FDA, CDC experts: What physicians need to know—TPOXX and monkeypox, Part 1
FDA, CDC experts: What physicians need to know about tecovirimat (TPOXX) for treatment of monkeypox, Part 1

Oct 28, 2022

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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.

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

Host

- Todd Unger, Chief Experience Officer, American Medical Association

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Transcript
Dr. Fryhofer: 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. 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.

Unger: That’s Dr. Sandra Fryhofer, chair of the AMA Board of Trustees, and liaison to ACIP, the CDC’s Advisory Committee on Immunization Practices.

Dr. Fryhofer: Tecovirimat, a.k.a. TPOXX, 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.

Unger: In this episode of Moving Medicine, Dr. Fryhofer moderates a panel covering what physicians need to know about Tecovirimat, or TPOXX, for treatment of Monkeypox.

She is joined by Dr. Adam Sherwat, deputy director for the Office of Infectious Disease at the FDA Center for Drug Evaluation and Research.

Dr. Brett Peterson, captain of the U.S. Health Service and deputy chief of the CDC Poxvirus and Rabies branch.

And Dr. Timothy Wilkin, professor of medicine and assistant dean for Clinical Research Compliance for Human Research Protections at Weill Cornell Medicine.

Now, here’s part 1 of our 2-part series.

Dr. Fryhofer: 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.

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.

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.
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.

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.


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CDC has played a critical role in our ongoing response to monkeypox, and we'll also hear more about recent developments. 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. So tecovirimat is an antiviral drug that inhibits viral spread to uninfected cells by directly and specifically targeting the orthopox virus 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.

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 received placebo.

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.

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 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.

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.

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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.

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 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.

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.

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. Fryhoferr: 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: 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. So we have rapidly developed this protocol at the request of NIH and NIAID.

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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 on September 8, and we will ramp up the protocol in the weeks to come, as more and more sites come on board.

So the study is really two studies in one. First, we have a randomized double-blinded placebo-controlled portion, where we are 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.

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.

So 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.

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. 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.

So 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—so 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.

The second question we ask is, are they appropriate for randomization? So 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 orthopoxvirus 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.

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.

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.

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.

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There's the UK study that's ongoing, that's completely remote. There's a smaller-in-scale Canadian trial and a more complicated platform trial conducted by the WHO 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. So my goal is to really highlight some of the resources in terms of guidance and other data that is available from CDC regarding treatment with tecovirimat.

So 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.

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.

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 sequelae should also be considered for treatment.

Now, tecovirimat, 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 orthopox virus infections, including monkeypox. 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.

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.

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 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. We continue to collect information on the demographics of patients receiving tecovirimat.

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.

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 are—do have activity against orthopox virus 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.

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.

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 orthopox viruses, 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. 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.

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.
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. 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. And thank you again.

**Dr. Fryhofer:** Well, many thanks to all three of our guests for providing such valuable insight. We are so fortunate to have these three experts with us today.

**Unger:** Join us for part 2 of this discussion, where Dr. Fryhofer asks our panel of experts your questions about TPOXX. 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.