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Tecovirimat Use under Expanded Access to Treat Mpox in the United States, 2022–2023

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Abstract

BACKGROUND—During the ongoing outbreak of clade II *monkeypox virus* (MPXV), many U.S. patients were prescribed tecovirimat, an antiviral drug that was made available under an expanded access Investigational New Drug (EA-IND) program. We evaluated EA-IND data to summarize characteristics of treated patients, outcomes, and serious adverse events (SAEs).

METHODS—We evaluated data from patients prescribed tecovirimat from May 29, 2022, through July 10, 2023. Baseline patient characteristics, clinical courses, and outcomes were evaluated via intake forms, outcome forms, and patient diaries. Data were summarized in aggregate by human immunodeficiency virus (HIV) status and by comorbidities of special interest. Reported SAEs were also compiled.

RESULTS—Tecovirimat was prescribed for over 7100 patients in the United States, most often for lesions in sensitive anatomical areas, such as certain anogenital lesions (83.5%; 5135 out of 6148 patients), and pain (52.5%; 3227 out of 6148 patients). The demographic and clinical characteristics mirrored those of patients worldwide. Among the 7181 patients with returned intake forms, 1626 also had returned outcome forms (22.6%). Many patients with severe immunocompromise (e.g., HIV with CD4 counts <200 cells/μl) received multiple courses of tecovirimat (43.1%; 22 out of 51 patients), including intravenously, and often experienced poor outcomes (35.3%; 18 out of 51 patients). Overall, 223 SAEs and 40 deaths were reported. Most SAEs were among patients who were severely immunocompromised, one of whom experienced hallucinations after tecovirimat was administered at twice the standard dose.

CONCLUSIONS—Tecovirimat was used extensively. The returned EA-IND data suggest that life-threatening or protracted infections occurred in persons who were severely

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Disclosures

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immunocompromised. SAEs were not commonly reported. The EA-IND data are not definitive; controlled clinical trial data are essential to elucidating if and how tecovirimat should be used.

Introduction

Tecovirimat (Tpoxx) is a virostatic antiviral drug developed and stockpiled by the U.S. Government for preparedness against potential smallpox reintroduction. At the time of its development, naturally occurring smallpox had long been eradicated, but the biodefense threat of intentional exposures loomed.[1] Efficacy for smallpox was inferred via two lethal animal models involving other orthopoxviruses,[2] in which higher survival rates were observed among tecovirimat-treated animals than those administered a placebo, leading to approval by the Food and Drug Administration (FDA) for treatment of smallpox under the animal rule.[3] The only human trial data evaluated prior to FDA approval involved safety in 359 healthy adults.[4] Since 2012, the U.S. Centers for Disease Control and Prevention (CDC) has maintained an expanded access Investigational New Drug (EA-IND) protocol to allow unapproved use of tecovirimat to treat rare non–smallpox orthopoxvirus infections for which it might be useful (e.g., certain inadvertent needlestick injuries among laboratorians working with *Vaccinia virus*; serious adverse events [SAEs] resulting from receipt of a live, replication-competent smallpox vaccine among some individuals). By 2022, three such patients had been treated under the EA-IND protocol.[5–7]

Beginning in May 2022, a global outbreak of clade II *Monkeypox virus* (MPXV) infections occurred, which was primarily associated with mucosal exposures and mainly affected men who have sex with men. More than 30,000 patients with mpox were identified in the United States, amounting to approximately one third of known cases globally.[8–15] At the start of the outbreak, substantial pain and debilitating symptoms, such as proctitis, were reported by some infected patients. At that time, the scientific and public health community did not know the potential incidence of mpox and morbidity untreated MPXV would pose. It had already been established that a single viral amino acid mutation causes viral resistance to tecovirimat;[16] however, in the event that morbidity and mortality could be averted, tecovirimat that had been stockpiled in the U.S. Strategic National Stockpile for smallpox preparedness was leveraged for mpox. Although the quality of data received was anticipated to be imperfect, the EA-IND data were expected to be beneficial, at least in informing clinical and policy considerations for treatment given the evolving outbreak situation at the time. We evaluated EA-IND data to describe how tecovirimat was used in the United States, summarize patient outcomes, and characterize reported adverse events (AEs).

Methods

THE EXPANDED ACCESS INVESTIGATIONAL NEW DRUG PROTOCOL AND REPORT FORMS

The existing EA-IND protocol, which allowed use of stockpiled tecovirimat for treatment of non–variola orthopoxvirus infections, facilitated immediate tecovirimat access at the start of the MPXV outbreak. As the outbreak continued, concern over tecovirimat resistance increased.[17] The CDC issued public health alerts (e.g., https://emergency.cdc.gov/han/2022/han00481.asp) concordant with more mpox-specific indications for tecovirimat use; the EA-

IND protocol was amended to specify treatment under only certain conditions. For example, pain alone (regardless of location of pain) was advised to be managed with analgesics, rather than with tecovirimat.[18,19]

With increasing mpox cases, supplies of oral tecovirimat were prepositioned across the country from August 2022 through February 2023 for use in accordance with the EA-IND protocol.[20] Intravenous (IV) tecovirimat was in limited supply and available only for certain hospitalized patients who met the EA-IND criteria, such as those with intestinal issues which could impair absorption of oral tecovirimat. The CDC's clinical consultation service, which provided advice about management of patients, was most commonly for patients with life-threatening and protracted infections from uncontrolled viral replication and who were severely immunocompromised.[21] Often these patients needed additional treatment options such as vaccinia immune globulin IV, another stockpiled drug by the U.S. Government, which was available through the consultation service.

Regardless of whether clinicians prescribed tecovirimat using the prepositioned oral tecovirimat supplies or by obtaining tecovirimat after consultation with the CDC, they were bound by the FDA's IND regulations to fulfill certain responsibilities as a condition for tecovirimat access. For example, clinicians were required to obtain signed informed consent from patients before treatment and return certain report forms about patients' clinical characteristics and a signed Statement of Investigator (Form FDA 1572);[22] via the latter, clinicians agreed to comply with the regulatory requirements, including adhering to the tecovirimat EA-IND protocol and returning the required report forms.

The report forms included a patient intake form, clinical outcome form, and patient diary (Table S1 in the Supplementary Appendix). Both the intake and clinical outcome forms were mandatory per the requirements of the EA-IND protocol that was in place at the start of the outbreak. The outcome form collected data about clinical outcomes during days 1 to 7 of treatment, during days 8 to 14 of treatment, and posttreatment (i.e., after completion of treatment with tecovirimat). The forms were comprised of fields with prewritten choices to select from and/or provide free-text responses. There was no separate set of instructions accompanying the forms (Table S1 and accompanying sample EA-IND report forms). At the peak of the outbreak, in response to complaints about the number and length of the forms, the report forms were shortened and only the intake form remained mandatory; as such, outcome forms were most often received earlier in the outbreak (Fig. S3). The intake form was considered to contain the minimum information necessary to understand the baseline clinical characteristics of patients prescribed tecovirimat and to interpret outcome data if optional outcome forms were returned. While reminders about returning the mandatory intake form and optional outcome form were sent to prescribing clinicians, data collection depended on the providers' and facilities' compliance. When the CDC was contacted about EA-IND uses and/or for clinical consultation, CDC personnel used these encounters to obtain the clinical information on patients and requested return of the required forms.

DEFINITIONS AND ANALYSIS

We analyzed data returned for patients treated under the CDC's EA-IND protocol between May 29, 2022, and July 10, 2023, for whom there was return of at least the intake form. All

the returned patient diaries were analyzed. Patient-perceived improvement was evaluated via data reported in these diaries. Information on AEs, including SAEs reported in the returned outcome forms, the FDA's MedWatch forms, or direct communication with the CDC during consultations, were also compiled. Data from intake forms were assessed in aggregate by HIV status and by comorbidities of special interest. We defined comorbidities of special interest as those conditions that, based on extrapolation of data from treatment of smallpox and other orthopoxvirus infections, were thought to confer an increased risk for severe manifestations of mpox. These included severe immunocompromise, atopic dermatitis, and other conditions that affect skin integrity (e.g., concurrent herpes simplex virus eruption).[21] Severe immunocompromise was determined via an objective strategy developed with the help of clinicians who routinely care for patients with severe immunocompromise; it was ascribed to a patient with at least one of the following: HIV with CD4 counts <200 cells/μl within 1 year before tecovirimat initiation; HIV with undisclosed CD4 count, but accompanying forms that indicated advanced HIV or AIDS; a stem cell transplant within 1 year before mpox diagnosis; a history of solid organ transplant at any time before mpox diagnosis; a history of hematologic cancer, such as leukemia, lymphoma, or multiple myeloma, for which chemotherapy was given within 6 months before mpox diagnosis; and treatment at the time of mpox diagnosis with an immunosuppressive drug (e.g., rituximab, tacrolimus) or a drug that causes tumor necrosis factor inhibition (e.g., etanercept, infliximab).

We limited outcome analyses to the data of those patients for whom posttreatment outcome data were reported. We report overall outcomes and outcomes parsed by the number of lesions at intake (Tables S3 and S4). Orthopoxvirus polymerase chain reaction (PCR) test results were inconsistently reported, but when negative test results were reported, patients were excluded from the baseline and outcome analyses. Because forms were modified three times during the time period for this analysis in order to reduce the reporting burden and improve form return rates, not all data fields were available for all patients. Therefore, we provide both the numerator and denominator for most percentages. SAEs and other notable AEs reported to the CDC were compiled, were not routinely assessed for causality, and are enumerated herein as available for patients regardless of PCR test results.

The EA-IND protocol was reviewed and approved by the CDC's Institutional Review Board and authorized by the FDA.[23] The analyses were conducted using the software R, version 4.1.3. The descriptive data are reported as medians and interquartile ranges (IQRs), as appropriate. As no statistical hypotheses were tested, no P values are reported.

Results

A total of 7284 intake forms, 1996 outcome forms, and 176 patient diaries were received (Fig. 1). The EA-IND forms were deduplicated and analyses were performed on data from 7181 unique patients with intake forms, of whom 1626 (22.6%) had a returned outcome form. Of these 1626 forms, 583 did not include posttreatment completion outcome data, leaving 1043 unique patients with a matching intake form and outcome form containing posttreatment information, as shown in Figure 1 and Figure 2.

DATA FROM INTAKE FORMS ABOUT THE BASELINE CHARACTERISTICS OF PATIENTS

The intake forms analyzed were from 49 states, the District of Columbia, and Puerto Rico, most commonly California (1790; 24.9%), New York (1065; 14.8%), Florida (651; 9.1%), Texas (510; 7.1%), and Washington state (350; 4.9%). The proportion of returned intake forms changed as the national case counts increased and decreased (Fig. 3). The demographic characteristics of patients who were prescribed tecovirimat indicate that tecovirimat was most often prescribed for persons assigned male sex at birth with a median age of 35 years (IQR 30 to 43 years); however, some female patients (n=220), pregnant persons (n=12), and children less than 12 years of age (n=17) were also prescribed tecovirimat, including a 5-day-old infant (Table 1). Over half of the returned intake forms (3710 out of 7181; 51.7%) were for persons with HIV, typically well-controlled HIV infection, and 609 (8.5%) were for patients with comorbidities of special interest; of the latter, 310 out of 7181 (4.3%) were severely immunocompromised (including 277 patients with HIV with CD4 counts <200 cells/μl) and 299 out of 7181 (4.2%) had conditions affecting skin integrity, i.e., atopic dermatitis or eczema (n=240), psoriasis (n=40), cystic acne (n=4), and other conditions (n=15). Among persons with HIV with CD4 counts <200 cells/μl, 11 had an additional condition that met the definition for severe immunocompromise: 10 with a malignancy and 1 with a history of solid organ transplantation. Some patients (15.1%; 128 out of 846) had received JYNNEOS vaccine before reported mpox exposure.[26,27] The median number of lesions at intake was 7 (IQR 3 to 14 lesions) when at least one JYNNEOS vaccine dose was administered 15 or more days before mpox exposure (Tables S5 and S6).

Clinical characteristics were evaluated for all patients prescribed tecovirimat, including those with HIV with CD4 counts ≥200 cells/μl, severely immunocompromised persons, those with atopic dermatitis or other skin conditions affecting skin integrity, and pediatric patients (Table 2). The median time from illness onset to tecovirimat prescription was 7 days (IQR 4 to 10 days). Clinicians reported that for 2324 out of 3013 patients (77.1%) a rash was present at illness onset; it is unknown whether clinicians understood this question to be about clinical status at the time tecovirimat was being prescribed, or whether they would have considered patients' concerns consistent with proctitis (i.e., symptoms in the absence of visible lesions), or perceived the presence of a few scattered lesions as a rash. However, in response to a question on the intake form about reasons for prescribing tecovirimat, the location of lesions in sensitive anatomical areas was the most often reported reason (83.5%), followed by pain (52.5%). For 2282 out of 6148 patients (37.1%), clinicians reported that a reason for prescribing tecovirimat was the risk of severe disease developing in the patient. For 40.6% (2495 out of 6148) of patients, only one reason was reported for prescribing tecovirimat. Notably, pain alone was the reported reason for 3.7% of patients (228 of 6148). Most patients had a low number of lesions (median 15 lesions, IQR 6 to 25 lesions) and less than 25% of their body was affected by lesions at intake (Table 2). The skin (76.3%) and the anogenital region (73.1%) were the body sites most often affected at baseline; however, oral mucosal lesions and ocular lesions were also reported (17.3% and 4.2%, respectively).

DATA FROM INTAKE AND OUTCOME FORMS ABOUT TREATMENT, CLINICAL COURSE, AND OUTCOMES

Clinical outcome forms included in the analysis were evaluated for the same population groups for which demographic and clinical characteristics were evaluated (Table 3). The outcome forms included data during days 1 to 7 of treatment, days 8 to 14 of treatment, and posttreatment (Table S7). The demographic characteristics of patients with only an intake form and those with both intake and outcome forms were similar (Table S8). Most patients were prescribed oral tecovirimat (6445 out of 7181 patients; 89.8%), and were treated as outpatients (5200 out of 7181 patients; 72.4%); most patients also received a standard 14-day course (883 out of 1043; 84.7%), meaning that they did not receive prolonged or multiple courses of tecovirimat, presumably because their illnesses resolved (Table 3). Few patients (63 out of 1043; 6.0%) were reported to have received shorter courses (of those who received courses of less than 14 days, the median was 7 days, the range was 1 to 13 days, and the IQR was 5 to 10 days), one third of which were reported as being due to symptom resolution. Among the 1043 patients with both baseline and posttreatment outcome data, orthopoxvirus test results were not reported for 329 (31.5%) patients, including 26 out of 329 (7.9%) who were treated for less than 14 days.

Among the 11 patients less than 18 years of age, 8 received 14 days or less of oral tecovirimat and were primarily treated in the outpatient setting. Two pediatric patients, 8 and 17 years of age, were treated with 14 days of oral tecovirimat in the hospital, and one 21-week-old received 2 days of oral tecovirimat before the administration of vaccinia immune globulin IV. One 17-year-old patient was treated with IV tecovirimat, as reported on their returned intake form, but clinical outcomes were not available.

Among the 1043 patients for whom there was posttreatment outcome information, 3.9% (27 out of 693 patients) reported hospitalization after initiating treatment as an outpatient (Table 3). Of the 1043 patients, 39 (3.7%) patients received oral and/or IV tecovirimat for a duration longer than 14 days (range 15 to 111 days), typically because of continuing or progressing mpox signs in the context of severe immunocompromising conditions. Among the 310 patients who were severely immunocompromised, 135 (43.5%) were hospitalized at baseline (Table 2). Among these 135 patients, 12 (8.9%) had greater than 100 lesions at intake, 87 (64.4%) had between 10 and 100 lesions, 34 (25.2%) had between 0 and 9 lesions, and 2 (1.5%) had an unknown number of lesions. The reasons for hospitalization at intake among patients with between 0 and 9 lesions included pain, severe proctitis, lesion severity (e.g., a fungating lesion), a secondary bacterial infection (e.g., a methicillin-resistant *Staphylococcus aureus* infection, sepsis), ocular lesions, and admission for an issue unrelated to mpox (e.g., cord blood transplant, heart failure prior to the onset of mpox illness). The median duration of hospitalization for severely immunocompromised patients was 17 days (IQR 7 to 38 days), for persons with HIV and no reported severe immunocompromise the median was 7 days (IQR 6 to 10 days), and for all patients the median was 7 days (IQR 4 to 14 days).

Information regarding the length of time between the initiation of tecovirimat treatment and subjective improvement was available for 856 patients, and the time between the initiation of tecovirimat treatment and full clinical recovery was available for 337 patients with baseline

and posttreatment outcome information. Overall, the median length of time to subjective improvement was 3 days (range 1 to 83 days, IQR 2 to 4 days) and the median length of time to recovery was 10 days (range 1 to 45 days, IQR 7 to 14 days) (Table 3). The median time between the initiation of tecovirimat treatment and recovery was 12 days (IQR 10.5 to 14 days) among 19 patients with atopic dermatitis and other conditions affecting skin integrity. Patient-reported decrease in pain and number lesions were available through the returned patient diaries: pain improved starting on day 2 of treatment for 35 out of 90 patients (38.9%) and had completely resolved for 48 out of 91 patients (52.7%) by day 9 of treatment (Fig. S1); lesions began to resolve on day 3 for some patients and were completely resolved for most patients by day 14 of treatment (Fig. S2).

Most patients (801 out of 1043; 76.8%) recovered without sequelae (Table 3). The sequelae reported among patients who recovered with sequelae included scarring (447 out of 892; 50.1%) and strictures (3 out of 64; 4.7%). Death was reported for 20 patients (1.9%) for whom both intake and outcome forms were returned (Table 3); 18 were known to be severely immunocompromised and went on to develop many lesions. Of the two patients who died and did not meet our definition for severe immunocompromise, one had HIV with no reported CD4 count and antiretroviral therapy noncompliance and the other died by suicide after his lesions were reported to have been completely healed after 12 days of treatment. For patients with lesions in a sensitive area alone, hospitalization after starting tecovirimat was reported in 1.8% (3 out of 164); 78.0% (149 out of 191) recovered without sequelae. Patients with atopic dermatitis and other conditions affecting skin integrity were generally treated as outpatients, received a standard 14-day course of oral tecovirimat, and recovered.

SERIOUS ADVERSE EVENTS AND OTHER NOTABLE ADVERSE EVENTS

A total of 223 SAEs were reported among 132 patients (Table S9). The reported SAEs included 40 deaths; 25 were reported via an outcome form (of which 20 had a matching intake form, as described above and included in Table 3) and 15 were reported via FDA MedWatch reports and/or by direct communication with the CDC. Of the 40 patients who died, 37 (92.5%) met our definition for severe immunocompromise. Of these, 35 had HIV with CD4 counts <200 cells/μl (range 0 to 137 cells/μl, median 16.5 cells/μl, IQR 9.8 to 32.8 cells/μl); 1 patient had a history of myelodysplastic syndrome with refractory anemia, a renal transplant, a cord blood stem cell transplant, and hemodialysis; and 1 patient had a history of solid organ transplantation. The remaining 3 of the 40 patients who died had no reported severe immunocompromise. One patient died the day after a virtual clinical assessment, during which tecovirimat was prescribed but an MPXV test result was eventually reported as negative. The etiology of the illness for which this patient sought treatment remains unknown and the other two patients were described above. The most commonly reported SAEs other than death were headache (n=12), nausea (n=10), vomiting (n=10), elevated levels of liver enzymes (n=8), urticaria (n=8), fatigue (n=7), acute kidney injury (n=7), abdominal pain (n=6), dizziness (n=5), and tremor (n=5). One severely immunocompromised patient received double the standard oral tecovirimat dose, a protocol deviation, which was administered twice a day for 12 days because of worsening illness. The patient experienced hallucinations, which resolved after the high tecovirimat dose was

discontinued; the patient received subsequent treatment at the standard tecovirimat dose without experiencing hallucinations.

Discussion

From May 2022 through July 2023, tecovirimat was used extensively in the United States. At least one intake form was returned for over 7100 unique patients, but we believe that more patients were treated under the EA-IND protocol for which no forms were returned to the CDC. Treated patients had demographic and clinical characteristics similar to those of the broader population of people with mpox through the present time. That is, infections occurred predominantly among men, most commonly 30 to 43 years of age, often with HIV. These patients had fewer than 15 lesions, which involved less than 25% of body surface area, and were managed as outpatients. The fatality rate in the cohort in this report was higher than has been reported nationally.[8] We speculate that this is because, when a death occurred, it was required to report the event as an SAE, irrespective of causality to tecovirimat. Moreover, for patients that CDC was consulted, active follow-ups occurred that helped to ensure return of EA-IND forms. Patients with advanced HIV and CD4 counts <200 cells/μl and those with other severely immunocompromising conditions comprised the majority of those consultations and accounted for nearly all U.S. deaths. Black patients were 27.7% (1990 out of 7181) of all patients treated with tecovirimat, but, likely due to inequities in access to healthcare, comprised a disproportionate percentage of patients with concomitant advanced HIV, which is also consistent with observations from CDC's consultation service. These patients received intravenous and multiple courses of tecovirimat, and experienced protracted illness often eventually leading to death.

Despite inclusion of many of the patients with severe disease for whom CDC was consulted, for most of the treated patients in this cohort, outcomes were favorable. This included many patients with lesions affecting sensitive anatomical locations and persons with HIV. Patients were started on tecovirimat a median of 7 days after illness onset, and most recovered by completion of a 14-day treatment course, a time interval consistent with the recovery time of 2 to 4 weeks expected of the natural course of mpox in the absence of tecovirimat treatment.[28]

Safety and effectiveness cannot be determined from these data. Although relatively few SAEs were reported, because of the passive nature of reporting, we cannot definitively conclude that tecovirimat treatment was always safe. Similar to data from case reports and other published observational studies,[29–39] our data, in the absence of comparison data from untreated patients, cannot be used to infer clinical effectiveness, or lack thereof, of tecovirimat treatment.

It is important to note that tecovirimat-resistant MPXV was first identified in 2022 among tecovirimat-naive persons, suggesting that drug resistance acquired via tecovirimat use was transmitted to other persons.[40] For example, in one recently identified cluster, patients with tecovirimat-resistant disease appeared to be epidemiologically linked across five states over a 5-month time period (October 2023 through February 2024).[41] We posit that the number of patients with such resistance is underestimated because specimens are not deposited for

CDC sequencing from all jurisdictions. This alters the risk–benefit calculus in favor of a more judicious use of tecovirimat until several clinical trials are completed worldwide.[42]

Despite the limitations of our analysis, the EA-IND data suggest life-threatening or protracted infections occurred in patients with severe immunocompromise, but typically not in patients with HIV who had CD4 counts greater than 200 cells/μl, which is also consistent with observations from CDC's consultation service. In June 2024, the CDC amended the EA-IND protocol to clarify the eligibility criteria based on the conclusions of this analysis.[22] These changes preserve tecovirimat access for patients with, or at-risk for, protracted or life-threatening manifestations of mpox, while encouraging enrollment in the National Institute of Allergy and Infectious Disease-sponsored Study of Tecovirimat for Human Mpox Virus (STOMP) randomized trial (ClinicalTrials.gov number: NCT05534984). Children, pregnant persons, and those with conditions affecting skin integrity did not experience severe outcomes in our dataset; however, these populations can continue to access tecovirimat via both the EA-IND protocol and the STOMP trial, since it has previously been observed that they experience more serious orthopoxvirus infections, particularly in endemic countries.[43] Multiple clinical trials are underway to evaluate the effectiveness of tecovirimat; preliminary data from one of the studies (PALM007) was recently released; it indicates that while tecovirimat is safe, it did not reduce the duration of mpox lesions among patients with clade 1 mpox in the Democratic Republic of Congo. Until more definitive data are available, tecovirimat treatment for mpox under the EA-IND protocol will remain available for the aforementioned populations. While the EA-IND data provide descriptive analysis of patients treated with tecovirimat, data from PALM007 and other ongoing global trials (e.g., PLATINUM, STOMP, UNITY) are essential to determine the role of tecovirimat in treating MPXV infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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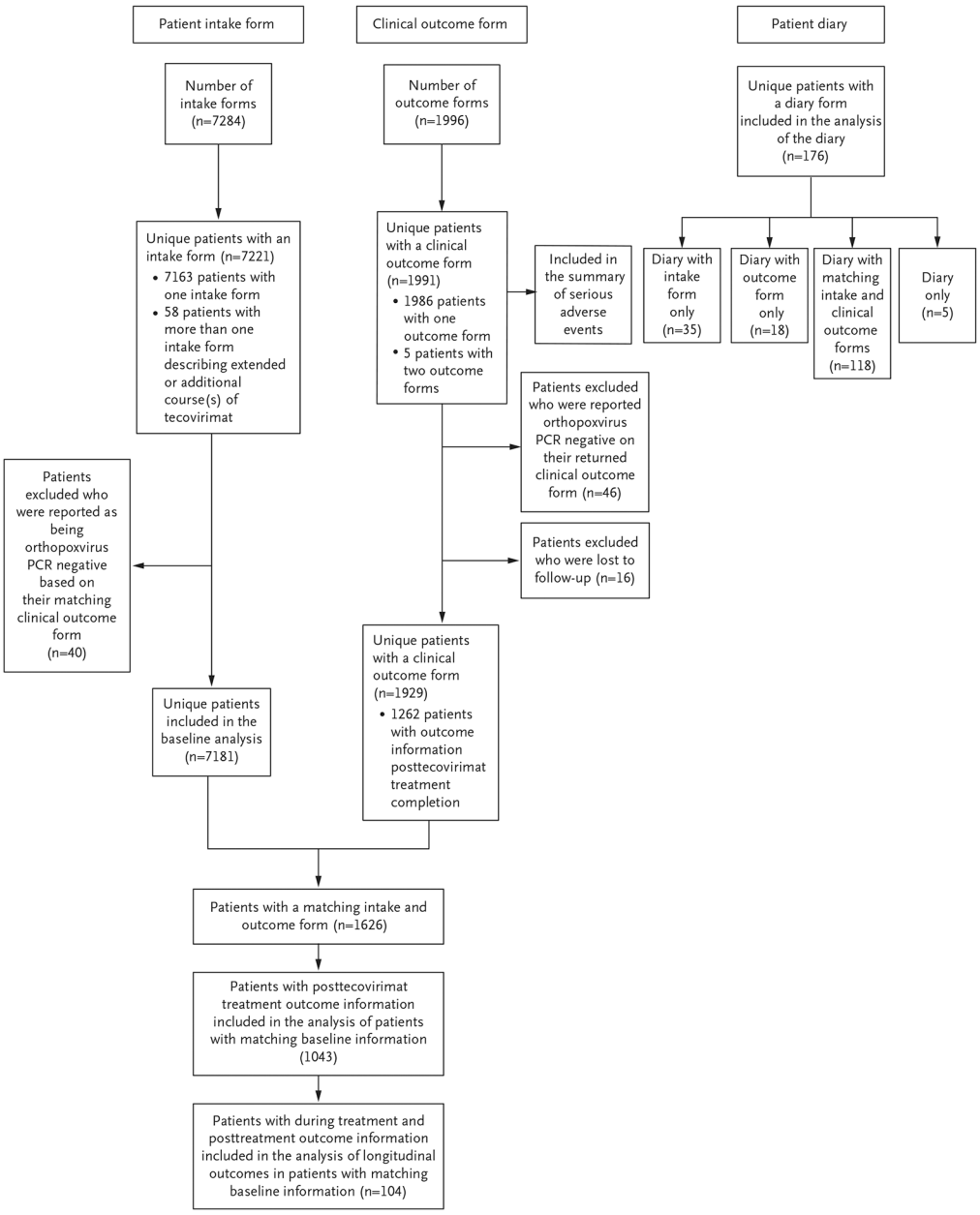

Figure 1.

Assessment of Returned EA-IND Report Forms for Patients Prescribed Tecovirimat for Treatment of Mpox from May 29, 2022, through July 10, 2023.

PCR denotes polymerase chain reaction; and, EA-IND, expanded access Investigational New Drug.

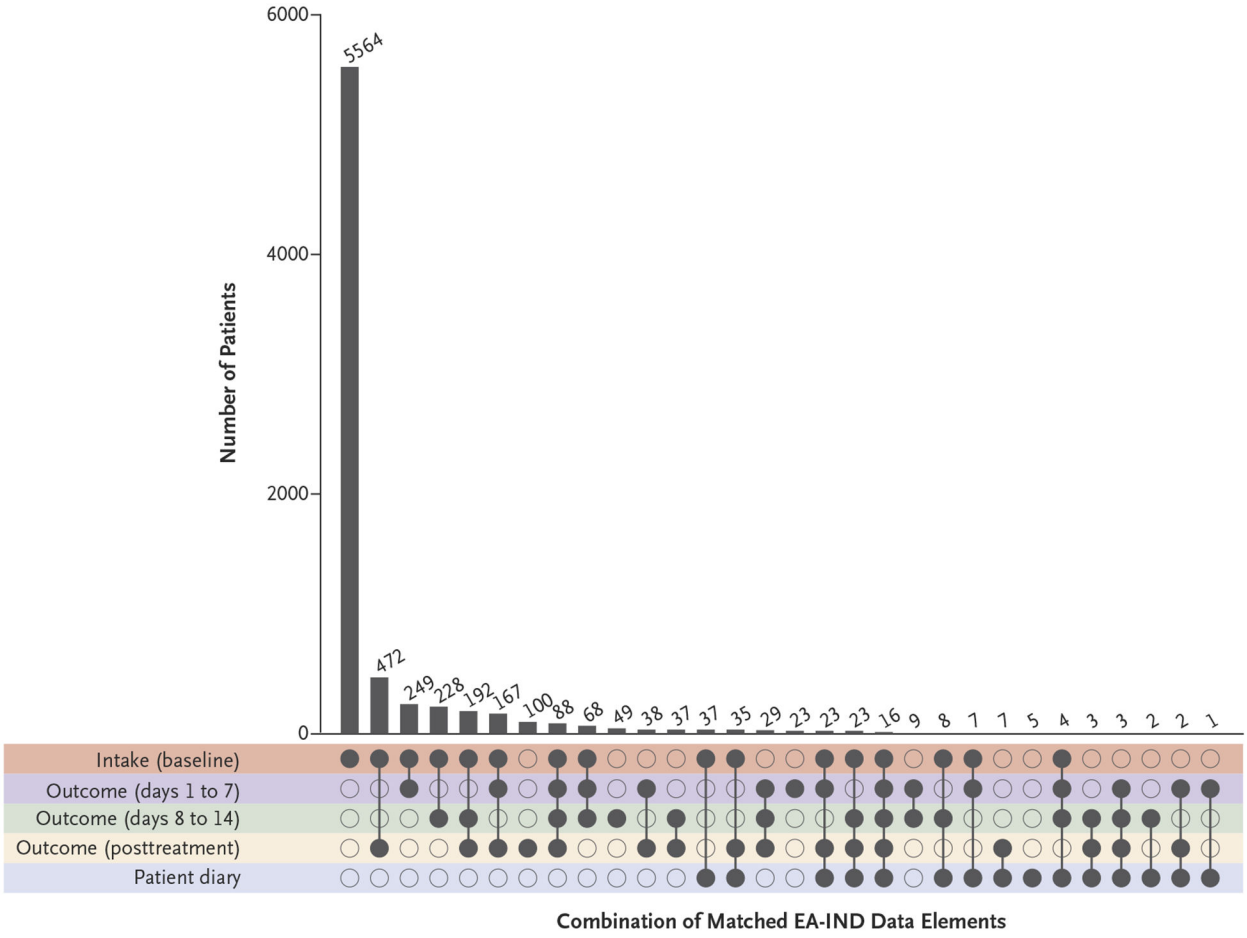

Figure 2.

Summary of Returned EA-IND Data Elements Matched and Analyzed for Patients Prescribed Tecovirimat for Treatment of Mpox from May 29, 2022, through July 10, 2023. The figure shows the assessment time points that correspond to each expanded access Investigational New Drug form: assessment with the intake form at baseline, when tecovirimat was prescribed; an outcome form for days 1 to 7 of tecovirimat treatment; an outcome form with data for days 8 to 14 of tecovirimat treatment; the outcome form with data after the completion of tecovirimat treatment (posttreatment); and/or a patient diary, filled in daily from the start to the completion of tecovirimat treatment. A single outcome form may have included one or more assessments during treatment and/or posttreatment. The figure was created using the UpSetR software package.[24,25] EA-IND denotes expanded access Investigational New Drug.

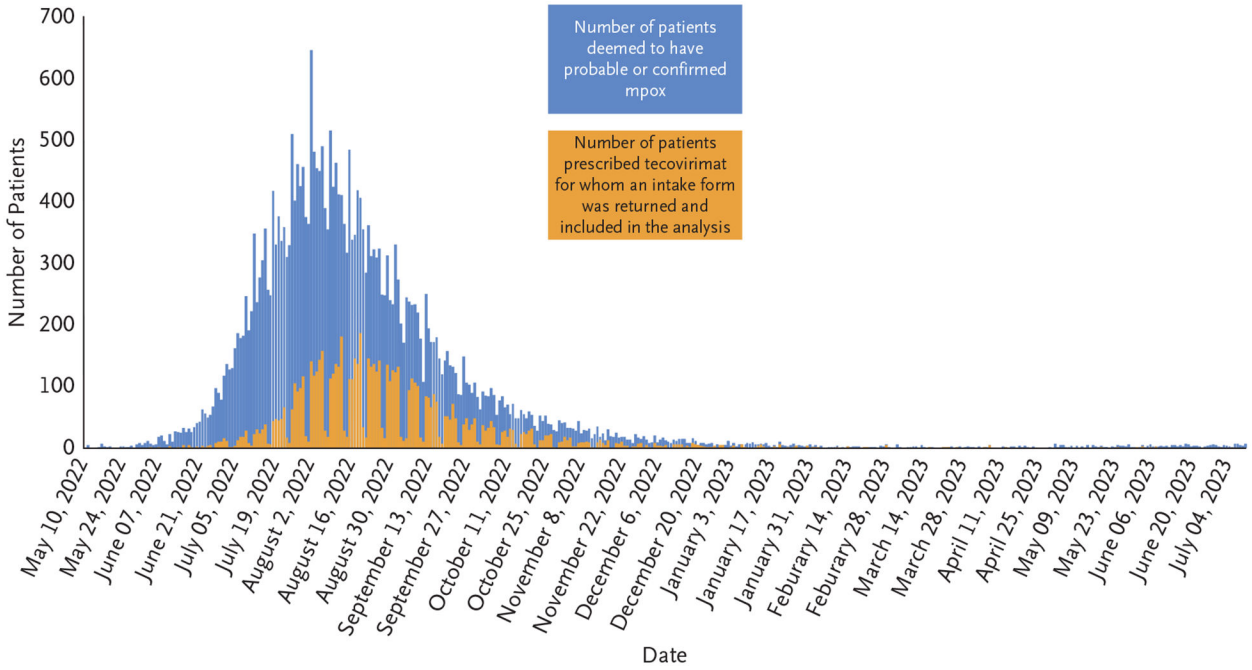

Figure 3.

The Number of Patients Deemed to Have Probable or Confirmed Mpox in the United States versus the Number of Patients Prescribed Tecovirimat for Whom Intake Form Was Returned and Included in Analysis from May 29, 2022, through July 10, 2023.

Mpox outbreak case surveillance data are available at https://www.cdc.gov/poxvirus/mpox/response/2022 (accessed February 1, 2024). It is not known how many of the patients prescribed tecovirimat would also have been deemed to have a probable or confirmed mpox infection.

Table 1.

Demographic Characteristics of Patients Prescribed Tecovirimat (n=7181) from May 29, 2022, through July 10, 2023.

Demographic Characteristic	All Patients (n=7181)	Patients with HIV Excluding Those with CD4 Counts <200 cells/μl and Other Severe Immunocompromise (n=3413)*	Severely Immunocompromised Patients (n=310)†	Patients with Atopic Dermatitis or Other Conditions Affecting Skin Integrity (No Documented Severe Immunocompromise) (n=299)‡	Pediatric Patients <18 Years of Age (n=29)
Sex assigned at birth — no. of patients (% of total)§					
Male	6867 (95.6)	3344 (98.0)	300 (96.8)	278 (93.0)	20 (69.0)
Female	220 (3.1)	19 (0.6)	6 (1.9)	18 (6.0)	9 (31.0)
Unknown	94 (1.3)	50 (1.5)	4 (1.3)	3 (1.0)	0 (0)
Gender identity — no. of patients (% of total)					
Male	5769 (80.3)	2890 (84.7)	273 (88.1)	247 (82.6)	15 (51.7)
Female	193 (2.7)	18 (0.5)	7 (2.3)	16 (5.4)	8 (27.6)
Transgender female	112 (1.6)	62 (1.8)	10 (3.2)	5 (1.7)	0 (0)
Transgender male	33 (0.5)	7 (0.2)	0 (0)	1 (0.3)	0 (0)
Other	44 (0.6)	21 (0.6)	0 (0)	2 (0.7)	0 (0)
Unknown	1030 (14.3)	415 (12.2)	20 (6.5)	28 (9.4)	6 (20.7)
Median age — yr (IQR)	35.0 (30.0 to 43.0)	37.0 (31.0 to 44.0)	38.0 (32.0 to 45.0)	34.0 (28.0 to 41.0)	7.0 (1.0 to 16.0)
Age group — no. of patients (% of total)					
<6 months	4 (0.1)	0 (0)	0 (0)	1 (0.3)	4 (13.8)
6 to <12 months	2 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (6.9)
1 to <6 years	7 (0.1)	0 (0.0)	0 (0.0)	2 (0.7)	7 (24.1)
6 to <12 years	4 (0.1)	0 (0.0)	0 (0)	1 (0.3)	4 (13.8)
12 to <18 years¶	12 (0.2)	3 (0.1)	0 (0.0)	1 (0.3)	12 (41.4)
18 to <65 years	6976 (97.1)	3323 (97.4)	306 (98.7)	284 (95.0)	0 (0.0)
≥65 years	62 (0.9)	20 (0.6)	2 (0.6)	3 (1.0)	0 (0.0)
Unknown	114 (1.6)	67 (2.0)	2 (0.6)	6 (2.0)	0 (0.0)
Ethnicity — no. of patients (% of total)					
Hispanic or Latino	2081 (29.0)	1069 (31.3)	51 (16.5)	61 (20.4)	3 (10.3)
Not Hispanic or Latino	3985 (55.5)	1844 (54.0)	218 (70.3)	192 (64.2)	21 (72.4)
Unknown	1115 (15.5)	500 (14.6)	41 (13.2)	46 (15.4)	5 (17.2)
Race — no. of patients (% of total)					

Demographic Characteristic	All Patients (n=7181)	Patients with HIV Excluding Those with CD4 Counts <200 cells/μl and Other Severe Immunocompromise (n=3413)*	Severely Immunocompromised Patients (n=310)†	Patients with Atopic Dermatitis or Other Conditions Affecting Skin Integrity (No Documented Severe Immunocompromise) (n=299)‡	Pediatric Patients <18 Years of Age (n=29)
White	3190 (44.4)	1307 (38.3)	99 (31.9)	129 (43.1)	9 (31.0)
African American/Black	1990 (27.7)	1241 (36.4)	169 (54.5)	93 (31.1)	15 (51.7)
Asian	191 (2.7)	55 (1.6)	4 (1.3)	17 (5.7)	0 (0.0)
Other//	894 (12.4)	435 (12.7)	20 (6.5)	41 (13.7)	2 (6.9)
Unknown	916 (12.8)	375 (11.0)	18 (5.8)	19 (6.4)	3 (10.3)

*This includes patients with HIV who had CD4 counts ≥200 cells/μl and patients with missing CD4 counts. It excludes the 310 patients with HIV with CD4 counts <200 cells/μl and/or another severely immunocompromising condition. AIDS denotes acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HSV, herpes simplex virus; and, IQR, interquartile range.

†Severe immunocompromise was defined as at least one of the following: HIV with CD4 counts <200 cells/μl within 1 year before tecovirimat treatment initiation; HIV with undisclosed CD4 count, but accompanying forms indicated advanced HIV or AIDS; report of stem cell transplant within 1 year before diagnosis of mpox in the patient; a history of solid organ transplant at any time before mpox diagnosis; a history of hematologic cancer, such as leukemia, lymphoma, and multiple myeloma, for which chemotherapy was given within 6 months before mpox diagnosis; and treatment at the time of mpox diagnosis with an immunosuppressive drug (e.g., rituximab, mycophenolate, tacrolimus) or a drug that causes tumor necrosis factor inhibition (e.g., etanercept, infliximab, adalimumab). Patients with severely immunocompromising conditions included 277 patients with HIV with a CD4 count <200 cells/μl (including 10 with a malignancy and 1 with a history of solid organ transplantation); 23 patients had a history of solid organ transplant; 3 were on concomitant immunosuppressive medication at the time of tecovirimat treatment; 2 had a history of cancer and solid organ transplant; 1 had cancer and a recent cord blood transplant; 3 had cancer; and 1 had a history of bone marrow/organ transplant and was on a concomitant immunosuppressive medication at the time of tecovirimat treatment. Six severely immunocompromised patients had atopic dermatitis or another condition affecting skin integrity.

‡Skin conditions included atopic dermatitis or eczema (n=238), psoriasis (n=40), HSV (n=11), cystic acne (n=3), atopic dermatitis and HSV (n=2), cystic acne and HSV (n=1), and other conditions (n=4).

§The version of the patient intake form used before July 2022 contained only one question on sex, which was considered sex assigned at birth, and which was completed for 700 patients. The versions of the patient intake form dated from July 2022 onwards, distinguished between sex assigned at birth and gender identity.

¶Among patients 12 to <18 years of age, as for most adults, exposures were reported as sexual exposures (or presumed to be sexual exposures because lesions were located in the anogenital region). Among children less than 12 years of age, exposures were generally attributed to close interactions (e.g., cuddling) with an ill parent or guardian.

//Includes patients reported as American Indian or Alaska Native (n=52), or Native Hawaiian or other Pacific Islander (n=25), multiracial (n=112), or other race (n=705).

Table 2.

Clinical Characteristics of Patients Prescribed Tecovirimat (n=7181) from May 29, 2022, through July 10, 2023.

Clinical Characteristic	All Patients (n=7181)	Patients with HIV Excluding Those with CD4 Counts <200 cells/μl and Other Severe Immunocompromise (n=3413)	Severely Immunocompromised Patients (n=310)	Patients with Atopic Dermatitis or Other Conditions Affecting Skin Integrity (No Documented Severe Immunocompromise) (n=299)	Pediatric Patients <18 Years of Age (n=29)
Time from mpox illness onset to tecovirimat being prescribed — no. of patients	6244	2958	244	270	22
Median (IQR) [*] — days	7.0 (4.0–10.0)	7.0 (4.0–10.0)	9.0 (5.0–15.3)	7.0 (5.0–10.0)	6.0 (4.0–9.0)
Signs and symptoms documented at start of treatment (not mutually exclusive) — no. of patients (% of total) [†]					
Rash	2324/3013 (77.1)	1209/1489 (81.2)	153/176 (86.9)	117/135 (86.7)	14/14 (100.0)
Pain	1593/3013 (52.9)	849/1489 (57)	92/176 (52.3)	62/135 (45.9)	4/14 (28.6)
Lymphadenopathy	845/3013 (28.0)	422/1489 (28.3)	46/176 (26.1)	58/135 (43.0)	4/14 (28.6)
Fever	1131/3013 (37.5)	595/1489 (40)	59/176 (33.5)	59/135 (43.7)	4/14 (28.6)
Reason for tecovirimat treatment (not mutually exclusive) — no. of patients (% of total) [‡]					
Lesions in anatomical areas that might result in serious sequelae	5135/6148 (83.5)	2333/3005 (77.6)	197/290 (67.9)	237/279 (84.9)	21/28 (75.0)
Pain	3227/6148 (52.5)	1586/3005 (52.8)	137/290 (47.2)	150/279 (53.8)	5/28 (17.9)
At risk of severe disease due to one or more conditions	2282/6148 (37.1)	1808/3005 (60.2)	260/290 (89.7)	112/279 (40.1)	18/28 (64.3)
Other	138/6148 (2.2)	54/3005 (1.8)	7/290 (2.4)	12/279 (4.3)	3/28 (10.7)
Categorical number of lesions — no. of patients (% of total)					
0 to 9 lesions	2907 (40.5)	1301 (38.1)	84 (27.1)	117 (39.1)	8 (27.6)
10 to 100 lesions	3741 (52.1)	1890 (55.4)	203 (65.5)	169 (56.5)	18 (62.1)
>100 lesions	203 (2.8)	110 (3.2)	18 (5.8)	9 (3.0)	2 (6.9)
Unknown	330 (4.6)	112 (3.3)	5 (1.6)	4 (1.3)	1 (3.4)
Percentage of body affected by lesions — no. of patients (% of total)					
0 to <10%	2530 (35.2)	1188 (34.8)	93 (30.0)	121 (40.5)	12 (41.4)
10 to <25%	987 (13.7)	501 (14.7)	63 (20.3)	36 (12.0)	1 (3.4)
25 to <50%	418 (5.8)	219 (6.4)	22 (7.1)	16 (5.4)	2 (6.9)
50 to <75%	273 (3.8)	151 (4.4)	21 (6.8)	10 (3.3)	0 (0.0)
75 to 100%	276 (3.8)	159 (4.7)	13 (4.2)	12 (4.0)	1 (3.4)

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Clinical Characteristic	All Patients (n=7181)	Patients with HIV Excluding Those with CD4 Counts <200 cells/μl and Other Severe Immunocompromise (n=3413)	Severely Immunocompromised Patients (n=310)	Patients with Atopic Dermatitis or Other Conditions Affecting Skin Integrity (No Documented Severe Immunocompromise) (n=299)	Pediatric Patients <18 Years of Age (n=29)
Unknown	2697 (37.6)	1195 (35.0)	98 (31.6)	104 (34.8)	12 (41.4)
Location of lesions (not mutually exclusive), — no. of patients (% of total)[§]					
Skin	4481/5876 (76.3)	2309/2863 (80.6)	246/291 (84.5)	214/263 (81.4)	24/26 (92.3)
Anogenital	4296/5876 (73.1)	2058/2863 (71.9)	195/291 (67.0)	192/263 (73.0)	9/26 (34.6)
Oral mucosa	1016/5876 (17.3)	494/2863 (17.3)	82/291 (28.2)	49/263 (18.6)	5/26 (19.2)
Ocular	246/5876 (4.2)	109/2863 (3.8)	15/291 (5.2)	15/263 (5.7)	3/26 (11.5)
Tecovirimat route of administration — no. of patients (% of total)					
Oral[¶]	6445 (89.8)	3090 (90.5)	277 (89.4)	269 (90)	24 (82.8)
Intravenous[‖]	58 (0.8)	29 (0.8)	18 (5.8)	3 (1.0)	1 (3.4)
Unknown	678 (9.4)	294 (8.6)	15 (4.8)	27 (9.0)	4 (13.8)
Hospitalization status at baseline — no. of patients (% of total)					
Outpatient	5200 (72.4)	2511 (73.6)	152 (49.0)	243 (81.3)	15 (51.7)
Inpatient	890 (12.4)	473 (13.9)	135 (43.5)	27 (9.0)	12 (41.4)
Intensive care unit	47/890 (5.3)	19/473 (4.0)	10/135 (7.4)	1/27 (3.7)	1/12 (8.3)
Unknown	1091 (15.2)	429 (12.6)	23 (7.4)	29 (9.7)	2 (6.9)

[*] The time from illness onset to when tecovirimat was prescribed was calculated based on the availability of illness onset data from before the date of tecovirimat initiation. The tecovirimat initiation date was defined as either the date on which tecovirimat was first administered, the date tecovirimat was prescribed, or the date of the assessment/the completion of an intake form, in order of priority. HIV denotes human immunodeficiency virus; IQR, interquartile range; and, IV, intravenous.

[†] Signs/symptoms were queried in a version of the patient intake form dated August 2022 and included categories for rash, pain, lymphadenopathy, and fever. Additional categories, including proctitis, abscess, cellulitis, dysuria, headache, malaise, and shortness of breath, were added to the intake form dated October 2022. Only patients with no missing data and at least one sign/symptom were included. The form does not distinguish between the absence of a symptom and unknown symptom status.

[‡] The reasons for tecovirimat treatment that included risk of a severe outcome due to immunosuppression, lesions in sensitive anatomical areas, pain, or other reasons were queried starting with the intake form version dated July 2022. With the intake form version dated October 2022, the risk category was redefined as a risk of a severe outcome due to uncontrolled HIV or other conditions, pregnancy, being a pediatric patient, or having a condition affecting skin integrity. In addition, a new category was added for severe infections (e.g., a large number of lesions such that they are confluent, sepsis, encephalitis). A severe infection was not systematically captured in the free-text field for the “Other” category in forms returned prior to the intake form dated October 2022, which did not include a specific option for severe infection.

[§] The distribution of lesions was queried as categorical options in the patient intake form starting with the intake form dated July 2022 and included overall categories of skin, anogenital, ocular, and oral mucosa lesions.

[¶] Of patients administered tecovirimat orally, two patients in the severely immunocompromised group and one patient in the HIV group excluding those severely immunocompromised received tecovirimat via a nasogastric tube.

‖Based on intake form information, one patient was treated initially with oral tecovirimat as an outpatient followed by IV tecovirimat as an inpatient; one patient initially received IV tecovirimat followed by oral tecovirimat. Among pediatric patients, one 17-year-old was treated with IV tecovirimat as an inpatient.

Table 3.

Clinical Outcomes of Patients Treated with Tecovirimat and with Returned Intake and Outcome Forms (n=1043) from May 29, 2022, through July 10, 2023.

Treatment Details	All Patients with Information at Baseline and Posttreatment Outcome (n=1043)	Patients with HIV Excluding Those with CD4 Counts <200 cells/μl and Other Severe Immunocompromise (n=437)	Severely Immunocompromised Patients (n=51)	Patients with Atopic Dermatitis or Other Conditions Affecting Skin Integrity (No Documented Severe Immunocompromise) (n=47)	Pediatric Patients <18 Years of Age (n=11)
Tecovirimat route of administration — no. of patients (% of total)					
Oral*	1006/1038 (96.5)	429/436 (98.2)	30/51 (58.8)	47/47 (100.0)	11/11 (100.0)
Intravenous	32/1038 (3.1)	7/436 (1.6)	21/51 (41.2)	0/47 (0.0)	0/11 (0.0)
Duration of tecovirimat treatment — no. of patients (% of total)					
<14 days	63 (6.0)	31 (7.1)	5 (9.8)	2 (4.3)	2 (18.2)
Shorter therapy owing to symptom resolution	20/63 (31.7)	9/31 (29.0)	1/5 (20.0)	1/2 (50.0)	1/2 (50.0)
14 days	883 (84.7)	374 (85.6)	23 (45.1)	41 (87.2)	6 (54.5)
>14 days†	39 (3.7)	6 (1.4)	22 (43.1)	2 (4.3)	0 (0.0)
Unknown	58 (5.6)	26 (5.9)	1 (2.0)	2 (4.3)	3 (27.3)
Duration of tecovirimat treatment — no. of patients	985	411	50	45	8
Range (median) (IQR)	1.0 to 110.0 days (14.0 days) (IQR 14.0 to 14.0 days)	1.0 to 38.0 days (14.0 days) (IQR 14.0 to 14.0 days)	1.0 to 110.0 days (14.0 days) (IQR 14.0 to 28.8 days)	7.0 to 26.0 days (14.0 days) (IQR 14.0 to 14.0 days)	2.0 to 14.0 days (14.0 days) (IQR 14.0 to 14.0 days)
Hospitalization after tecovirimat initiation among patients treated as outpatients at baseline — no. of patients (% of total)					
No	649/693 (93.7)	277/293 (94.5)	14/29 (48.3)	35/37 (94.6)	7/7 (100.0)
Yes	27/693 (3.9)	7/293 (2.4)	14/29 (48.3)	1/37 (2.7)	0/7 (0.0)
Intensive care unit	3/27 (11.1)	0/7 (0.0)	2/14 (14.3)	0/1 (0.0)	0/0 (0.0)
Unknown	17/693 (2.5)	9/293 (3.1)	1/29 (3.4)	1/37 (2.7)	0/7 (0.0)
Days from tecovirimat initiation to subjective improvement‡					
No. of patients	856	362	27	41	9
Range (median) (IQR)	1.0 to 83.0 days (3.0 days) (IQR 2.0 to 14.0 days)	1.0 to 33.0 days (3.0 days) (IQR 2.0 to 4.0 days)	1.0 to 83.0 days (4.0 days) (IQR 3.0 to 7.0 days)	1.0 to 8.0 days (3.0 days) (IQR 2.0 to 4.0 days)	2.0 to 5.0 days (3.0 days) (IQR 3.0 to 3.0 days)
Recovery status — no. of patients (% of total)					

Treatment Details	All Patients with Information at Baseline and Posttreatment Outcome (n=1043)	Patients with HIV Excluding Those with CD4 Counts <200 cells/μl and Other Severe Immunocompromise (n=437)	Severely Immunocompromised Patients (n=51)	Patients with Atopic Dermatitis or Other Conditions Affecting Skin Integrity (No Documented Severe Immunocompromise) (n=47)	Pediatric Patients <18 Years of Age (n=11)
Recovered without sequelae	801 (76.8)	360 (82.4)	15 (29.4)	36 (76.6)	10 (90.9)
Recovered With sequelae	119 (11.4)	41 (9.4)	5 (9.8)	8 (17.0)	1 (9.1)
Not recovered	99 (9.5)	34 (7.8)	13 (25.5)	3 (6.4)	0 (0.0)
Death	20 (1.9)	1 (0.2)	18 (35.3)	0 (0.0)	0 (0.0)
Unknown	4 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Days from tecovirimat initiation to recovery					
No. of patients	337	149	6	19	5
Range (median) (IQR)	1.0 to 45.0 days (10.0 days) (IQR 7.0 to 14.0 days)	1.0 to 28.0 days (10.0 days) (IQR 7.0 to 14.0 days)	10.0 to 45.0 days (13.0 days) (IQR 10.0 to 19.8 days)	4.0 to 21.0 days (12.0 days) (IQR 10.5 to 14.0 days)	8.0 to 30.0 days (17.0 days) (IQR 10.0 to 17.0 days)
New lesions developed after tecovirimat initiation — no. of patients (% of total)					
Yes	104 (10.0)	42 (9.6)	10 (19.6)	7 (14.9)	1 (9.1)
No	811 (77.8)	357 (81.7)	28 (54.9)	35 (74.5)	7 (63.6)
Unknown	128 (12.3)	38 (8.7)	13 (25.5)	5 (10.6)	3 (27.3)
Unresolved lesions still present after completion of tecovirimat treatment — no. of patients (% of total)					
Yes	183 (17.5)	68 (15.6)	20 (39.2)	9 (19.1)	2 (18.2)
No	660 (63.3)	278 (63.6)	13 (25.5)	31 (66.0)	9 (81.8)
Unknown	200 (19.2)	91 (20.8)	18 (35.3)	7 (14.9)	0 (0.0)
Number of lesions present after treatment completion — no. of patients (% of total)					
0 lesions	492 (47.2)	208 (47.6)	8 (15.7)	22 (46.8)	2 (18.2)
1 to 9 lesions	254 (24.4)	95 (21.7)	25 (49.0)	15 (31.9)	8 (72.7)
10 to 100 lesions	49 (4.7)	24 (5.5)	9 (17.6)	2 (4.3)	0 (0.0)
>100 lesions	4 (0.4)	2 (0.5)	2 (3.9)	0 (0.0)	0 (0.0)
Unknown	244 (23.4)	108 (24.7)	7 (13.7)	8 (17.0)	1 (9.1)
Number of lesions posttreatment					
No. of patients	675	279	28	30	4
Median (IQR) lesions	0.0 (IQR 0.0 to 1.0)	0.0 (IQR 0.0 to 1.0)	6.0 (IQR 0 to 20.0)	0.0 (IQR 0.0 to 0.8)	0.5 (IQR 0.0 to 2.0)

[*] Of the 1006 patients administered tecovirimat orally, six patients received tecovirimat via a nasogastric tube. HIV denotes human immunodeficiency virus; and, IQR, interquartile range.

[†] Among patients with HIV, excluding those with CD4 counts <200 cells/μl, two patients with CD4 counts 200 to 400 cells/μl were treated with tecovirimat as inpatients for a duration of 16 to19 days for disseminated lesions, as described in one patient, and unspecified reasons for the other patient. In four patients with an unknown CD4 count, the duration of tecovirimat treatment was 16 to 38 days. One patient had active atopic dermatitis as well as HIV with an unknown CD4 count and was given 25 days of tecovirimat treatment. For the patient who received 38 days of treatment, the most recent CD4 count was unknown, but the patient had known history of CD4 counts <200 cells/μl. Among patients with atopic dermatitis or other conditions affecting skin integrity, lesion size decreased by day 4 of treatment and no new lesions developed after tecovirimat was initiated. One patient was given 26 days of tecovirimat treatment because the patient took one capsule twice a day (instead of three capsules twice a day). Despite the lower dose, the patient did not develop any new lesions.

[‡] Multiple iterations of this question were asked across three versions of the clinical outcome form. The outcome form dated July 2022 defined this as “time to first observed (including patient-reported) improvement — signs/symptoms first started to improve on Tecovirimat treatment day #.” The outcome form dated August 2022 defined this as “lesions or pain first started to improve on TPOXX (tecovirimat) treatment day #.” The outcome form dated October 2022 defined this as “lesions first started to improve on tecovirimat treatment day #.”