What physicians need to know about tecovirimat (TPOXX) for treatment of monkeypox

On Sept. 13, 2022, the AMA hosted episode 12 in the "COVID-19: What physicians need to know" webinar series.

Experts from the AMA, FDA and CDC discuss tecovirimat, or TPOXX, for the treatment of monkeypox in infected individuals. The discussion provides background on tecovirimat, including its current status, availability and access while the drug is under an investigational new drug application. An overview of the recently announced National Institute of Allergy and Infectious Diseases sponsored Phase 3 clinical trial evaluating TPOXX is also be provided.

Speakers

Host

- Sandra Fryhofer, MD, Chair, AMA Board of Trustees

Guests

- Adam Sherwat, MD, Deputy Director, Office of Infectious Disease at FDA’s Center for Drug Evaluation and Research
- Brett W. Petersen, MD, MPH, Deputy Chief, Poxvirus and Rabies Branch, CDC’s Division of High-Consequence Pathogens and Pathology
- Timothy Wilkin, MD, MPH, Professor of Medicine and Assistant Dean for Clinical Research Compliance for Human Research Protections at Weill Cornell Medicine and TPOXX clinical trial lead

Transcript
Dr. Fryhofer: Hello, everyone, and thank you for joining us for the latest in AMA’s "What Physicians Need to Know," webinar series. Today, we’re talking about monkeypox, with a special focus on the antiviral, tecovirimat, also known as TPOXX, its use, as well as its availability as a treatment for this disease.

I'm Dr. Sandra Fryhofer, board chair of the American Medical Association. I'm in private practice, general internal medicine in Atlanta, I'm also adjunct Associate Professor of Medicine at Emory, and AMA's liaison to ACIP, the CDC Advisory Committee on Immunization Practices. And I'm delighted to be here today to take part in this important discussion.

In just a moment, I'll introduce today's experts, from FDA and CDC. They'll talk about monkeypox, what it is, and what it isn't, what it means for physicians, as well as current treatment options, and what happens next. But before we get to the topic that brings us here today, allow me to acknowledge each of you.

We've been through a lot over the past two years, more than we could have imagined, and honestly, more than what we were prepared for. But today, there's progress. The daily average of new reported COVID cases has continued to fall—a trend we've been seeing since the beginning of August.

Cases are falling in all but a few states. Americans are vaccinated and boosted, and more help is on the way. A new bivalent COVID booster targeting both the original virus strain as well as Omicron BA.4 and BA.5 subvariants is now widely available for those 12 and older.

We strongly encourage you to talk to your patients about the importance of getting this updated booster at least two months after completing a primary COVID vaccine series or their last COVID booster dose. It's crucial that we continue our progress to protect patients from hospitalizations and deaths due to COVID. We've learned from our uncoordinated response to COVID how important it is to contain an outbreak in its early stages.

Already in the U.S., more than 20,000 cases of monkeypox have been reported. Just like COVID, the total number of infections is certainly higher than current figures indicate. Already, there are more than 54,000 cases in 93 countries—countries that have not historically reported monkeypox in the past.

And unlike COVID, where we had to invent vaccines and antivirals, we already have vaccines and therapeutics that can be used to protect and treat patients for monkeypox. Tecovirimat, a.k.a. TPOXX, which we're going to discuss in depth today, was FDA approved for treatment of smallpox in adults and children in 2018. Its use for other orthodox virus infections, including monkeypox, is not approved by FDA.

However, this drug is being made available through EA-IND, Expanded Access Investigational New Drug Protocol, which we'll explain here today. Now, this is different than EUA, Emergency Use...
Authorizations, that we've all become accustomed to during the pandemic. It's important to understand the distinctions.

We've heard from many of you that the process for obtaining and utilizing TPOXX has been cumbersome and has led to significant delays and treatment in some cases. CDC and FDA have worked together to update protocols for use of TPOXX in order to make it easier to increase access to treatment. We'll talk more about that with today’s panel of experts.

Here's the plan. After introductions, each of our guests will share a presentation. Then, we'll move into a Q&A session to address some of the questions you've submitted. First, I'd like to welcome Dr. Adam Sherwat, Deputy Director of the Office of Infectious Diseases at the FDA’s Center for Drug Evaluation and Research. Dr. Sherwat will provide his expert insight on the status of TPOXX as an IND, Investigational New Drug, and what that means for us as physicians and for our patients. Thank you for being with us today, Dr. Sherwat.

We're also delighted to have infectious disease expert, Dr. Timothy Wilkin, Professor of Medicine and Assistant Dean for Clinical Research Compliance for Human Research Protections at Weill Cornell Medicine. Dr. Wilkin's a clinical trial researcher, with a focus on prevention of HPV-related cancer and people living with HIV. he also chairs a clinical trial looking at tecovirimat for treatment of monkeypox in humans.

Also joining us today is Dr. Brett Petersen. Dr. Petersen is captain of the U.S. Public Health Service and Deputy Chief of CDC’s Pox Virus and Rabies Branch. Dr. Petersen will tell us more about the streamlined process required for TPOXX, which eases the burden of physicians by making it easier to access this treatment for our patients.

CDC has played a critical role in our ongoing response to monkeypox, and we'll also hear more about recent developments. We are so fortunate to have these three experts with us today. So let's get started. Dr. Sherwat, we'll start with you.

Dr. Sherwat: So I am going to provide a regulatory perspective on tecovirimat. Next slide, please. This is my disclaimer. Next slide, please. So tecovirimat is an antiviral drug that inhibits viral spread to uninfected cells by directly and specifically targeting the orthopoxvirus protein, VP37, which is involved in producing extracellular enveloped virions.

Tecovirimat was approved for the treatment of smallpox disease under a regulation known as the Animal Rule. The Animal Rule allows for approval of drugs when human efficacy studies are not ethical, and field trials to study the effectiveness of drugs or biological products are not feasible. Under the Animal Rule, efficacy is established based on adequate and well-controlled studies in animal models of the human disease or condition of interest. Next slide, please.
So establishing efficacy under the Animal Rule—in this case, conducting clinical trials to study tecovirimat for the treatment of smallpox was neither feasible nor ethical. Smallpox is an eradicated disease, and exposing study participants to variola virus or the smallpox virus is not ethical. And there were scientific and logistical constraints with the use of variola virus in animal models.

Therefore, efficacy was established based on studies of non-human primates infected with monkeypox and rabbits infected with rabbitpox virus. These studies demonstrated improved survival in animals that received tecovirimat, compared to animals that receive placebo. Next slide, please.

I just provided this slide to remind you that you can reference the U.S. prescribing information for additional details on efficacy. This table is taken directly out of the prescribing information, and it outlines in detail what the results were from the efficacy studies. Next slide, please.

So establishing safety under the Animal Rule—approvals that go forward under the Animal Rule still require establishing an adequate safety database, like any other drug or biologic product. The safety of tecovirimat was evaluated in 359 healthy adult subjects aged 18 to 79 years, in a placebo-controlled clinical trial. These subjects had neither smallpox nor monkeypox.

Adverse reactions occurring in greater than or equal to 5% of subjects receiving tecovirimat included headache in 12% and nausea in 5%. There were no deaths or serious adverse events that were considered to be related to tecovirimat. Next slide, please.

Select an effective dose. Tecovirimat exposures achieved in healthy human subjects were compared with those observed in the animal models of rabbitpox and monkeypox infection at the doses that were associated with maximum effectiveness. With tecovirimat, the selection of a maximum human dose was constrained by neurologic findings and animal toxicology studies. However, tecovirimat exposures achieved in healthy humans at the recommended dose are higher than the therapeutic exposures in the relevant animal models. Next slide, please.

So there are a number of uncertainties that are inherent in Animal Rule approvals. One is that drugs that are effective in animal studies are not always effective in humans. And we’ve seen that before in clinical development programs.

Another is that a drug safety and pharmacokinetic profile may differ in healthy people versus people with a disease of interest—in this case, monkeypox. So post-marketing studies, such as field studies, are required to verify and describe a drug’s clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Next slide, please.

So a question that we’ve received before is, why was tecovirimat not approved for treatment of monkeypox under the Animal Rule? So monkeypox disease did not meet the Animal Rule requirement that human efficacy studies are not ethical, and field trials to study the effectiveness of drugs or

URL: https://www.ama-assn.org/about/events/what-physicians-need-know-about-tecovirimat-tpoxx-treatment-monkeypox
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biological products are not feasible. At the time of tecovirimat approval, there were parts of the world, including in Western Central Africa, where monkeypox disease was endemic and clinical trials could be conducted.

Next slide, please. For this slide, I just wanted to cover some of the knowledge gaps and potential liabilities of the use of tecovirimat. The efficacy, safety, and pharmacokinetics of tecovirimat in the treatment of monkeypox in humans have not been demonstrated. Also, tecovirimat must be administered with a moderate- to high-fat meal to achieve target drug exposures.

Another significant issue is the low barrier to resistance of the drug. This was based on results in cell culture, animal studies, and clinical case reports. Some of the resistance pathways require only a single amino acid change in the viral VP37 drug target to cause a substantial reduction in tecovirimat activity. Next slide, please.

So current access to tecovirimat is via an NIAID-sponsored, randomized controlled clinical trial, and also via an intermediate-size Expanded Access IND protocol, or EAP, held by the CDC. Data from randomized controlled trials are critically needed to address knowledge gaps related to efficacy, safety, pharmacokinetics in humans with monkeypox and to monitor for development of resistance to tecovirimat.

All are essential in guiding clinical and regulatory decision-making.

Therefore, health care providers should encourage their patients with monkeypox infection to be evaluated for enrollment in NIAID's randomized controlled trial. For patients for whom enrollment in this trial is not feasible—for example, a clinical trial site is not geographically accessible—the use of tecovirimat under CDC's Expanded Access protocol should be consistent with applicable guidelines for tecovirimat use.

**Dr. Wilkin:** Thank you. I'm happy to present the study on behalf of my co-investigators, as well as the National Institutes of Allergy and Infectious Diseases. Great. So we have rapidly developed this protocol at the request of NIH and NIAID.

This protocol is part of our national plan for responding to the monkeypox—human monkeypox epidemic. So we are—I'm glad to say that we enrolled our first person last week on September 8, and we will ramp up the protocol in the weeks to come, as more and more sites come on board. Next slide.

The study is really two studies in one. First, we have a randomized double-blinded placebo-controlled portion, where we are asking the question, is—trying to answer whether tecovirimat is effective for the treatment of human monkeypox disease. We also have a second portion of the study where we provide open-label tecovirimat for certain populations, including children, people who are pregnant, people with severe disease, severe immunosuppression, or severe skin disease, that puts them at risk...
for severe outcomes from this disease.

So the studied population are those with symptomatic human monkeypox virus infection. This is a superiority design. The primary outcome is time to clinical resolution that we'll discuss in a moment. And the participation for the participant is over two months.

Originally, we hoped to enroll the study in eight weeks. That may or may not be possible, as the number of cases starts to decline in the U.S. And we're studying weight-based oral tecovirimat. And of note, I have the clinicaltrials.gov information below as well. Next slide.

So our hypothesis is that tecovirimat will lead to faster clinical resolution of human monkeypox virus disease, compared to placebo. We'll compare the time to clinical resolution. And we're defining this primary endpoint of clinical resolution as when all skin lesions are scabbed over, desquamated, or healed, and all visible mucosal lesions are healed as well.

We're assessing this with a combination of sources of data, including daily skin checks by the participants as well as photographs. When the person reports clinical resolution, we'll conduct remote visits and video visits to confirm resolution, as well as confirming at an in-person visit when scheduled. Next slide.

Just to give you an idea of the primary endpoint, you can see on the left is a scabbed-over lesion, as well as on the second to the left, and further over, after the scabs have fallen off and these lesions have resolved. So this is clearly a subjective outcome, and people can be infected—or people can have upwards of 100 lesions.

So it is a difficult primary endpoint to assess. And I will note that there have been no clinical trials conducted in this area. So we are, in some ways, learning as we go. Next slide.

We have a whole host of secondary outcomes, including assessing pain, which is a major presenting symptom for patients. Progression of severe disease we'll look at clearance of human monkeypox virus in various places, with the hope that we can find a surrogate endpoint for future studies.

And we are assessing pharmacokinetics, as Dr. Sherwat mentioned. We have a dearth of data in this area. So we'll be assessing in the randomized portion as well as for people who are pregnant, and children across the age span. Next slide.

For eligibility, we ask two questions. The first is, does the person have symptomatic human monkeypox virus disease? So they can either have confirmed infection—so a laboratory report that was obtained within the last seven days—or presumptive diagnosis—skin mucosal lesions, proctitis, consistent with a high probability of human monkeypox virus, in the opinion of the site investigator, as well as an exposure—either sexual contact in the prior three weeks, or close household exposure with
someone known to be infected with human monkeypox virus.

We want to get enrolled people that are less than two weeks in duration of illness and have at least one active lesion or symptom to follow. People who are not pregnant should agree to contraception or abstinence, very flexible, and ability to provide informed consent. Next slide.

The second question we ask is, are they appropriate for randomization? So here are listed the groups where we’ve decided they’re not appropriate for randomization, that they should receive open-label tecovirimat. So for people less than 18 years of age, we want to really focus on safety and pharmacokinetics.

So everyone is—and that group is receiving open-label tecovirimat. Those with severe disease, we’ve defined that as suspected or confirmed ocular involvement. Lesions on the central face that could be disfiguring, hospitalization lesions that are severe and require intervention. We have—those with severe immunosuppression will receive open-label tecovirimat.

Those with certain skin conditions that we know from—that placed them at higher risk for these orthopox virus conditions, people who are pregnant or breastfeeding, and people that are expected to have significant drug-drug interactions with tecovirimat—we are enrolling them or providing open-label tecovirimat, so we can get more data on the drug interactions. Next slide.

So the follow-up is scaffolded with weekly visits for a month, so five weekly visits for a month, and then a visit two months after. We assess with detailed examinations, swabs, blood. People have a detailed STI screen at baseline.

There’s participant reported outcomes as well as a daily study diary through the first month. And I will point out that those that are originally in the randomized arm can move to open-label tecovirimat if at any point they have progression to severe disease. So they develop eye lesions, central facial lesions, they’re hospitalized—any of that, they move to open-label tecovirimat—as well as people that have persistent severe pain that lasts for five days or more, are able to move to open-label tecovirimat. Next slide.

So we're powering the study for a faster resolution of three days—three days, faster resolution of symptoms. We believe that would be clinically meaningful. Next slide.

And as I said, we are open to accrual. We hope to have 80 sites, eventually, at most major metropolitan areas. So we will update the lists on the clinicaltrials.gov. We will have broader press releases that we'll have our open website, so you'll—as well as a call center, so there'll be easy ways to refer patients to the study. There are other trials.
There's the UK study that's ongoing, that's completely remote. There's a smaller-in-scale Canadian trial that's opening soon, and a more complicated platform trial conducted by the WHO that we'll open in the coming weeks as well. So overall, we are open to accrual.

We try to address the concern of the community to have access for government while still being able to have a controlled assessment of efficacy. So we do hope to have most people infected with tecovirimat in a community where the protocol is open to be referred to the protocol.

**Dr. Fryhofer:** I love the name of this study, STOMP, S-T-O-M-P. And I wonder if we google clinical trial STOMP, if we'll come up with it. But thank you so much for presenting that. And next, we'll hear from Dr. Petersen. Take it away.

**Dr. Petersen:** Great. Thank you very much, and thank you for the invitation to join this webinar. All right, next slide. So my goal with my presentation is to really highlight some of the resources in terms of guidance and other data that is available from CDC regarding treatment with tecovirimat.

I want to start by noting that many individuals infected with monkeypox do have a mild self-limiting disease course, even in the absence of specific therapies. So for many patients, supportive care and pain control is really sufficient in treating this disease. However, the prognosis for monkeypox does depend on multiple factors, such as the previous vaccination status, initial health status, and concurrent illnesses or comorbidities. Next slide.

And so with this in mind, CDC has tried to develop some treatment considerations for monkeypox. The website is noted here, and I would suggest that folks keep a close eye on this website, as there are some expected updates coming very soon—likely, this week.

But the main treatment considerations is that persons should be considered for treatment who have either severe disease or at high risk for severe disease—for example, people with immunocompromising conditions, pediatric populations, pregnant or breastfeeding people, people with a history of or presence of atopic dermatitis or other skin conditions, and people with one or more complications.

And lastly, persons who do have lesions on sensitive anatomic areas that might lead to increased risk of serious ... should also be considered for treatment. Next slide.

Now, tecovirimat, the subject of our webinar today, as we've discussed, is really the first-line treatment for monkeypox. I think we've heard about most of this already. I'll note that this drug has been licensed as both an oral and IV formulation, and both of these formulations are available from the strategic national stockpile.
And as noted earlier, CDC does hold an expanded access IND, which allows the use of this product for non-variola orthopoxvirus infections, including monkeypox. Next slide. Now, in terms of the EA-IND, CDC has worked with FDA to really make it easier for health care providers to provide this treatment to patients with monkeypox.

The EA-IND provides an umbrella of regulatory coverage, so that clinicians and facilities don't need to individually request INDs. And this ensures that there's liability coverage under the PREP Act, if there are patients injured and they can receive compensation under the countermeasure injury compensation program.

In terms of implementing EA-IND, treatment with TPOXX can begin upon receipt of the medication and after obtaining informed consent. There's no requirement for preregistration for clinicians or facilities. And the forms that are required under the EA-IND can all now be returned to CDC after treatment begins. Next slide.

The forms that are currently required include the informed consent form, a patient intake form, and the FDA form 1572. A Serious Adverse Event form, the MedWatch form, is also required if adverse events occur during treatment. A number of other optional forms and resources are available, including a patient diary, which patients can use to record how they feel, and any side effects to TPOXX.

And what was previously required but is now optional is a clinical outcome form, which is still very helpful for us to document progress and outcome information post-treatment. Additionally helpful are photos of the lesions. And in situations where resistance may be suspected, lesion samples can be collected and sent to CDC to assess for the development of antiviral resistance. And pharmacokinetic samples can also still be submitted optionally to monitor TPOXX levels for adequate drug exposures. Next slide.

The CDC has recently summarized the information that we've received from patients and providers under the EA-IND and published this in a recent MMWR. What we've learned is that among 549 patients who have been treated under the EA-IND, 99.8% received it orally and as an outpatient, and among the 369 patients for which we have data available, few adverse events were reported. So this really supports the continued provision of this drug under EA-IND.

And I'll also note in the figure here that the time from onset of symptoms to initiation of treatment has also decreased, likely due to a number of factors, but some of which are being the simplification of the process as well as increased awareness and accessibility of the product. Next slide. We continue to collect information on the demographics of patients receiving tecovirimat.

As you can see here, we're up to almost 2,000 patients, for which we've received the patient intake form. And what we've seen is the demographics of the patients being treated with the government has closely tracked the demographics of the cases being reported. So we continue to monitor this to
ensure access and equitable use of tecovirimat in this outbreak. Next slide.

I want to point out that there are some other treatment options available—VIGIV is a product licensed for treatment of complications due to vaccinia vaccination or smallpox vaccination. Cidofovir is an antiviral medication that is approved by FDA for treatment of CMV retinitis in patients with AIDS. Both of these products do have activity against orthopoxvirus infections, although there's limited data to support their use specifically for monkeypox.

CDC does hold an expanded access IND protocol to allow the use of these products for the treatment of monkeypox. And both of these products are also available in the SNS. These products could be helpful adjuncts in treating severe cases of monkeypox who are already receiving tecovirimat, for example. Next slide.

One other treatment option is brincidofovir, which is an antiviral medication approved by FDA for treatment of smallpox. It is not currently available from the SNS, but the BARDA has awarded a contract to procure brincidofovir for the SNS, and we do expect it to be available soon. And CDC is currently developing an expanded access IND protocol to help facilitate the use of this product as a treatment for monkeypox as well. Next slide.

Lastly, for ocular infections, which, unfortunately, we have seen during this outbreak, trifluridine, or Viroptic, is an antiviral medication that's licensed for treatment of herpes, keratoconjunctivitis, or keratitis, and there is in vitro evidence of trifluridine activity against orthopoxviruses, and we do have case reports of trifluridine being used for vaccinia virus infections, for example, following smallpox vaccination, as well as, during this outbreak, for monkeypox.

And previous anecdotal reports do suggest some benefit for treatment of ocular infections with trifluridine. Next slide. So lastly, I just did want to highlight that there are some guidance and considerations for specific populations. So for treatment and prophylaxis in people with HIV, it is known that people with advanced HIV or those who are not virologically suppressed with antiretroviral therapy can be at increased risk of severe disease.

And we have unfortunately seen some severe cases related to uncontrolled HIV. Post-exposure prophylaxis and antiviral treatments are available for these individuals, and antiviral treatments have few interactions that we've noted with antiretroviral therapy. And more information is available at this link here. Next slide.

In terms of people who are pregnant or breastfeeding, this is another population where there is increased risk for severe disease. And these individuals should be prioritized for medical treatment when needed. Tecovirimat can be considered the first-line antiviral, given that there are no known fetal effects that were observed in animal studies, although human data is limited.
However, with cidofovir and brincidofovir, there is evidence of teratogenicity in animal model studies, so use in this population should be used with caution. Lastly, VIG administration can be considered after evaluating the risk and benefits for individual patients. Other immune globular products have been widely used during pregnancy for many years without any apparent negative reproductive effects. Next slide.

Lastly, we do also have clinical considerations for monkeypox in children and adolescents. This is another population that has been seen to be at high risk for severe disease, particularly in children with eczema or other skin conditions. And so treatment can be considered on case-by-case basis for children and adolescents who are at risk for severe disease or who develop complications of monkeypox.

And tecovirimat is generally the first-line medication to treat monkeypox in children and adolescents. Next slide. In terms of requesting medical countermeasures, government and other medical countermeasures can be requested for suspected, probable, or confirmed monkeypox cases. And contacting your state or territorial health department is really the first step in making these requests.

Many of these jurisdictions do have government already pre-positioned and available use. But of course, CDC is available for urgent clinical situations and consultations after hours on weekends, and we can be reached through our CDC Emergency Operation Center. The number is listed here. So I think that is my last slide. And thank you again.

Dr. Fryhofer: Well, many thanks to all three of our guests for providing such valuable insight. And I know you have lots of questions. And so let's get to those now. Whitney, if you're able to queue up the questions submitted, let's jump right in.

OK. The top question we've received from physicians around the country is about EUA. So here's the question. TPOXX is already approved for use in the European Union as a treatment for monkeypox. There's already a significant amount of clinical outcome data from IND patients. European Patients, JAMA and Lancet peer-reviewed articles, et cetera. Many scientists and physicians have advocated for immediate EUA based on this data. So why isn't that data being taken into consideration in addition to the risk-benefit ratio? Why is it not at least authorized to EUA to improve access here?

The bottom line—what additional data do we need on TPOXX to have EUA granted? And let's—I think FDA's Dr. Sherwat, I think you're in the hot seat for this one.

Dr. Sherwat: First, I want to provide a short overview of the regulatory framework related to emergency use authorizations. It's important to note that there are two types of relevant declarations—the 319 declaration and 564 declarations. A determination under Section 319 of the
Public Health Service Act—the public health emergency exists, such as the Declaration made on August 4, 2022, does not enable FDA to issue emergency use authorizations.

A separate determination and declaration are needed under Section 564 of the Federal Food, Drug, and Cosmetic Act to enable FDA to issue emergency use authorizations, provided other statutory criteria are met. On August 9, 2022, and September 7, 2022, the HHS Secretary declared under Section 564 of the Federal Food, Drug, and Cosmetic Act, that circumstances exist justifying the authorization of emergency use of vaccines for monkeypox and in vitro diagnostics for the detection or diagnosis of infection of monkeypox virus, respectively.

Neither of these EUA declarations cover the emergency use of therapeutics for treatment of monkeypox disease. And therefore, FDA is not enabled to issue EUAs for therapeutics for the treatment of monkeypox disease at this time. Importantly, even if the requisite declaration for therapeutics were to be made, FDA would need to consider the circumstances and appropriateness of an EUA for a particular medical countermeasure and determine whether the criteria for issuance of an EUA have been met.

Putting aside the explanation of the regulatory framework, we have been working very closely with our colleagues at CDC to finetune access via the Expanded Access Protocol, and with our colleagues at NIH and academia to facilitate the development of a randomized clinical trial that is now open for enrollment.

As previously noted, at present, we have no data from randomized controlled trials demonstrating the safety or efficacy of tecovirimat for the treatment of monkeypox in humans.

Data from randomized controlled trials are critically needed to address knowledge gaps related to efficacy, safety, pharmacokinetics, and to systematically monitor for the development of resistance to tecovirimat, all of which are essential in guiding clinical and regulatory decision-making. Therefore, health care providers should encourage their patients with monkeypox infection to be evaluated for enrollment in the randomized controlled trial.

Dr. Fryhofer: Wow. It sounds like TPOXX EUA is caught in a lot of red tape. Thank you for that very complete answer, which leads us to the next question. How can physicians obtain TPOXX? How has this process been simplified? And are there any plans to simplify this process further?

Dr. Petersen, I know one of your slides addressed that. And I know CDC has made—has tried to make this easier. I guess it’s easier than it could be. But can you reinforce what you told us earlier about that process, please?

Dr. Petersen: Of course. So in terms of requesting tecovirimat, the best first source is always your state territorial local health department. As I mentioned, many of those jurisdictions do already have
tecovirimat available and pre-positioned. In terms of the process of implementing the EA-IND, as I mentioned, treatment can be started as soon as informed consent is obtained.

All of the required forms can be submitted after treatment is initiated. We’ve drastically decreased the number of forms that are required, and many of the other processes have been made optional. So all of this is with the intent of simplifying the process of using this product under our EA-IND.

**Dr. Fryhofer:** So I counted, on your slide, about four required forms. And there are about eight others that were optional. So it does sound like you’ve simplified the process a good bit. So thank you there.

Another question—who is not eligible to receive TPOXX under the EA-IND? Can you answer that one as well, Dr. Petersen?

**Dr. Petersen:** Sure. So the only persons who are not eligible to receive treatment under our EA-IND are those who are not willing to sign the informed consent, or those who have allergies to the product or any of the ingredients of the product. Otherwise, the EA-IND is open for patients of all ages. There is weight-based dosing, but there's no age restriction in using the product under our EA-IND.

**Dr. Wilkin:** So the severity of disease doesn't matter, so a single lesion would qualify for the EA-IND.

**Dr. Petersen:** Well, we would refer to our treatment considerations. Obviously, those are the individuals that we think would benefit most from treatment with government. So I think those are what we would point to as the guiding principles for who should be receiving treatment. But in terms of eligibility, everyone is eligible under the requirements of the EA-IND.

**Dr. Fryhofer:** So you mentioned weight-based dosing. How many different size doses—dose capsules does it come in?

**Dr. Wilkin:** It's a single-dose capsule that's available, 200 milligrams. It's when you get below 13 kilograms that you would need to have partial dosing. And that, that's where some of the challenges lie in oral dosing.

**Dr. Fryhofer:** So how do you do that in your study? Do you just take the capsule apart and put it in a baby capsule? Or what do you do? That's not something I guess practitioners could do. But—

**Dr. Wilkin:** Basically, for the clinical trial, we have intensive instructions for the caregivers of the young children. But basically, the contents of the capsule are mixed in a fixed amount of liquid, mixed appropriately, and then the relevant portion is drawn up that can then be administered to the child.

**Dr. Fryhofer:** Dr. Petersen, is that what CDC is recommending as well, for the four physicians out and general practice?
Dr. Petersen: Yes, that's correct. For those patients between 3 kilograms and 13 kilograms, our EA-IND also does include instructions for opening the capsules and mixing the contents with various food products that can be apportioned out. Also, note that there is an IV formulation available, which can be used as well for some of those situations where there's a need to ensure appropriate dosing if there's any concerns about absorption with the drug. And again, with IV formulation, that's a weight-based dosing as well.

Dr. Wilkin: It's important to mention that the IV formulation—correct me if I'm wrong—has cyclodextrin, which has some concerns for renal toxicity. So the risk benefit does sort of does change with IV as compared to oral.

Dr. Fryhofer: So on one of the slides, I saw that you want to take it with a fatty meal. So what kind of foods do you recommend? I usually think of mixing medicine with applesauce for little kids, but I guess applesauce is not exactly fatty. What do y'all recommend, specifically, for these little ones?

Dr. Wilkin: It's been studied with milk and chocolate milk. But basically, it's—with our pediatric colleagues, anything you can get to mix it in that the kid will take is important. But definitely trying to get some fat in there—so ice cream, yogurt, things like that.

Dr. Fryhofer: Chocolate milk works every time. OK. Dr. Wilkin, you stay on, because this next question, I want to begin with you. Our AMA has a center for health equity. So we're really concerned about this.

How are we ensuring equitable access to TPOXX? And then, after Dr. Wilkin gives his point of view, Dr. Petersen, I'd love to hear from you as well.

Dr. Wilkin: Well, I think the way that we get equitable access is to get unfettered access to the drug—so for it to be available by a simple prescription and stocked widely in pharmacies. And so that is not the case now, and we cannot get there unless we commit to enrolling in the clinical trial, unless we get efficacy data.

I just think it's important to point out that there is no efficacy data in humans for any condition. And so although it's been approved in the EU, it's not based on efficacy data. While certainly, the experience has been that it's well-tolerated, people seem to do well, this is generally not a lethal disease, and it has a very subjective outcome.

And so we really to feel totally confident in our therapies. We need randomized data. And should we need to develop new therapies, it gets incredibly complicated if the therapy you're comparing it to has never been established for efficacy.
So I do think that the way that we get access is to have this randomized data, so that we can be approved on a more normal pathway. For our clinical trial, we work with clinical trial sites that have a historic—have historically enrolled communities of color in research.

There are—a lot of the studies have done a tremendous amount of studies in HIV infection. So we have long-standing collaborations with communities and community organizations to really increase our enrollment of those key populations.

Dr. Fryhofer: Thank you so much. Dr. Petersen, do you have anything to add? I know, with my work with the ACIP, we always talk about equity concerns with every vaccine we discuss.

Dr. Petersen: Yeah, absolutely. So I certainly agree with Dr. Wilkin's comments. And I would add that from the EA-IND perspective, we also are working diligently to simplify that process to improve access through the number of measures that we've discussed already. We are also working closely with our state partners to ensure that they are able to easily order the product, and in many cases, as I mentioned, pre-position the product, so it's available and accessible for immediate use.

And lastly, we continue to monitor the information that we receive about the individuals receiving tecovirimat under our EA-IND, and comparing those demographics to what we're seeing in the outbreak at large, to see if there's any discrepancies between who's coming down with monkeypox and who's being treated, so we can identify any inequitable treatment that may be occurring.

Dr. Fryhofer: So stay with us, Dr. Petersen, for this next question. How much does TPOXX cost?

Dr. Petersen: So TPOXX is available free of charge. In addition, if there is a desire to do the PK monitoring, or to do testing at CDC for serology or other virologic testing, antiviral resistance testing—that can also be done free of charge. However, there's not any funding to support any additional laboratory testing. But the product itself is free of charge.

Dr. Fryhofer: Great. And do any of you know what billing code should be used for TPOXX administration?

Dr. Wilkin: It's prescription of oral drugs, so you would use your standard office-based visits or video visits, telehealth codes.

Dr. Fryhofer: Thank you. All right. We have a bunch of questions about safety and efficacy. What does the current data demonstrate about efficacy of TPOXX in individuals with monkeypox? Let's start with Dr. Sherwat, and then go on with Dr. Wilkin, and then Dr. Petersen.

Dr. Sherwat: Great. I was just saying that I think I would just reiterate what was said earlier, which is, at present, we have no data from randomized controlled trials that demonstrate safety or efficacy of
tecovirimat for the treatment of monkeypox in humans. Much of what we’ve seen has been individual case reports or case series with no control, so it’s very difficult to, from a safety perspective, how much of the safety profile we’re seeing is driven by monkeypox disease, versus the drug, and what the time frame for healing is like when you don't have a control arm. So that’s why we’re stressing the importance of having control data and making an assessment of safety and efficacy in this setting.

**Dr. Fryhofer:** So Dr. Wilkin, I know you have your STOMP clinical trial in progress. But do you have any comments to make about efficacy at this point?

**Dr. Wilkin:** I understand providers’ desire for access to the drug. For people that we’ve treated at our institution, they do seem to respond very well. But we don't have the controlled data.

For the trial, we do have a data safety monitoring board that monitors along the way, and we will look at the data early. And so ideally, if it is such a strong effect, we will be able to stop the study early.

**Dr. Fryhofer:** So I'm going to add another little question on to that. Since you're involved in this clinical trial, so you're having to deal with these patients every day, what kind of side effects are you seeing? I know when Dr. Sherwat made his presentation, he said nausea and headache in, like, less than 5% of people. But what are you seeing in your trial?

**Dr. Wilkin:** Well, most of the experience comes through the Expanded Access trial, and people tolerate the drug very well. And sometimes it’s a little difficult to separate out the side effects from the drugs from the underlying disease, highlighting the need for controlled data. But I think people do very well with the drug that’s there.

**Dr. Fryhofer:** And they probably like having to take it with chocolate milk or ice cream as well, too. So Dr. Petersen, what about for what is the current data on average time to symptoms’ improvement, following initiation of treatment with TPOXX? What about for patients with HIV?

**Dr. Petersen:** Yeah, thank you. So we have monitored the data that we’re receiving for patients receiving treatment under our EA-IND, and we summarized that in our recent MMWR. And what we have seen is that the median time from initiation of the drug to subjective improvement reported by the patients is three days.

And there isn't any difference in that time point between individuals with HIV or without HIV. However, as noted before, this is not a randomized clinical control trial. We do not have a control group. So while we can do descriptive analyses of what we’re seeing with these patients treated, it’s not rigorous. We can't draw rigorous conclusions, in terms of either safety or efficacy, with what we’re seeing.

**Dr. Fryhofer:** So stay with me, Dr. Petersen. I know you reviewed this on one of your slides, but this question came up, so let's reinforce this. Can TPOXX be prescribed for pregnant or lactating...
individuals and children? And a follow-up to that—is there any efficacy data in this population?

**Dr. Petersen:** Yes, the second question first—no, there's no efficacy data in any human monkeypox cases. But this product can be considered for use in pregnant patients and in children and adolescents on a case-by-case basis. We have some limited case report information, and there haven't been any severe adverse events associated with those case reports.

And so with our limited experience to date, there's been no safety concerns. But again, this should be a decision made in close consultation with the patient, weighing all the risk and benefits of potential treatment.

**Dr. Wilkin:** Because of the uncertainties of dosing in children, especially younger children, our study collects detailed PK information that will run in near real time, so that we can actually update the dose for the next child enrolled. So we learn from one child, improve and refine the dosing for the next child.

**Dr. Fryhofer:** And so PK is the pharmacokinetics, right?

**Dr. Wilkin:** Yes.

**Dr. Fryhofer:** OK. So are there any—so Dr. Petersen, again, are there any known drug-drug interactions? And are there any drug-drug interactions in individuals receiving antiretroviral therapy and those receiving prophylaxis against opportunistic infections?

**Dr. Petersen:** Yes, so I think I will defer to my other colleagues. There are some drug-drug interactions that have been observed with some diabetic drugs. And in terms of antiretrovirals, that has been modeled, and there are a few interactions that have been identified. And I'll leave it to Dr. Sherwat and Dr. Wilkin, if they have other specific information.

**Dr. Sherwat:** I would echo the same comments that were just made. There are drug-drug interaction considerations. The health care providers should follow the instructions that are in NIAID's protocol for the RCT or CDC's protocol for the EAP, based on the mechanism under which the product is being given.

There is also general information on drug interactions in the U.S. prescribing information, and there's also information at the HHS, HIV treatment guidelines website—particularly detailed information with respect to drug-drug interactions in the setting of ART. But I would turn it over to Dr. Wilkin to talk about the approach to the RCT.

**Dr. Wilkin:** Yeah, we worked closely with the FDA and gathered the available PK information. And overall, it was thought for people with HIV that the magnitude of the drug interactions and the short duration of treatment—it was very unlikely for it to have any clinical impact. So we're not doing
anything specific with those drug-drug interactions. The one exception that was pointed out is injectable cabotegravir, or rilpivirine, at least initiating that injectable regimen, which has sort of a smaller window of error with that dosing, but that's really the only limitation.

**Dr. Fryhofer:** So one of you mentioned an interaction with the diabetes drug. Can you be a little more specific? Because a lot of our patients are on diabetes medication, unfortunately.

**Dr. Wilkin:** It's very—it's not a commonly used diabetic drug. So it's not the first-, second-, or third-line. The name of the drug is escaping me.

**Dr. Fryhofer:** OK. We'll follow up on that and let—

**Dr. Sherwat:** Oh, I was just going to say, it's repaglinide and what was seen was episodes of hypoglycemia in the drug-drug interaction study. I think that the actual mechanism of the hypoglycemia is a bit unclear. But that was the product, and it's actually outlined in the prescribing information for TPOXX as one of the warnings.

**Dr. Fryhofer:** Dr. Sherawat, I knew you would know the answer. Thank you. All right. Dr. Sherwat, stay with me. On one of your slides, you talked about neurological findings in the animal toxicology studies. Can you expand on that just a little bit?

**Dr. Sherwat:** Sure. So again, this information is also in the product labeling for the drug, so I'll go over that in a little bit of detail. So in a repeat dose toxicology study in dogs, convulsions were observed in one animal within six hours of a single dose of 300 milligrams per kilogram. And that's approximately four times higher than the highest observed human exposure at the recommended human dose, based on what we call Cmax, which is the maximum repeat concentration that a drug achieves after dosing.

During this study, EEGs were also performed. And EEG findings in this particular animal were consistent with seizure activity during the observed convulsions. Tremors were also observed at a lower dose, the 100 milligram per kilogram dose. That's similar to the highest observed human exposure at the recommended human dose, also based on Cmax.

Although in that case, there were no convulsions or EEG findings observed at this dose. And it's important to note also, on the healthy human study that was done as part of the development program, no seizure events occurred. There was one asymptomatic subject who discontinued tecovirimat, due to an abnormal EEG. The clinical significance of that finding is unknown.

**Dr. Fryhofer:** So I'm going to end with one last question. And it's sort of out of the scope of this webinar, but I'm going to ask it anyway. When available, should physicians be vaccinated against monkeypox? Any takers?
Dr. Petersen: So currently, CDC is not recommending that vaccine be used widely in the vast majority of health care workers. There are specific health care workers for which vaccination is recommended, including laboratory workers who are doing the diagnostic testing for orthopoxviruses. But by and large, what we’ve seen in this outbreak is that nosocomial transmission appears to be very rare.

So we believe that the risk to most health care workers is very low, and we’re not currently recommending that vaccination be given to most health care workers at this time.

Dr. Fryhofer: Well, we have covered so much today. And I would love to continue this discussion. There are lots of questions we didn't have time to answer. But unfortunately, we're out of time.

I’d like to thank Dr. Sherwat, Dr. Wilkin, and Dr. Petersen for joining us today. Thank you for such an incredibly insightful session on this important topic. And as we've heard from our panel of experts, this conversation is far from over.

Thankfully, agencies like CDC and FDA are leading efforts to prevent spread of monkeypox, to respond with adequate treatment, and to make that treatment more accessible. During a virtual dialogue earlier this month, the director of WHO, the World Health Organization, Tedros Adhanom Ghebreyesus reminded us we must continue to work hard to ensure that inequities and access to vaccines, testing, and treatment during the height of the COVID pandemic are not repeated.

At the end of last month, nearly 28% of monkeypox cases in the U.S. were among Black individuals, and 33% among Hispanics. AMA's headquarters are in Chicago, and Chicago's public health commissioner, Dr. Allison Arwady, said Chicago health officials have prioritized monkeypox vaccine distribution to providers who primarily serve Latino populations, who comprise 31% of cases in the city of Chicago.

Getting vaccines to those who need them most remains an ongoing and critical part of our response system, and ultimately, fighting this disease.

Together, CDC, FDA, the AMA, and each of you here today can be a part of the collective effort to respond to monkeypox. WHO director, Ghebreyesus, also said, if COVID has taught us nothing else, it's taught us that health is the most precious commodity on Earth.

It's a commodity that must be cherished, prized, and fought for every day. As you've heard here today, TPOXX is available in our strategic national stockpile. ACIP, the CDC Advisory Committee on Immunization Practices, recommends vaccination for those at high risk following a confirmed monkeypox exposure.

Again, we could talk about this for several more hours, but we are out of time. Many thanks again to our wonderful guests and to all of you for taking time out of your busy day to join us. And please join
us again for future segments in AMA’s “What Physicians Need to Know” webinar series. Thank you, and have a great day.

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