FDA, CDC experts: What physicians need to know—TPOXX and monkeypox, Part 2

Moving Medicine

FDA, CDC experts: What physicians need to know about tecovirimat (TPOXX) for treatment of monkeypox, Part 2

Nov 4, 2022

- Listen on Simplecast
- Listen on Apple Podcasts
- Listen on Spotify

Featured topic and speakers

Experts from the FDA and CDC continue their discussion on tecovirimat, or TPOXX, for the treatment of monkeypox in infected individuals. In part two of this mini-series, experts answer physicians' questions about treatment for monkeypox.

Speakers

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

Hosts

- Todd Unger, Chief Experience Officer, American Medical Association

Listen to the episode on the go on Apple Podcasts, Spotify or anywhere podcasts are available.

Transcript

[audio snippet] Dr. Fryhofer: The top question we've received from physicians around the country is about EUA. How can physicians obtain TPOXX? How has this process been simplified? And are there any plans to simplify this process further?

Unger: That's Dr. Sandra Fryhofer. In part two of this series on Moving Medicine, our experts continue the discussion on what physicians need to know about TPOXX. Dr. Fryhofer is again joined by experts: Dr. Adam Sherwat, Dr. Brett Peterson, and Dr. Timothy Wilkin.

Here's Dr. Fryhofer.

Dr. Fryhofer: 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? 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 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 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 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, 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: Dr. Petersen, 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. 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 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 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 Dr. Petersen. 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. Sherwat: 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, 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. 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 orthopox viruses. 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. 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 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 August, 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.

Many thanks again to our wonderful guests and to all of you for taking time out of your busy day to join us. Thank you and have a great day.

Unger: You can subscribe to Moving Medicine and other great AMA podcasts anywhere you listen to yours or visit ama - assn.org / podcasts. Thanks for listening.
