you await cultures.

But, the really key thing, and this is a lesson of all of infectious diseases, you've got to steward those antibiotics. If you keep them on too long, the next thing you know, you have an intensive care unit full of people with drug resistant bacteria. And that's what you don't want to have on top of COVID-19.

So, I would say, if your suspicion is there for bacterial super-infection, short courses of antibiotics while you get your data. Stop them as soon as you can. Most people with COVID-19 don't have super-infection.

DR. CURRIER: Yeah. I would agree with that. This sort of just giving antibiotics just in case approach, I don't think we really have evidence to support that now.

And it will be really important as we look at the dexamethasone data further, to really understand whether there is an added risk for bacterial infections.

Just one thing to go back to the merits of these adaptive trials, they do have the ability to look at other interventions that have been undertaken, and what their contribution to the outcomes are.

So, I think we'll be learning more about the role of antibiotics in the management of patients in the hospital with COVID-19.

DR. COHEN: Carlos, I would invert the whole question. Because I see a different problem.

And I would invert it like this, when we look at our own facility of three, four thousand people who have symptoms that could be COVID, depending on the week and month, less than 10

percent have COVID, that's for sure. Five percent have COVID.

So, the bigger challenge is to make sure you don't miss some other serious infection. You're so focused on COVID, you let some pneumococcal pneumonia go home. Or some other terrible infection.

I had that -- I didn't have that own personal experience. But I -- so, I just think of course it would be inappropriate to give antibiotics for an infection that's a viral infection. There's no way to endorse that. Especially early in the disease.

But, let's remember that most people with -- COVID is not that easy to diagnosis. Separating COVID from other respiratory infections is difficult. It's not easy.

So, let's not lose sight of the fact that there are other infectious diseases.

DR. GANDHI: Well, also in that regard, we've seen a number of what people thought was COVID that turned out to be something completely else,

something different.

We saw someone who had an acetaminophen, Tylenol overdose. They thought they had COVID, but it was actually a drug overdose.

We've seen people actually with HIV who were diagnosed in the hospital. We had a person with pneumocystis pneumonia. It turned out they had HIV. People thought they had COVID.

So again, I endorse that point.

DR. DEL RIO: Well, thank you very much. I want to thank the three panelists for this really exciting and interesting webinar.

As I reflect on what was presented today, I think it just is amazing to me to see how quickly clinical trials have been deployed. Clinical trials are getting us answers.

And I am convinced, maybe because I'm a clinical investigator, that clinical trials are actually the way we're going to find, just like we did in HIV, the answer for treatment. And the answer in prevention with both drugs and vaccines.

I think for all of us in HIV, when we

saw, you know, 1986, the first AZT trial, it took us ten years to get to 1996 when we had, you know, highly active antiretroviral therapy, and we had potent antiretroviral therapy that spread viral suppression and prolonged the life of individuals.

The speed of COVID is not going to take us ten years. It may take us ten months. And I just think it's one of the things that is really hard as an investigator, is that the standard of care is changing rapidly.

And trials are not being modified and being done very, very rapidly. And it's a very different environment.

I mean, consenting patients, enrolling patients, following patients, it's all new and as Dr. Currier said, we're all learning new ways of doing research that I don't think we've ever even thought about before we had COVID with us.

I think, as Dr. Gandhi says, you know, taking clinical trial results and transforming that into guidelines, is not an easy task. And I would again, recommend people look at both the

NIH and the IDSA treatment guidelines.

I think they are really up to date. And they are really where I go to when I want to see what is the latest in treating somebody with COVID-19.

And finally, I want to reflect on what Dr. Cohen said, is monoclonal antibodies are really an interesting road. Because it's telling us right now about immunity.

And it's telling us that an immune mechanism can be useful not only for treatment, but also for prevention. And I think it's opening the way into vaccines and into other therapies that we will have, and other preventions that we will have in the future.

But we also desperately need the availability of an oral agent. I mean, what we have right now, remdesivir, is injectable. You have to be sick. You have to be in the hospital.

And really, when you show up today to the outpatient clinic and you're diagnosed with COVID, we really have nothing to offer patients.

And I think it's really important that we start doing, you know, enrolling in the clinical trials, and getting the clinical trials off the ground, so we really know does it matter, can we make a difference?

And can we do two things? Number one, decrease the amount of time that that person is shedding virus. But number two, also decrease the likelihood that that person will go on to develop complications.

So, I think there's a lot of exciting research happening over the next year. And I would encourage you to stay engaged, because really, it's just a fascinating time to be doing clinical research in infectious disease.

So, with this, we'll conclude today's webinar. I want to invite everybody to the next webinar, which will take place on July 8 at 5:00 p.m.

And it's going to be dedicated to the following the signs to safely reopen colleges and universities during COVID-19. So, I'm sure it's

going to be a topic of significant interest to many of you.

Everyone who registered for today's webinar is going to receive an invitation for that webinar as well.

This webinar has been recorded. And the recording and transcript as well as the slides, will be available at covid19conversations.org.

And thanks again to our panelists and to the Association, the APHA and the National Academy of Medicine for sponsoring the webinar series.

And thanks to you, our listeners, for joining us today. Best wishes to you. And a healthy and safety -- please take care and wear your masks. Thank you for attending.

(Whereupon, the above-entitled matter went off the record at 6:28 p.m.)