Clinical Infectious Diseases

REVIEW ARTICLE

Antivirals With Activity Against Mpox: A Clinically Oriented Review

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Mpox virus is an emergent human pathogen. While it is less lethal than smallpox, it can still cause significant morbidity and mortality. In this review, we explore 3 antiviral agents with activity against mpox and other orthopoxviruses: cidofovir, brincidofovir, and tecovirimat. Cidofovir, and its prodrug brincidofovir, are inhibitors of DNA replication with a broad spectrum of activity against multiple families of double-stranded DNA viruses. Tecovirimat has more specific activity against orthopoxviruses and inhibits the formation of the extracellular enveloped virus necessary for cell-to-cell transmission. For each agent, we review basic pharmacology, data from animal models, and reported experience in human patients.

Keywords. mpox; tecovirimat; brincidofovir; cidofovir.

Human mpox, caused by the mpox virus, a member of the genus *Orthopoxvirus* within the Poxviridae family of double-stranded DNA (dsDNA) viruses (Figure 1) [1–4], was first described in a 9-month-old infant in the Democratic Republic of Congo in 1970 [5]. Since then, it has resulted in multiple outbreaks in Central and West Africa, and occasionally in Europe and North America [6], most notably 47 human cases in the US Midwest in 2003 [7]. This outbreak was attributed to prairie dogs that became infected though contact with rodents imported from Ghana [8]. Human infections in endemic areas have been described in association with close contact with infected animals through hunting and skinning, or household rodent infestation [9]. Human-to-human transmission has also been described in household contacts of index cases, particularly among those who are unvaccinated against smallpox [10]. Proposed routes of transmission include salivary or respiratory secretions; contact with skin lesions, body fluids, or contaminated fomites; and possibly fecal shedding [10–12]. It is estimated that smallpox vaccination provides 85% protection against mpox, explaining the increase in susceptible hosts since smallpox eradication and discontinuation of routine smallpox vaccination [13]. The clinical course and possible complications of human mpox are illustrated in Figure 2 [9, 14–16]. Genomic sequencing of mpox isolates from the United States, West Africa, and Central Africa demonstrated the existence of 2 clades: the Congo Basin (CB) clade and the West African (WA) clade, including the 2003 US samples [17]. The CB clade is associated with increased human-to-human transmission, more pronounced rash, viremia, severe illness, and a higher case fatality rate (10.6% vs 3.6%) compared with the WA clade [6, 17]. Diagnosis is made by combining the clinical and epidemiological picture with a viral assay, most commonly a viral DNA detection assay by real-time polymerase chain reaction [18]. The optimal specimen is a lesion exudate or crust material. Infections can be diagnosed retrospectively with serological testing [19]. For years, the management of mpox infections has relied on supportive care and management of complications; however, the recent development of new antivirals, such as tecovirimat and brincidofovir, has opened new therapeutic opportunities [20].

As of 17 June 2022, 2525 confirmed cases of mpox have been reported from 37 countries not known to be endemic for mpox. The highest number of cases have been described in the United Kingdom, Spain, and Germany [21]. Preliminary data suggest the ongoing outbreak is related to the WA clade. A particular clinical manifestation reported is the initial appearance of the rash in the genital or perianal area, suggesting close physical contact as the route of transmission [22]. In light of this unprecedented outbreak, this review aims to provide a clinically oriented discussion of 3 antiviral agents with known activity against mpox: cidofovir (CDV), brincidofovir (BCV), and tecovirimat.

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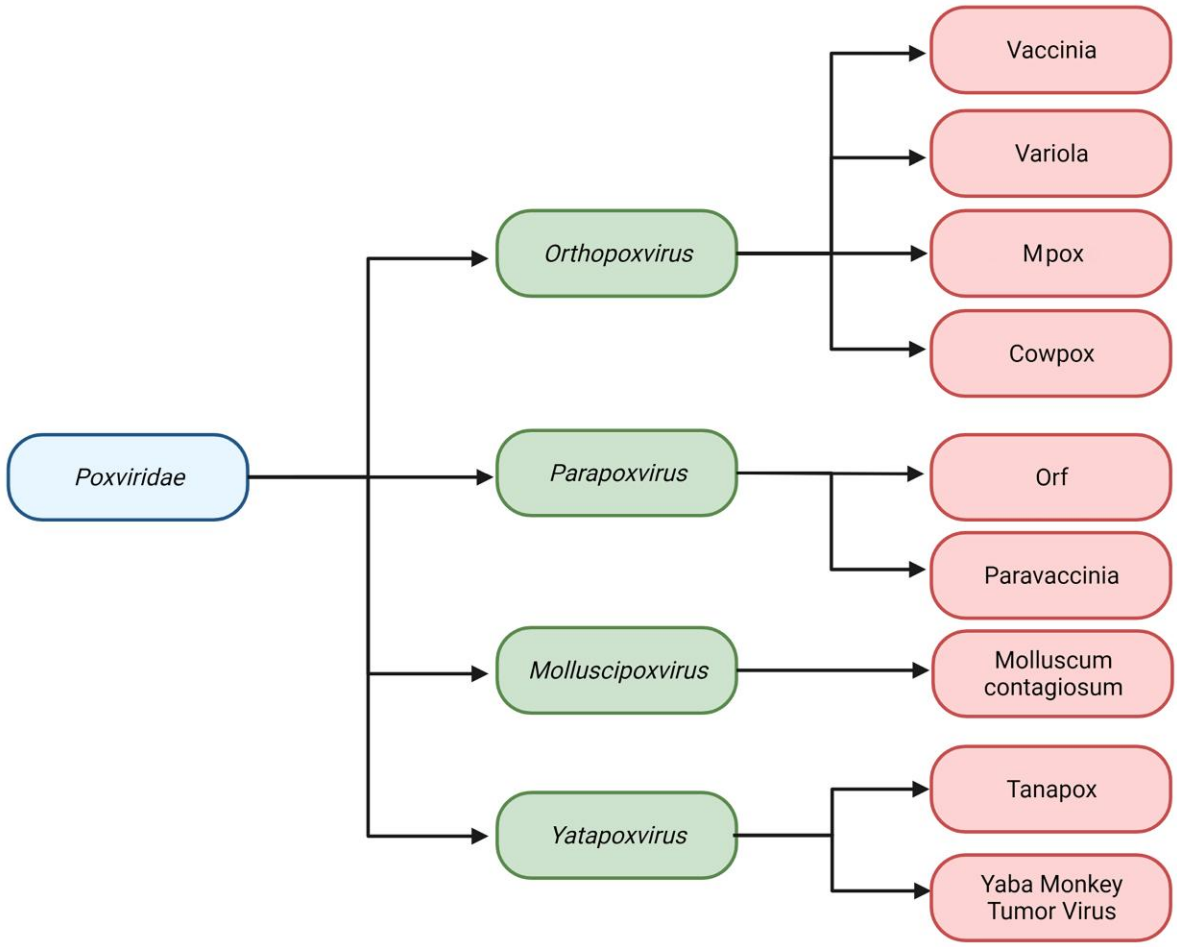

Figure 1. Poxviruses known to infect humans within the Poxviridae family; 4 genera include the species that are most commonly known to infect humans. While not characterized as human pathogens, additional orthopoxviruses, such as mousepox and rabbitpox, serve as the infectious agent in animal models that most closely replicate human infections with other orthopoxviruses such as smallpox (variola). Figure created with BioRender.com.

CIDOFOVIR

Basic Pharmacology

Although CDV (Vistide, Gilead) has broad activity against many DNA viruses including orthopoxviruses, it is only Food and Drug Administration (FDA) approved for the treatment of cytomegalovirus retinitis [23, 24]. Cidofovir is a prodrug, which must first enter host cells, then is phosphorylated by cellular enzymes into the active form, CDV diphosphate (CDV-pp) [24]. Once phosphorylated, CDV-pp has a prolonged intracellular half-life [25, 26]. During DNA replication, CDV-pp is incorporated into the growing DNA strand and slows synthesis of DNA (Figure 3). Cidofovir diphosphate may also inhibit DNA polymerase 3′–5′ exonuclease activity [24].

Resistance to CDV has been well described. Using serial passage with increasing CDV concentrations, resistant poxviruses can be selected in vitro [27]. These mutations appear to be similar in mpox and vaccinia virus and are due to point mutations in the conserved poxvirus DNA polymerase 3′–5′ exonuclease and the DNA polymerase catalytic domains [27, 28]. Resistance to CDV typically occurs in a stepwise fashion, with moderate resistance occurring with single mutations and higher levels of resistance occurring with multiple mutations [27]. Studies have demonstrated that CDV-resistant virus is significantly less virulent than wild-type strains, as challenges with wild-type virus were commonly lethal, while CDV-resistant virus caused a mild disease course. These data indicate that CDV resistance is slow to develop and is associated with a fitness cost for orthopoxviruses [27, 29].

Pharmacokinetic Data

Cidofovir is poorly absorbed orally and only available by intravenous infusion. Plasma CDV is rapidly renally filtered and secreted, whereas intracellular phosphorylated metabolites have a prolonged half-life, which allows for weekly or biweekly dosing (Table 1) [30, 31].

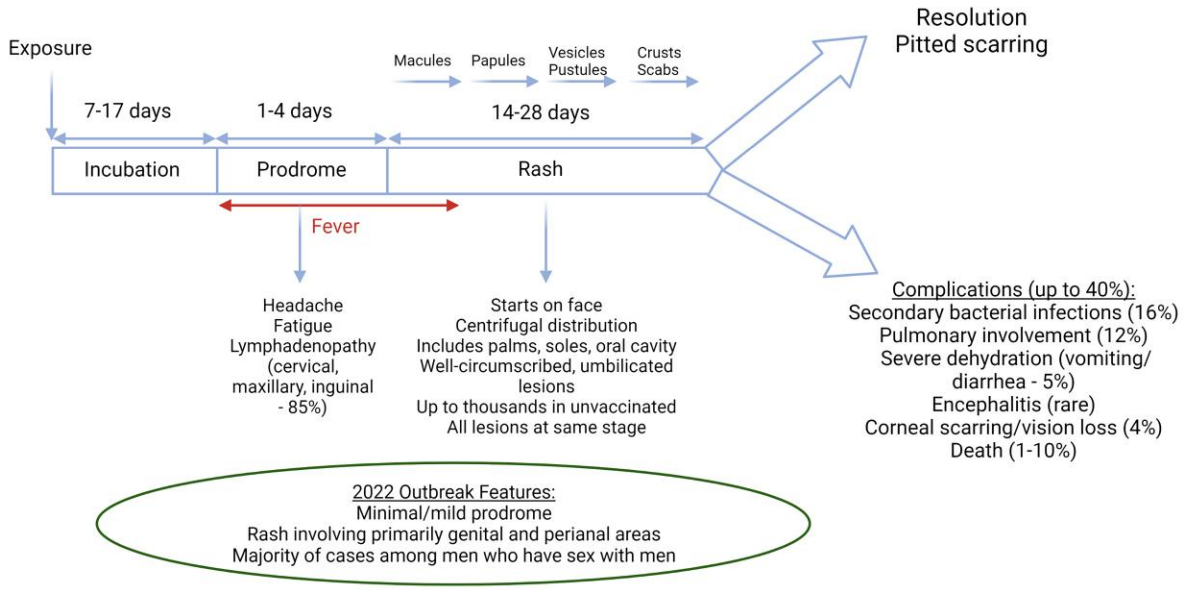

Figure 2. Natural history and clinical manifestations of human mpox infection after initial exposure. The virus replicates at the initial infection site, resulting in a local inflammatory response. The virus then spreads to the regional lymph nodes and via the bloodstream (primary viremia) to lymphoid organs, which explains the signs and symptoms seen during the prodrome phase, including lymphadenopathies. The virus spreads again to the bloodstream (secondary viremia), leading to the end-organ involvement with the skin rash and other complications. Fever starts during the prodrome phase and resolves within 3 days of rash onset. Lymphadenopathy is a specific manifestation of mpox, differentiating it from smallpox and varicella. The skin lesions evolve from macules, to papules, to vesicles and pustules, and finally to crusts and scabs, each phase taking about 2 days on average. The skin lesions then resolve, often with pitted scarring. Additional complications can occur from secondary bacterial infection or viral spread to other organs and could lead to death. The frequency of these complications is reported based on a description of cases from the 1981–1986 outbreak in the Democratic Republic of Congo and might not reflect the severity of other outbreaks caused by a different clade of the virus. Specific characteristics of t-he 2022 outbreak are highlighted. Figure created with BioRender.com.

Animal Data

Various animal models have evaluated the efficacy of CDV for the treatment of multiple orthopoxvirus infections, including cowpox, vaccinia, mpox, and ectromelia (mousepox) viruses [32]. The majority of these studies evaluated the use of CDV at the time of orthopoxvirus exposure or soon (24–48 hours) thereafter, and it is unclear how time to treatment in these models correlates with the timeline of human infection. Nevertheless, in mice infected with vaccinia and cowpox viruses, intraperitoneal CDV prevented mortality when given up to 96 hours after infection, a time point almost halfway through the disease course in this animal model. Cidofovir reduced viral titers in the lungs, liver, kidney, and spleen [33] in a T-cell–deficient murine model of progressive vaccinia. Topical CDV prevented disease progression when given within 2 days of infection and decreased lesion severity up to 5 days postinfection, while systemic CDV decreased lesion severity when administered up to 15 days postinfection [34]. Further, in mice infected with cowpox virus, CDV has been shown to not only decrease viral loads but also to decrease cytokine levels in plasma and tissue, including interleukin (IL)-2, IL-3, IL-6, and IL-10 [35]. It is unclear if CDV has immunomodulatory effects or if these results are due to reduced viral titers.

In cynomolgus monkeys vaccinated with vaccinia virus, systemic CDV reduced the size of lesions at the vaccine site and promoted more rapid healing of the initial lesion [36]. In nonhuman primates exposed to mpox, CDV has been shown to prevent lesion development when given up to 48 hours after infection, while monkeys treated with placebo had numerous lesions and viremia [37]. Taken together, systemic CDV appears to be most effective when given early after mpox exposure, but may be useful at decreasing disease manifestations even when given relatively late in the mpox disease course.

Toxicity

Cidofovir is associated with dose-limiting nephrotoxicity, which is characterized by proteinuria followed by glucosuria, decreased bicarbonate, uric acid, and phosphate. If CDV is continued, this leads to serum creatinine elevation, which can be severe [31–33]. Nephrotoxicity due to CDV is dose-related [32] and is due to accumulation of CDV in kidney proximal tubule cells through organic anion transporter 1 (OAT1) [34]. Nephrotoxicity can be partially ameliorated by probenecid, which is an inhibitor of OAT1 transport and reduces CDV accumulation in proximal tubular cells [34]. In phase I/II studies

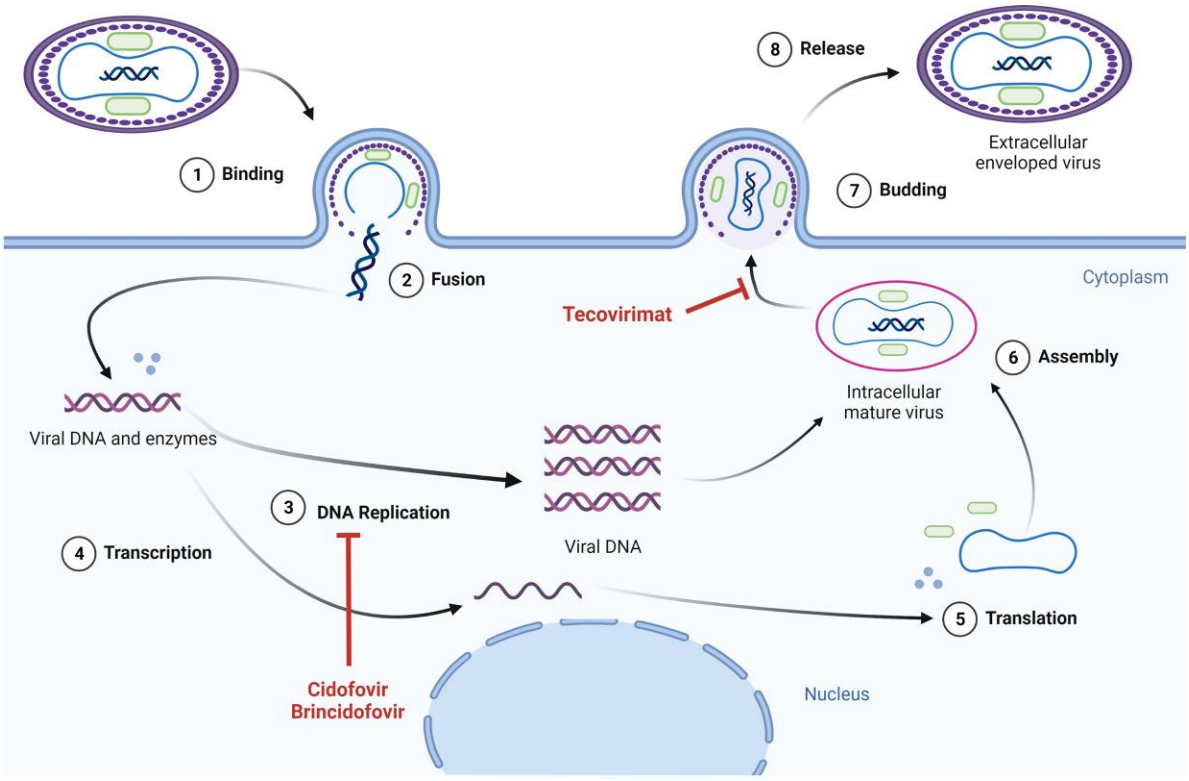

Figure 3. Mpox life cycle and mechanisms of action of antivirals. This simplified diagram describes the life cycle of mpox virus inside human cells. Notably, mpox virus undergoes its entire life cycle inside the cytoplasm since it carries all the enzymes it needs for DNA replication and protein synthesis, thus obviating the need for an intranuclear stage. Viral particles are assembled into intracellular mature viruses, then released as extracellular enveloped viruses during cell lysis. Cidofovir and its prodrug brincidofovir inhibit DNA synthesis by incorporation of cidofovir diphosphate into the growing DNA strand. Tecovirimat inhibits membrane protein p37, which is essential for the formation of the extracellular enveloped virus upon cell lysis. Figure adapted from "Generic Viral Life Cycle" by BioRender.com (2022); publication and licensing rights obtained from BioRender. Retrieved from https://app.biorender.com/biorender-templates.

in patients with AIDS, pre-hydration and probenecid reduced rates of nephrotoxicity, especially at CDV doses greater than 3 mg/kg (Table 1) [36]. Due to this nephrotoxicity, CDV is contraindicated in patients with serum creatinine greater than 1.5 mg/dL, creatinine clearance of 55 mL/minute or less, or 2+ or greater proteinuria, and it is recommended to avoid concomitant nephrotoxic medications [33].

Clinical Data in Humans

In humans, CDV has been used to treat cases of infection with poxviruses. The activity of the intravenous (IV) formulation was documented in patients with molluscum contagiosum receiving CDV for a concomitant AIDS-associated cytomegalovirus (CMV) retinitis, with subsequent resolution of molluscum lesions [38]. Additional case reports mention the use of IV CDV as part of a multipronged management approach for ocular cowpox [39, 40]. It has also been used in 1 patient with eczema vaccinatum in combination with tecovirimat [41]. Topical CDV has been successfully used to treat children and adults with molluscum contagiosum or orf. The strengths of the compounded creams varied from 1% to 3%, and the used vehicles differed, although vehicles containing propylene glycol were preferred, given that propylene glycol can enhance the bioavailability of CDV [42–44]. The lesions typically demonstrate acute inflammation after application of CDV, followed by dramatic resolution [45]. In some patients, the lesions recurred after discontinuation of topical CDV; however, they were successfully managed with either an additional course of topical CDV [43] or curettage [44]. In 1 patient with recalcitrant molluscum contagiosum, 1% CDV was injected into skin lesions with a 0.05-mL volume per lesion, with complete remission of the treated lesions without scarring, and with the antiviral activity being limited to the treated skin lesions [46].

BRINCIDOFOVIR

Basic Pharmacology

Brincidofovir is a lipid-conjugated CDV analogue that is marketed under the brand name Tembexa (Chimerix). Brincidofovir was FDA-approved in 2021 for the treatment of smallpox [47]. Like CDV, BCV has broad activity against dsDNA viruses but has lower half-maximal effective

Table 1. Pharmacokinetic and Pharmacodynamic Characteristics of Tecovirimat, Brincidofovir, and Cidofovir

Characteristics	Tecovirimat	Brincidofovir	Cidofovir
Mpox EC_{50}	0.07–0.16 μM	0.07–1.2 μM	27–78 μM
Mechanism of action	Inhibits production of extracellular virus, reducing transmission of virus to distant sites	DNA polymerase inhibitor	DNA polymerase inhibitor
Activity against other dsDNA viruses (not orthopoxviruses)	No	Yes	Yes
How supplied	200-mg capsules; 200-mg/20-mL vial for injection	100-mg film-coated tablets; 10-mg/mL lemon/lime-flavored suspension (refrigerate)	375-mg/5-mL vial for injection
FDA approval	Adults and children weighing at least 3 kg for treatment of human smallpox	Adult, pediatric, neonates for treatment of human smallpox	Treatment of CMV retinitis in patients with AIDS
Dosing (PO)	13 kg–24 kg: 200 mg Q12h; 25 kg–39 kg: 400 mg Q12h; 40 kg–119 kg: 600 mg Q12h; 120 kg or above: 600 mg Q8h	<10 kg: 6 mg/kg (suspension) once weekly ×2 doses (day 1 and 8); 10 kg to <48 kg: 4 mg/kg (suspension) once weekly ×2 doses (day 1 and 8); 48 kg and above: 200 mg (20 mL or 1 tablet) once weekly ×2 doses (day 1 and 8)	N/A
Dosing (IV)	3 kg–34 kg: 6 mg/kg Q12h over 6 hours; 35 kg–119 kg: 200 mg Q12h over 6 hours; 120 kg and above: 300 mg Q12h over 6 hours	N/A	5 mg/kg IV once a week ×2 weeks (may repeat 5 mg/kg every over week thereafter); no definitive dosing data in poxviruses
Renal dose adjustment	No dose adjustments for capsules; B-cyclodextrin is present in IV formulation and is contraindicated in CrCl <30 mL/minute per package insert	None	Reduce maintenance dose from 5 mg/kg to 3 mg/kg if SCr increases 0.3–0.4 mg/dL from baseline and discontinue if ≥0.5 mg/dL above baseline or development of ≥3+ proteinuria
Hepatic dose adjustment	None	Consider holding second dose if ALT >10× ULN, or if signs and symptoms of liver inflammation exist	None
Administration	Food increases absorption, should be taken within 30 minutes after moderate- to high-fat meal; capsule can be opened and put in milk or soft food for children 13 kg or above	Tablets: Take on an empty stomach or with low-fat meal (400 kcal, 25% kcal from fat). Do not crush or divide. Suspension: Shake before use. Take on an empty stomach. Can be given via NG or G tubes	Diluted in 100 mL NS prior to administration infused over 1 hour WITH probenecid 2 g given 3 hours prior to CDV, 1 g given at 2 and 8 hours after completion AND 1 L NS with each CDV infusion over 1–2 hours immediately prior to infusion. Consider an additional liter NS started at start of CDV or after over 1–3 hours if volume can be tolerated.
Duration of treatment	14 days in most animal studies, safety data for 21 days, ongoing trials for 28 days	2 doses given 1 week apart	Limited data, mpox model gave 5 mg/kg as a single dose
Use in pregnancy	No observed fetal/embryo toxicity in animal studies	May cause fetal harm; embryotoxic in rats and rabbits. Pregnancy testing should be done prior to initiation. Childbearing potential: contraception should be used during and for 2 months after the last dose. Partners of people of childbearing potential: condoms should be used during and at least 4 months after last dose.	Embryotoxic in rats and rabbits at lower than typical human exposures; not recommended in pregnancy
IV/PO availability	IV and PO	PO only	IV only
t1/2	18–26 hours	19.3 hours (CDV diphosphate 113 hours)	3.2–4.4 hours (intracellular t1/2 significantly longer)
Protein binding	77–82%	>99.9%	<6%
Elimination	<1% urinary excretion as unchanged drug; fecal elimination; weak CYP 3A4 inducer; weak CYP 2C8, 2C19 inhibitor; UGT1A1 and 1A4 substrate	51% excreted in urine as metabolites; 40% excreted in feces as metabolites; undergoes hydrolysis	70–85% excreted in urine unchanged within 24 hours; tubular secretion via OAT1
Major adverse drug reactions	Headache, abdominal pain, nausea, vomiting, dry mouth, and hypersensitivity have been reported	Diarrhea, nausea, vomiting, abdominal pain (may be dose limiting and second dose may need to be held), and elevations in transaminases and bilirubin	Neutropenia, decreased ocular pressure, nephrotoxicity; probenecid: hypersensitivity reactions, rash, nausea, vomiting
US availability	Available through CDC Expanded Access Investigational New Drug Protocol (EA-IND)	CDC is working on Expanded Access Protocol; no current availability	Available through normal wholesalers

Table 1. Continued

Characteristics	Tecovirimat	Brincidofovir	Cidofovir
Notes	Avoid rapid infusion; contains 8 g (per 200 mg tecovirimat) B-cyclodextrin	Should not be co-administered with CDV. Avoid concomitant use with OAT 1B1 and 1B3 inhibitors.	Consider monitoring proteinuria as potential early marker of nephrotoxicity; probenecid has drug interactions due to inhibition of OAT1

Abbreviations: ALT, alanine aminotransferase; BID, bis in die (twice daily); CDC, Centers for Disease Control and Prevention; CDV, cidofovir; CMV, cytomegalovirus; CrCl, creatinine clearance; CYP, cytochrome P; dsDNA, double-stranded DNA; EC50, half-maximal effective concentration; FDA, Food and Drug Administration; G, gastric; IV, intravenous; N/A, not applicable; NG, nasogastric; NS, normal saline; OAT1, organic anion transporter 1; PO, per os (by mouth); Q8h, every 8 hours; Q12h, every 12 hours; SCr, serum creatinine; t1/2, half-life; UGT, Uridine 5'-diphospho-glucuronosyltransferase; ULN, upper limit of normal.

concentration (EC_{50}) than CDV against many dsDNA viruses, including adenoviruses, herpesviruses, and orthopoxviruses (Table 1) [46–50]. The added alkoxyalkyl moiety in BCV is structurally similar to lysophosphatidylcholine (LPC), which allows BCV to be taken up by the small intestines [25]. Contrary to CDV, which slowly crosses cellular membranes, BCV readily enters host cells due to its lipophilicity [25]. Brincidofovir is then hydrolyzed by cellular phospholipases into CDV [25] and phosphorylated into CDV-pp. Cidofovir diphosphate reaches higher intracellular concentrations after BCV administration due to its ability to cross cellular membranes more efficiently. Like CDV, BCV has a prolonged intracellular half-life and inhibits poxviruses DNA replication (Figure 3) [25, 26]. As BCV is converted into CDV, cross-resistance between BCV and CDV is expected.

Pharmacokinetic Data

Initial studies in humans have shown that oral BCV is absorbed in the fasting state and has lower peak CDV concentrations in plasma [51]. This gives BCV the convenience of oral dosing (Table 1). In addition, BCV demonstrated a significantly higher penetration into lung, spleen, and liver tissues, albeit with lower concentrations in the kidneys [52]. Unlike CDV, which is transported into the proximal convoluted tubules by OAT1, where it accumulates and causes renal damage, BCV is not a substrate for OAT1 [52, 53]. Thus, BCV does not accumulate in the kidneys and has a lower risk for nephrotoxicity [52, 53].

Animal Data

Brincidofovir has been tried in multiple poxvirus animal models [54–57]. In mice infected with ectromelia virus, CDV and BCV reduced mortality significantly compared with placebo [54]. Furthermore, BCV prevented mortality when given within 5 days of intranasal ectromelia virus challenge, which is thought to be analogous to the time of first lesion appearance in mpox [54]. In a rabbitpox model in which therapy was initiated on the first day of lesion appearance, rabbits treated at day 3 postinfection had improved survival (88%) compared with those treated at day 4 (67%) [55]. There was no statistical improvement from placebo if given later than day 4, regardless of when lesions occurred [55]. Similarly, an intradermal rabbitpox model showed BCV improved survival when started immediately at the time of fever (around day 2 postinfection) or within 24 to 48 hours with 100% versus 93% survival, respectively [56].

The prairie dog mpox model is very similar to the mpox infection course in humans and is characterized by a 10- to 13-day incubation period, followed by about 2 days of fever, ultimately leading to the appearance of generalized lesions [57]. In prairie dogs, BCV was shown to improve survival when given shortly after mpox exposure [57]. Taken together, these models indicate that early treatment with BCV is key for treatment efficacy, and ideally this would be taken as soon as infection is known, or as soon as prodrome or lesions develop.

Toxicity

Pooled data from phase I/II/III studies indicate that common adverse effects with BCV include gastrointestinal and hepatocellular toxicity (Table 1) [58]. These adverse effects appear to be dose and frequency related [58]. Compared with CDV, BCV has lower rates of nephrotoxicity and the advantage of oral administration [58].

Clinical Data in Humans

Brincidofovir has been administered to select patients with infections caused by poxviruses. A summary of the published case reports is presented in Table 2. Additionally, BCV has been evaluated for the prevention and treatment of other dsDNA viruses. A phase II trial studying BCV for primary CMV prophylaxis in allogeneic hematopoietic cell transplant (HCT) recipients showed a significant reduction in CMV events in the 100-mg twice-weekly arm compared with placebo. In this trial, diarrhea was dose-limiting at 200 mg twice weekly [59]. Nevertheless, a subsequent phase III trial evaluating the same indication failed to demonstrate a difference in clinically significant CMV infection between BCV 100 mg twice weekly and placebo and showed a higher rate of serious adverse events in the BCV arm. The increased rate of adverse events was mostly driven by acute graft-versus-host disease and diarrhea. Additionally, there was slightly higher all-cause mortality at week 24 in the BCV group [60]. Another phase II trial evaluated

Table 2. Case Reports of Brincidofovir Use in Humans With Poxvirus Infections

Case	Age (Years), Sex	Virus	Risk Factor	Site of Infection	Brincidofovir Dose/Frequency	Duration of Brincidofovir	Additional Therapies	Outcome	Reference
1	Adult M	Vaccinia	Acute myeloid leukemia diagnosis after smallpox vaccine	Skin (progressive vaccinia)	100 mg orally once a week (initial dose 200 mg)	6 weekly doses	Intravenous vaccinia immunoglobulin, tecovirimat	Complete resolution	[67]
2	30–40, M	Mpox	Travel to endemic area	Skin	200 mg orally	One dose	None	Complete resolution	[20]
3	30–40, M	Mpox	Travel to endemic area	Skin, deep soft tissue abscesses	200 mg orally once a week	Two doses	Abscess drainage	Complete resolution	[20]
4	30–40, F	Mpox	Exposure to patient with mpox	Skin, conjunctivitis, subungual lesion	200 mg orally once a week	Two doses	None	Complete resolution	[20]
5	17, M	Cowpox	Exposure to pet cat, renal transplant recipient	Skin, tonsils, disseminated	Not reported	Not reported	Cidofovir prior to brincidofovir, vaccinia immunoglobulin	Progression and death	[81]

Abbreviations: F, female; M, male.

BCV for preemptive therapy of adenovirus viremia in allogeneic HCT recipients and showed a numerically lower rate of treatment failure and all-cause mortality in the BCV 100-mg twice-weekly arm. This did not reach statistical significance, likely due to a lack of power. Nevertheless, the BCV group had a higher rate of acute graft-versus-host disease [61]. Additional retrospective studies of BCV have shown its activity when used for resistant CMV and herpes simplex treatment [62] and for herpes simplex and varicella zoster prophylaxis [63]. There is currently an ongoing phase II clinical trial evaluating intravenous BCV in patients with adenovirus infection (NCT04706923).

TECOVIRIMAT

Basic Pharmacology

Tecovirimat (ST-246) was FDA approved in 2018 for the treatment of smallpox and is marketed under the brand name TPOXX. Tecovirimat has activity against orthopoxviruses but has no notable activity against other dsDNA viruses. Tecovirimat targets the V061 gene in cowpox, a gene that is homologous to the vaccinia virus F13L gene. This encodes for membrane protein p37, which is a well-conserved protein in orthopoxviruses and is responsible for the formation of extracellular enveloped virus (EV) [64, 65]. EV is thought to be the major contributor to cell-to-cell transmission and transmission through the bloodstream to distant tissues [65, 66]. Tecovirimat does not inhibit DNA or protein synthesis and does not inhibit the formation of mature virus, which remains in the host cell until cell lysis (Figure 3) [64].

Resistance to tecovirimat can occur with a single amino acid mutation at position 277 [65]. It is unknown if mutation of the p37 protein confers a fitness disadvantage to orthopoxviruses, although vaccinia viruses with engineered mutations in the F13L gene had decreased plaque size and a decrease in extracellular EV formation [65]. Tecovirimat has activity against CDV-resistant vaccinia virus strains, and there is no documented cross-resistance between tecovirimat and CDV or BCV [65].

Pharmacokinetic Data

Tecovirimat is available in IV and oral formulations. When administered in the fed state, tecovirimat can achieve a better absorption, with up to 1.6 times greater Cmax than at fasting. Tecovirimat appears to have saturable absorption at doses greater than 400 mg, with higher doses resulting in nonproportional increases in Cmax and area under the curve (AUC) [68].

Animal Data

Tecovirimat has been shown to be effective in multiple animal models of orthopoxviruses, including against mpox virus in macaque monkeys [69, 70] and prairie dogs [71]. Tecovirimat decreases lesion severity even when administration is delayed [69, 72]. Administration of tecovirimat within 4–72 hours after poxvirus exposure demonstrated efficacy at preventing death and a reduction in the severity of lesions in various animal models [70, 73–75]. Tecovirimat has been shown to decrease viral spread of vaccinia virus to distant tissues [64, 66]. Altogether, tecovirimat is a promising agent in animal models for the treatment of mpox infection.

Tecovirimat appears to have synergistic activity when coadministered with BCV. In cell culture experiments with cowpox and vaccinia virus, the addition of tecovirimat reduced EC_{50} values of BCV [76]. In mice infected with cowpox, BCV

and tecovirimat appeared to be synergistic, especially when therapy was significantly delayed, as the combination reduced mortality compared with either drug alone [76].

The duration of treatment with tecovirimat has been studied in various animal models. Fourteen-day courses have been shown to be more protective against death [73]. Courses of less than 5–7 days in duration may lead to rebound of infection, as discontinuation of tecovirimat prior to day 10, when T-cell immunity develops, may lead to worse outcomes [74]. In immunocompromised patients, prolonged courses or combination therapy may need to be considered.

Toxicity

Phase I and II studies of tecovirimat have demonstrated that tecovirimat is safe and well tolerated (Table 1) [69]. Due to poor water solubility, IV tecovirimat is solubilized with B-cyclodextrin. Although the drug labeling recommends caution in patients with renal impairment, previous studies evaluating IV voriconazole and remdesivir, which are formulated with B-cyclodextrin, have not shown significant toxicities of this solubilizer in patients with renal impairment [77, 78]. Furthermore, rapid infusion with the IV product should be avoided, as elevated Cmax following rapid infusion in animal models resulted in reversible central nervous system toxicities, including ataxia, tremors, and lethargy [79].

Clinical Data in Humans

Tecovirimat has been administered to select human patients with infections caused by orthopoxviruses. A summary of the case reports is presented in Table 3. Two patients received it for mpox. Limited details are available about the first patient, except for complete recovery [80]. The second patient received a 2-week oral course initiated 5 days after rash onset, achieved full recovery with no treatment-related complications, and was discharged

Table 3. Case Reports of Tecovirimat Use in Humans With Orthopoxvirus Infections

Case	Age (Years), Sex	Virus	Risk Factor	Site of Infection	Tecovirimat Dose/ Frequency	Duration of Tecovirimat	Additional Therapies	Outcome	Reference
1	2, M	Vaccinia	Household contact of a smallpox vaccinee	Skin (eczema vaccinatum)	5 mg/kg × 2 days, 7.5 mg/kg × 2 days, 10 mg/kg × 10 days via nasogastric tube	14 days	Intravenous vaccinia immunoglobulin, cidofovir	Complete resolution	[41]
2	Adult, M	Vaccinia	Acute myeloid leukemia diagnosis after smallpox vaccine	Skin (progressive vaccinia)	400 mg then 800 mg then 1200 mg orally (total 75 g) + 0.5 mL of 1% topical once daily then twice daily	73 days (oral); 68 days (topical)	Intravenous vaccinia immunoglobulin, brincidofovir	Complete resolution (despite increasing EC_{50} to tecovirimat)	[67]
3	31, F	Cowpox	Exposure to wild rodents	Ocular (keratitis)	400 mg orally twice a day	14 days	Polyclonal gammaglobulin, amniotic membrane transplantations, corneal collagen cross-linking, autologous limbal stem cell transplantation	Complete resolution (after additional therapies)	[82]
4	26, F	Vaccinia	Occupational needlestick	Left index finger	600 mg orally twice a day	14 days	Intravenous vaccinia immunoglobulin	Complete resolution	[83]
5	19, M	Vaccinia	Acute myeloid leukemia diagnosis after smallpox vaccine	Skin, preemptive treatment during chemotherapy	600 mg orally twice a day	62 days	Intravenous vaccinia immunoglobulin	Complete resolution, no recurrence	[84]
6	28, F	Cowpox	Pet cat with lesions	Ocular	Not reported	Prolonged course	Surgical debridement	Complete resolution with sequelae	[85]
7	Middle-aged, M	Mpox	Travel to endemic area	Skin	Not reported	Not reported	Not reported	Complete resolution	[80]
8	30–40, F	Mpox	Exposure to child who traveled to endemic area	Skin	600 mg orally twice a day	14 days	None	Complete resolution	[20]
9	35, F	Vaccinia	Contact with raccoon rabies vaccine bait	Skin	Not reported	14 days	Intravenous vaccinia immunoglobulin	Complete resolution	[86]

Abbreviations: EC_{50}, half-maximal effective concentration; F, female; M, male.

from the hospital after a 10-day stay [20]. Of interest, 1 immunocompromised patient developed resistance to tecovirimat during a prolonged treatment course for progressive vaccinia; however, he received BCV concomitantly and he completely recovered [67]. There are 4 registered ongoing clinical trials evaluating tecovirimat as oral or intravenous formulation for orthopoxviral exposure (NCT02080767, NCT05380752) and its safety, tolerability, and pharmacokinetics when administered for 28 days (NCT04971109, NCT04957485).

FUTURE DIRECTIONS

In conclusion, the 3 antivirals reviewed here demonstrate activity against mpox. Given their favorable tolerability profile, tecovirimat and BCV are promising therapeutic options. Larger studies should seek to identify the patients at highest risk of complications due to mpox infection (eg, immunocompromised, pregnant women, children, older adults) who might benefit the most from antiviral therapy, and to determine the optimal starting time and duration of antiviral therapy.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Heymann DL, Szczeniowski M, Esteves K. Re-emergence of monkeypox in Africa: a review of the past six years. Br Med Bull **1998**; 54:693–702.
2. Alakunle E, Moens U, Nchinda G, Okeke MI. Monkeypox virus in Nigeria: infection biology, epidemiology, and evolution. Viruses **2020**; 12:1257.
3. Petersen BW, Damon I. Orthopoxviruses vaccinia (smallpox vaccine), variola (smallpox), monkeypox, and cowpox. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 9th ed. Vol 2. Philadelphia, PA: Elsevier, **2020**:1809–17.
4. Petersen BW, Damon I. Other poxviruses that infect humans: parapoxviruses (including orf virus), molluscum contagiosum, and yetapoxviruses. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 9th ed. Vol 2. Philadelphia, PA: Elsevier, **2020**:1818–21.
5. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu territory, Democratic Republic of the Congo. Bull World Health Organ **1972**; 46:593–7.
6. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox—a potential threat? A systematic review. PLoS Negl Trop Dis **2022**; 16: e0010141.
7. Reynolds MG, Yorita KL, Kuehnert MJ, et al. Clinical manifestations of human monkeypox influenced by route of infection. J Infect Dis **2006**; 194:773–80.
8. Centers for Disease Control and Prevention. Update: multistate outbreak of monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR Morb Mortal Wkly Rep **2003**; 52:642–6.
9. McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis **2014**; 58:260–7.
10. Jezek Z, Grab B, Szczeniowski MV, Paluku KM, Mutombo M. Human monkeypox: secondary attack rates. Bull World Health Organ **1988**; 66:465–70.
11. Hutson CL, Olson VA, Carroll DS, et al. A prairie dog animal model of systemic orthopoxvirus disease using West African and Congo basin strains of monkeypox virus. J Gen Virol **2009**; 90:323–33.
12. Learned LA, Reynolds MG, Wassa DW, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. Am J Trop Med Hyg **2005**; 73:428–34.
13. Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. Int J Epidemiol **1988**; 17:643–50.
14. Kabuga AI, El Zowalaty ME. A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria. J Med Virol **2019**; 91:533–40.
15. Jezek Z, Fenner F. Human monkeypox. In: **Preiser W**, ed. Monographs in virology. 1st ed. Vol 17. Basel: Karger, **1988**.
16. Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Negl Trop Dis **2019**; 13: e0007791.
17. Likos AM, Sammons SA, Olson VA, et al. A tale of two clades: monkeypox viruses. J Gen Virol **2005**; 86:2661–72.
18. Li Y, Olson VA, Laue T, Laker MT, Damon IK. Detection of monkeypox virus with real-time PCR assays. J Clin Virol **2006**; 36:194–203.
19. Karem KL, Reynolds M, Braden Z, et al. Characterization of acute-phase humoral immunity to monkeypox: use of immunoglobulin M enzyme-linked immunosorbent assay for detection of monkeypox infection during the 2003 North American outbreak. Clin Diagn Lab Immunol **2005**; 12:867–72.
20. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis **2022**; 22: 1153–62.
21. Centers for Disease Control and Prevention. 2022 Monkeypox and orthopoxvirus outbreak global map. Available at: https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html. Accessed 18 June 2022.
22. World Health Organization. Multi-country monkeypox outbreak: situation update. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393. Accessed 18 June 2022.
23. De Clercq E. Cidofovir in the treatment of poxvirus infections. Antiviral Res **2002**; 55:1–13.
24. Magee WC, Hostetler KY, Evans DH. Mechanism of inhibition of vaccinia virus DNA polymerase by cidofovir diphosphate. Antimicrob Agents Chemother **2005**; 49:3153–62.
25. Hostetler KY. Alkoxyalkyl prodrugs of acyclic nucleoside phosphonates enhance oral antiviral activity and reduce toxicity: current state of the art. Antiviral Res **2009**; 82:A84–98.
26. Aldern KA, Ciesla SL, Winegarden KL, Hostetler KY. Increased antiviral activity of 1-O-hexadecyloxypropyl-[2-(14)C]cidofovir in MRC-5 human lung fibroblasts is explained by unique cellular uptake and metabolism. Mol Pharmacol **2003**; 63: 678–81.
27. Andrei G, Gammon DB, Fiten P, et al. Cidofovir resistance in vaccinia virus is linked to diminished virulence in mice. J Virol **2006**; 80:9391–401.
28. Farlow J, Ichou MA, Huggins J, Ibrahim S. Comparative whole genome sequence analysis of wild-type and cidofovir-resistant monkeypoxvirus. Virol J **2010**; 7:110.
29. Kornbluth RS, Smee DF, Sidwell RW, Snarsky V, Evans DH, Hostetler KY. Mutations in the E9L polymerase gene of cidofovir-resistant vaccinia virus strain WR are associated with the drug resistance phenotype. Antimicrob Agents Chemother **2006**; 50:4038–43.
30. Lalezari JP, Drew WL, Glutzer E, et al. (S)-1-[3-hydroxy-2-(phosphonylmethoxy) propyl]cytosine (cidofovir): results of a phase I/II study of a novel antiviral nucleotide analogue. J Infect Dis **1995**; 171:788–96.
31. Cundy KC, Li ZH, Lee WA. Effect of probenecid on the distribution, metabolism, and excretion of cidofovir in rabbits. Drug Metab Dispos **1996**; 24:315–21.
32. Yu J, Mahendra Raj S. Efficacy of three key antiviral drugs used to treat orthopoxvirus infections: a systematic review. Global Biosecurity **2019**; 1:28.
33. Quenelle DC, Collins DJ, Kern ER. Efficacy of multiple- or single-dose cidofovir against vaccinia and cowpox virus infections in mice. Antimicrob Agents Chemother **2003**; 47:3275–80.
34. Neyts J, Leyssen P, Verbeken E, De Clercq E. Efficacy of cidofovir in a murine model of disseminated progressive vaccinia. Antimicrob Agents Chemother **2004**; 48:2267–73.
35. Smee DF, Gowen BB, Wandersee MK, et al. Differential pathogenesis of cowpox virus intranasal infections in mice induced by low and high inoculum volumes and effects of cidofovir treatment. Int J Antimicrob Agents **2008**; 31:352–9.
36. Wei H, Huang D, Fortman J, Wang R, Shao L, Chen ZW. Coadministration of cidofovir and smallpox vaccine reduced vaccination side effects but interfered with vaccine-elicited immune responses and immunity to monkeypox. J Virol **2009**; 83:1115–25.
37. Huggins JW, Martinez M, Hartmann CJ, et al. 17th International Conference on Antiviral Research. In: Successful cidofovir treatment of smallpox-like disease in variola and monkeypox primate models. Antiviral Res **2004**; 62:A27–90.
38. Meadows KP, Tyring SK, Pavia AT, Rallis TM. Resolution of recalcitrant molluscum contagiosum virus lesions in human immunodeficiency virus-infected patients treated with cidofovir. Arch Dermatol **1997**; 133:987–90.
39. Becker C, Kurth A, Hessler F, et al. Cowpox virus infection in pet rat owners: not always immediately recognized. Dtsch Arztebl Int **2009**; 106:329–34.

40. Graef S, Kurth A, Auw-Haedrich C, et al. Clinicopathological findings in persistent corneal cowpox infection. JAMA Ophthalmol **2013**; 131:1089–91.
41. Vora S, Damon I, Fulginiti V, et al. Severe eczema vaccinatum in a household contact of a smallpox vaccinee. Clin Infect Dis **2008**; 46:1555–61.
42. Toro JR, Wood LV, Patel NK, Turner ML. Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. Arch Dermatol **2000**; 136:983–5.
43. Geerinck K, Lukito G, Snoeck R, et al. A case of human orf in an immunocompromised patient treated successfully with cidofovir cream. J Med Virol **2001**; 64:543–9.
44. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study. J Eur Acad Dermatol Venereol **2000**; 14:484–8.
45. Davies EG, Thrasher A, Lacey K, Harper J. Topical cidofovir for severe molluscum contagiosum. Lancet **1999**; 353:2042.
46. Quintana-Castanedo L, Tarin-Vicente EJ, Chiloeches-Fernández C, Sendagorta-Cudós E, Herranz-Pinto P. Recalcitrant molluscum contagiosum successfully treated with intralesional cidofovir in a patient with HIV/AIDS. Int J Dermatol **2021**; 60:372–5.
47. Chimerix. Tembexa (Brincidofovir) [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf. Accessed 18 June 2022.
48. Hartline CB, Gustin KM, Wan WB, et al. Ether lipid-ester prodrugs of acyclic nucleoside phosphonates: activity against adenovirus replication in vitro. J Infect Dis **2005**; 191:396–9.
49. Beadle JR, Hartline C, Aldern KA, et al. Alkoxyalkyl esters of cidofovir and cyclic cidofovir exhibit multiple-log enhancement of antiviral activity against cytomegalovirus and herpesvirus replication in vitro. Antimicrob Agents Chemother **2002**; 46:2381–6.
50. Kern ER, Hartline C, Harden E, et al. Enhanced inhibition of orthopoxvirus replication in vitro by alkoxyalkyl esters of cidofovir and cyclic cidofovir. Antimicrob Agents Chemother **2002**; 46:991–5.
51. Painter W, Robertson A, Trost LC, Godkin S, Lampert B, Painter G. First pharmacokinetic and safety study in humans of the novel lipid antiviral conjugate CMX001, a broad-spectrum oral drug active against double-stranded DNA viruses. Antimicrob Agents Chemother **2012**; 56:2726–34.
52. Ciesla SL, Trahan J, Wan WB, et al. Esterification of cidofovir with alkoxyalkanols increases oral bioavailability and diminishes drug accumulation in kidney. Antiviral Res **2003**; 59:163–71.
53. Tippin TK, Morrison ME, Brundage TM, Momméja-Marin H. Brincidofovir is not a substrate for the human organic anion transporter 1: a mechanistic explanation for the lack of nephrotoxicity observed in clinical studies. Ther Drug Monit **2016**; 38:777–86.
54. Parker S, Touchette E, Oberle C, et al. Efficacy of therapeutic intervention with an oral ether-lipid analogue of cidofovir (CMX001) in a lethal mousepox model. Antiviral Res **2008**; 77:39–49.
55. Trost LC, Rose ML, Khouri J, et al. The efficacy and pharmacokinetics of brincidofovir for the treatment of lethal rabbitpox virus infection: a model of smallpox disease. Antiviral Res **2015**; 117:115–21.
56. Grossi IM, Foster SA, Gainey MR, et al. Efficacy of delayed brincidofovir treatment against a lethal rabbitpox virus challenge in New Zealand white rabbits. Antiviral Res **2017**; 143:278–86.
57. Hutson CL, Kondas AV, Mauldin MR, et al. Pharmacokinetics and efficacy of a potential smallpox therapeutic, brincidofovir, in a lethal monkeypox virus animal model. mSphere **2021**; 6:e00927–20.
58. Chittick G, Morrison M, Brundage T, Nichols WG. Short-term clinical safety profile of brincidofovir: a favorable benefit-risk proposition in the treatment of smallpox. Antiviral Res **2017**; 143:269–77.
59. Marty FM, Winston DJ, Rowley SD, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med **2013**; 369:1227–36.
60. Marty FM, Winston DJ, Chemaly RF, et al. A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant **2019**; 25:369–81.
61. Grimley MS, Chemaly RF, Englund JA, et al. Brincidofovir for asymptomatic adenovirus viremia in pediatric and adult allogeneic hematopoietic cell transplant recipients: a randomized placebo-controlled phase II trial. Biol Blood Marrow Transplant **2017**; 23:512–21.
62. El-Haddad D, El Chaer F, Vanichanan J, et al. Brincidofovir (CMX-001) for refractory and resistant CMV and HSV infections in immunocompromised cancer patients: a single-center experience. Antiviral Res **2016**; 134:58–62.
63. Lee YJ, Neofytos D, Kim SJ, et al. Efficacy of brincidofovir as prophylaxis against HSV and VZV in hematopoietic cell transplant recipients. Transpl Infect Dis **2018**; 20:e12977.
64. Yang G, Pevear DC, Davies MH, et al. An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge. J Virol **2005**; 79:13139–49.
65. Duraffour S, Snoeck R, de Vos R, et al. Activity of the anti-orthopoxvirus compound ST-246 against vaccinia, cowpox and camelpox viruses in cell monolayers and organotypic raft cultures. Antivir Ther **2007**; 12:1205–16.
66. Berhanu A, King DS, Mosier S, et al. ST-246 inhibits in vivo poxvirus dissemination, virus shedding, and systemic disease manifestation. Antimicrob Agents Chemother **2009**; 53:4999–5009.
67. Lederman ER, Davidson W, Groff HL, et al. Progressive vaccinia: case description and laboratory-guided therapy with vaccinia immune globulin, ST-246, and CMX001. J Infect Dis **2012**; 206:1372–85.
68. Jordan R, Chinsangaram J, Bolken TC, et al. Safety and pharmacokinetics of the antiorthopoxvirus compound ST-246 following repeat oral dosing in healthy adult subjects. Antimicrob Agents Chemother **2010**; 54:2560–6.
69. Grosenbach DW, Honeychurch K, Rose EA, et al. Oral tecovirimat for the treatment of smallpox. N Engl J Med **2018**; 379:44–53.
70. Huggins J, Goff A, Hensley L, et al. Nonhuman primates are protected from smallpox virus or monkeypox virus challenges by the antiviral drug ST-246. Antimicrob Agents Chemother **2009**; 53:2620–5.
71. Smith SK, Self J, Weiss S, et al. Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with monkeypox virus. J Virol **2011**; 85:9176–87.
72. Russo AT, Grosenbach DW, Brasel TL, et al. Effects of treatment delay on efficacy of tecovirimat following lethal aerosol monkeypox virus challenge in cynomolgus macaques. J Infect Dis **2018**; 218:1490–9.
73. Quenelle DC, Buller RML, Parker S, et al. Efficacy of delayed treatment with ST-246 given orally against systemic orthopoxvirus infections in mice. Antimicrob Agents Chemother **2007**; 51:689–95.
74. Zaitseva M, Shotwell E, Scott J, et al. Effects of postchallenge administration of ST-246 on dissemination of IHD-J-Luc vaccinia virus in normal mice and in immune-deficient mice reconstituted with T cells. J Virol **2013**; 87:5564–76.
75. Mucker EM, Goff AJ, Shamblin JD, et al. Efficacy of tecovirimat (ST-246) in nonhuman primates infected with variola virus (smallpox). Antimicrob Agents Chemother **2013**; 57:6246–53.
76. Quenelle DC, Prichard MN, Keith KA, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. Antimicrob Agents Chemother **2007**; 51:4118–24.
77. Pettit NN, Pisano J, Nguyen CT, et al. Remdesivir use in the setting of severe renal impairment: a theoretical concern or real risk? Clin Infect Dis **2021**; 73:e3990–e5.
78. Turner RB, Martello JL, Malhotra A. Worsening renal function in patients with baseline renal impairment treated with intravenous voriconazole: a systematic review. Int J Antimicrob Agents **2015**; 46:362–6.
79. Chen Y, Amantana A, Tyavanagimatt SR, et al. Comparison of the safety and pharmacokinetics of ST-246(R) after IV infusion or oral administration in mice, rabbits and monkeys. PLoS One **2011**; 6:e23237.
80. Rao AK, Schulte J, Chen TH, et al. Monkeypox in a traveler returning from Nigeria—Dallas, Texas, July 2021. MMWR Morb Mortal Wkly Rep **2022**; 71: 509–16.
81. Gazzani P, Gach JE, Colmenero I, et al. Fatal disseminated cowpox virus infection in an adolescent renal transplant recipient. Pediatr Nephrol **2017**; 32:533–6.
82. Kinnunen PM, Holopainen JM, Hemmilä H, et al. Severe ocular cowpox in a human, Finland. Emerg Infect Dis **2015**; 21:2261–3.
83. Whitehouse ER, Rao AK, Yu YC, et al. Novel treatment of a vaccinia virus infection from an occupational needlestick—San Diego, California, 2019. MMWR Morb Mortal Wkly Rep **2019**; 68:943–6.
84. Lindholm DA, Fisher RD, Montgomery JR, et al. Preemptive tecovirimat use in an active duty service member who presented with acute myeloid leukemia after smallpox vaccination. Clin Infect Dis **2019**; 69:2205–7.
85. Kiernan M, Koutroumanos N. Orbital cowpox. N Engl J Med **2021**; 384:2241.
86. Centers for Disease Control and Prevention. Human vaccinia infection after contact with a raccoon rabies vaccine bait—Pennsylvania, 2009. MMWR Morb Mortal Wkly Rep **2009**; 58:1204–7.