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Rédacteur : C. Jackson / P. Vetter		

Monkeypox virus: specific antiviral treatment

1. Introduction

The monkeypox virus (MPXV) is endemic in Sub Saharan Africa, but there has been a recent unprecedented rise in cases mediated by human-to-human transmission and acquired outside of Africa since mid-May 2022.
Monkeypox (MPX) disease is usually self-limited, consisting of a fever and a rash, but serious complications such as encephalitis, pneumonia or even death have been described from sub-Saharian Africa (more common in children and immunocomprised). Fetal loss have been described in infected pregnant women.
Some treatments known to be active against orthopoxviruses may have an effect, both as post-exposure prophylaxis and treatment of monkeypox. There is little clinical data for the use of these treatments in human monkeypox infections.
The aim of this document is to review the available literature and develop recommendations based on clinical evidence.

2. Summary of evidence for available treatments

Few drugs have shown to be effective *in vivo* and in animal models against orthopoxviruses infection.
Tecovirimat, a direct antiviral treatment acting as an egress inhibitor against orthopoxviruses is validated under exceptional circumstances by the EMA for the treatment of orthopoxviruses, including monkeypox.
Brincidofovir, an oral prodrug of the cidofovir, both direct antivirals acting as a DNA polymerase inhibitors, is approved by the FDA against smallpox (not monkeypox).
Cidofovir and tecovirimat showed encouraging results against monkeypox disease in lethal model of NHP, by preventing death when administered after inoculation. The evidence in human is very limited with only few case reports and/or case series of treatment with tecovirimat and/or brincidofovir during monkeypox infection.
Only cidofovir is licensed and available in Switzerland, for the treatment of another viral disease (CMV retinitis). Neither brincidofovir nor tecovirimat are available and/or licensed in Switzerland.

3. Antiviral treatments to be considered: existing literature

A) Tecovirimat (TPOXX®, ST-246®)

- *Summary of the evidence (see below):*

There is evidence for the efficacy of Tecovirimat in Monkeypox disease in both *in vitro* and *in vivo* non-human studies. On the current circulating MPXV strain B.1, Tecovirimat showed an in vitro efficacy at the nanomolar range. As of July 28, 2022, B.1 MPXV do not harbor any mutations known to lead to Tecovirimat resistance.

When treatment is initiated early (within 3 days of exposure) animals were protected from death and had reduced viral loads and skin lesions (Zaire/Congo strain). In animal studies Tecovirimat has been given in conjunction with the vaccine and has been shown to reduce side effects, whilst not impacting the efficacy of the vaccine (see below- treatment combinations).
Note that diffusion into the CSF has been shown in animal models (dogs and NHP).
At least one randomized human clinical trials investigating the effectiveness of Tecovirimat for Monkeypox virus infections is ongoing in the UK.

Status: not licensed in Switzerland, approved by FDA for the treatment of Smallpox in children > 13 kg (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208627s006lbl.pdf) approval under agency's animal rule. Expanded access as Investigational New Drug (EA-IND) protocol that allows for the use of tecovirimat for primary or early empiric treatment of non-variola orthopox infections, including monkeypox, in adults and children of all ages.
Approved in Canada.
Marketing authorization by EMA under exceptional circumstances for the treatment of orthopoxvirus disease (smallpox, monkeypox, cowpox, and vaccinia complications).
Oral capsules, 200 mg. Dose varies by body weight: 200-600 mg BID for 14 days. US FDA recently approved IV

- *Accessibility*:
    - 50 treatment courses to be delivered by Siga to Geneva University Hospitals at the beginning of August 2022. Drug will be sent on demand to other Swiss University Hospitals in case of need. (clinical trial ongoing)

- *In vitro data*:
    - In vitro phenotype data shows that Tecovirimat reduces the production and release of enveloped orthopox viruses (Smith, AAC, 2009 Mar) (Duraffour, Antivir Ther., 2007) (Bailey, J Med Chem, 2007) --> specific for orthopoxviruses.
    - Tecovirimat interacts with the p37 membrane protein (highly conserved orthopoxviruses protein), which plays a central role in the envelopment of viral pox particles and is coded by a highly conserved F13L gene and has no mammalian homologs (Shiryaev, Eur. J. Med. Chem., 2021) --> acts as an egress inhibitor.
    - Blocking of viral spread allows for development of an adaptive immune response to clear the virus? (to consider in immunocompromised)
    - *In vitro* IC50 of 12.07 nM, complete abolition of MPXV production above 100 nM on the 2022 B.1 circulating strain. (Freynois-Veyrat, MedRxiv, 2022)

- *Small Animal data (monkeypox virus)*:
    - Tecovirimat has been shown to provide protection against a lethal monkeypox virus challenge in mice studies. (Stabenow, J. Virol., 2010)
    - Prairie dogs infected with monkeypox virus, treated with Tecovirimat prophylactically and 3-day-postexposure were protected from death and most signs of disease (Smith, J. Virol., 2011)
    - Ground squirrels given a lethal dose of MPXV and started treatment on days 0, 1, 2, 3, 4. All animals starting treatment on days 0-3 survived, 67% of animals starting treatment on day 4 survived. (Sbrana, Am J Trop Med Hyg, 2007)

- *Small Animal data in immunodeficient mice:*

- Mouse model using Western Reserve strain of vaccinia virus. Nude, SCID, and J(H) knockout mice additionally depleted of CD4(+) and CD8(+) T cells were not fully protected by Tecovirimat, although survival was significantly extended (Grosenbach, PNAS, 2009).
- Immune deficient (nu(-)/nu(-)) mice model using vaccinia virus. Immune-deficient animals with partial T cell reconstitution can control virus replication after a course of Tecovirimat and survive lethal vaccinia virus challenge. (Zaitseva, J. Virol., 2013)

- *Small Animal data (other orthopox viruses)*:
  - Rabbit model. Tecovirimat given once daily for 14 days beginning 1 h post-exposure, resulted in 100% survival in a lethal aerosolized rabbitpox model. But when the treatment was started on days 3 or 4 post-exposure, survival was 67% and 33%, respectively. (Nalca, Antivir. Res. 2008 79:121-127.)
  - Mouse model using cowpox virus, vaccinia virus, and ectromelia virus. Tecovirimat proved to be highly effective even when treatment was delayed up to 72 h after viral inoculation and dosing was reduced to once daily (Quenelle, AAC, 2007 Feb)
  - Tecovirimat provides protection in mice against ecromelia virus, maximal protective effect required 14 days of dosing, with 5-day dosing periods protecting 80% of the mice from lethal viral challenge.(Yang, J. Virol.79:13139-13149, 2005)

- *Non-Human Primate data (monkeypox virus):*

  - Cynomolgus monkeys were infected via IV injection with the MPXV (Zaire ’79 strain -> Congo basin clade), and started Tecovirimat on day 1 or 3 post infection. In both treatment groups, Tecovirimat protected animals from disease and death, reduced viral loads by almost 5logs and no skin lesions were observed. (Huggins, AAC, 2009 Jun)

  - A randomized, placebo-controlled, parallel-group, longitudinal study of oral Tecovirimat in cynomolgus monkeys infected i.v. with MPXV (Zaire ’79 strain -> Congo basin clade). Treatment was started on day 3 post infection and was continued once daily for 14 days. An oral dose of approximately 10 mg/kg/day (comparable to 400mg dose in humans) not only protected the animals from death but also significantly reduced the levels of viremia and the lesion counts. (Jordan, AAC, 2009 May)

  - Cynomolgus macaques were challenged with a lethal dose of monkeypox virus by aerosol. Tecovirimat treatment initiated up to 8 days post infection improves survival and, when initiated earlier than 5 days after challenge, provides protection from clinical effects of disease (Russo, J. Infect. Dis. 2018:218, 2018 Nov)

  - In nonhuman primate (monkeypox) and rabbit (rabbitpox) models, the minimum dose of tecovirimat required in order to achieve more than 90% survival in the monkeypox model was 10 mg per kilogram of body weight for 14 days (Grosenbach, NEJM, 2018)

- Tecovirimat treatment (either alone or as an adjunct to vaccination), but not vaccination alone, is fully protective when administered 3 days after monkeypox virus (MPXV) infection in both mice and NHP. (Berhanu, AAC, 2015)

- *Non-Human Primate data (other orthopox viruses):*

  - Monkeys infected with the Harper strain of VARV, received Tecovirimat on either day 0 or day 1 post infection. All animals in the treatment group survived and did not develop poxvirus lesions. (Huggins, AAC, 2009 Jun)

  - Cynomologus macaques were infected by i.v. injection with VARV. Treatment with Tecovirimat on day 2 reduced total body lesion count (from avg 1500 to avg 225), and resulted in a statistical significant difference in viral load and titres of virus shedding in the oropharynx. Treatment with Tecovirimat on day 4 resulted in reduced body lesion count (from avg 1550 to 440), but no statistical significance in viral load or titres of virus shedding in the oropharynx (Mucker, AAC, 2013 Nov)

- *Human data :*
  - Case report of monkeypox virus in a returning traveler who was treated with tecovirimat because of severe disease. (Rao, MMWR, 2021)
  - Case report of one patient infected by monkeypox virus in a female treated with tecovirimat in order to prevent progression to more severe disease -> no lesions appeared 24 hours after tecovirimat was started (Adler, NEJM 2022)
  - Case report of a vaccinia virus infection from an occupational needle stick injury treated with tecovirimat (Whitehouse, MMWR, 2019)
  - Case report of preemptive tecovirimat treatment in a patient with acute leukemia who was vaccinated with smallpox vaccine (Lindholm, Clin Infect Dis, 2019)
  - Case report of a 28 months old child with eczema vaccinatum consecutive to smallpox vaccination treated without complication by VIG and tecovirimat (Vora, Clin Infect Dis 2008)
  - Case report of 28 year old male with cowpox orbital infection treated with tecovirimat (Kiernan, NEJM, 2021)

- *Safety profile*:

  - A phase II, double-blind, randomized, placebo-controlled, multicenter trial. 91 subjects received Tecovirimat PO (either 400mg or 600mg) and it was found to be safe, well tolerated, and predictable when administered as a single daily oral dose for 14 days to 18- to 74-year-old fed volunteers. Commonly reported: mild nausea and headache, no significant adverse events. (Chinsangram, AAC, 2012 Aug).

  - Phase I, double-blind, randomized, placebo-controlled, escalating multiple-dose study was conducted to determine the safety, tolerability, and pharmacokinetics of Tecovirimat administered as a single daily oral dose of 250, 400, or 800 mg for 21 days to nonfasting healthy human volunteers. Based on these results,

administration of 400 mg/day ST-246 can be expected to provide plasma concentrations above the efficacious concentration demonstrated in nonhuman primate models in earlier studies. (Jordan, AAC, 2010)

- In a phase I, double-blind, randomized, placebo-controlled trials, Tecovirimat was well tolerated with no serious adverse events. Absorption was greater in nonfasting volunteers than in fasting volunteers. (Jordan, AAC, 2008)

- Phase I, double-blind, randomized, crossover, exploratory study was conducted to compare two polymorph forms of Tecovirimat. Tecovirimat form I was more thermostable. (Chinsangaram, AAC, 2012 June)

B) Cidofovir

- *Summary of the evidence (detailed below):*

The efficacy of Cidofovir in Monkeypox disease has been studied in both *in vitro* and *in vivo* non-human studies. The IC_{50} of cidofovir against the current circulating B.1 MPXV strain is 3000 fold higher than the tecovirimat one. Available pharmcokinetics data suggest that plasmatic concentrations in human after CDV administration allows to reach more than twice the IC50 of CDV to inhibit the current MPXV circulating strain. Of note this doesn't take in account the short CDV half-life in plasma, which is known to not be a good proxy of the intracellular activity of the drug.
Current circulating MPXV strain B.1 do not harbour any of the diversity mutations previously described in the literature associated with cidofovir resistance.
Non-human primates who received post-exposure treatment with Cidofovir were able to survive a lethal monkeypox virus challenge. Animal studies in which other orthopox viruses were studied, found evidence to suggest the administration of topical cidofovir may accelerate lesion recovery, and aerosolised cidofovir may be effective in treating severe respiratory infections. There are no human clinical trials investigating the effectiveness of Cidofovir for Monkeypox virus infections.

Status, security profile and availability: Cidofovir is approved and available in Switzerland for the treatment of cytomegalovirus retinitis in humans. Most common SI: renal failure +++ (to be administered with probenecide), uveitis among severe known side effects. Expensive, IV treatment. Preparation for topical treatment (pomade/lotion) possible (around 3 000 CHF for 28g).

- *In vitro data*
    - In Vero cells, poxviruses (including the monkeypox virus) fall within the activity spectrum of cidofovir. (Safrin, Rev Med Virol, 1997)

    - The sensitivity of 35 different strains of variola virus to cidofovir, cHPMPC, and ribavirin demonstrated that all isolates appear to have similar drug sensitivities. (Baker, Antivir. Res. 2003)

    - Cidofovir has good activity in tissue culture assays and in animal model infections with vaccinia and cowpox virus infections. (Kern, Antivir. Res., 2003)

- The most-active compounds within the Cidofovir series were (S)-HPMPA and (butyl L-alaninyl) cyclic HPMPC, with 50% effective concentrations (EC50s) from 4 to 8 µM, compared with 33 to 43 µM for Cidofovir. (Keith, AAC, 2003)
- Less (3000 fold) potent than Tecovirimat on the current B.1 MPXV circulating strain, with IC50 around 30 µM *in vitro* (Frenois-Veyrat, MedRxiv, 2022)
- Plasmatic concentrations in human after CDV administration allows to reach more than twice the IC50 of CDV to inhibit the current MPXV circulating strain (Pharmacokinetic assessment, Clinical pharmacology unit, Geneva University Hospitals). Caveat: do not take in account the short (2.5 hours) half-life of cidofovir in plasma, which do not reflect the intracellular effect.
- Current circulating MPXV B.1 strain do not harbour any of the diversity mutations previously known in the literature to be associated with cidofovir resistance (private communication, analysis conducted by E. Hodcroft).

- *Small Animal data (monkeypox virus):*
  - Dormice treated with a single dose of cidofovir 4 h following challenge with monkeypox virus were significantly protected from mortality, whereas dormice in the vehicle treated control group experienced uniform mortality. (Shultz, Virology, 2009)
- *Small Animal data (other orthopox virus)*:
  - When SCID mice were inoculated intraperitoneally with cowpox virus or VARV and treated for 7 to 30 days with Cidofovir, all the mice eventually died during or after cessation of treatment; however, significant delays in time to death and reduction of virus replication in organs occurred in most treated groups, and no resistance to CDV was detected. (Quenelle, AAC, 2003)
  - Mice were lethally infected with cowpox virus by intranasal inoculation, followed 24 h later by antiviral treatment for 5 consecutive days. Cidofovir was 100% protective at 30 mg/kg per day and reduced lung and nasal virus titers by approximately ten-fold (Smee, Antivir. Res., 2002)
  - Treatment of intranasal cowpox virus infections in mice with cidofovir (100 mg/kg/day for 2 days starting 24 h after virus exposure) led to survival and suppression of tissue virus titres (Smee, Int. J. Antimicrob. Agents, 2008)
  - Cidofovir delayed but did not prevent the death of cowpox intranasally infected mice with severe combined immunodeficiency. Treatment at the time of tail scarification with vaccinia virus did not block vaccination efficacy (Smee, J. Infect. Dis., 2000)
  - Comparative Effects of Cidofovir and Cyclic HPMPC on Lethal Cowpox and Vaccinia Virus Respiratory Infections in Mice. Although cyclic HPMPC is reported to exhibit reduced nephrotoxicity in vivo, it is also less potent than cidofovir against orthopoxvirus infections. For this reason, cyclic HPMPC may not offer any advantage over cidofovir in treating these infections in humans. (Smee, Chemotherapy, 2003)

- Aerosolized Cidofovir is retained in the respiratory tract and protects mice against intranasal cowpox virus challenge. (Roy, AAC, 2003)
- Treatment of aerosolized cowpox virus infection in mice with aerosolized cidofovir. The results suggest that aerosolized cidofovir would be effective for prophylaxis or early post-exposure therapy of human smallpox or monkeypox virus infection. (Bray, Antivir. Res., 2002).
- Treatment of lethal Vaccinia Virus respiratory infections in mice with Cidofovir on days 1 and 4 after virus challenge, reduced mortality by 60–100%. (Smee, Antivir Chem Chemother, 2001)
- Cidofovir treatment in murine models of cowpox and vaccinia virus infection significantly suppressed certain cytokine (IFN- γ, IL-6, IL-10, IL-11, IP-10, LIF, MCP-1, MCP-3, MCP-5, MIP-1γ, and TIMP-1) levels to near normal relative to uninfected animals, as well as prevented mortality and reduced virus titers significantly. (Knorr, Antivir. Res., 2006)
- Cidofovir is effective in treating severe respiratory infections caused by vaccinia virus Mice, whereas equivalent oral doses of ribavirin were completely ineffective. (Smee, Int. J. Antimicrob. Agents, 2004).
- Micronized dry powder formulation of pharmaceutical-grade cidofovir (NanoFOVIRTM; Nf) to treat rabbits exposed to aerosolized rabbitpox virus (RPXV). Nf groups showed an antiviral-dose associated survival of 50% (0.5 mg/kg), 80% (1.0 mg/kg) and 100% (1.75 mg/kg). Significant reduction of rabbitpox virus-induced pathological changes was observed (Verreault, Antivir. Res., 2012).
- Treatment of Progressive Vaccinia in Immunocompromised Mice: topical treatment with 1%-cidofovir cream starting 9 days after infection delayed death by 10 days, (compared with treatment with placebo). Combining topical and parenteral cidofovir treatments provided the greatest reduction in lesion severity and prolongation of life. (Smee, J. Infect. Dis., 2004)
- Topical treatment with cidofovir, initiated at the day of infection of vaccinia or at day 1 post infection, completely protected against virus-induced cutaneous lesions and against associated mortality. When treatment was initiated at a later time (day 2 to 5 p.i.), a partial but marked protective effect was noted. Infected mice who were left untreated until the time (~2 weeks p.i.) at which disseminated vaccinia had developed then received IV cidofovir, and it caused lesions to heal and regress. In most of these animals, lesions had completely (or almost completely) disappeared by day 10 to 15 after the start of therapy. (Neyts, AAC, 2004)
- Cidofovir was evaluated for camelpox virus infection in athymic nude mice. It provided 100% protection from morbidity. It appeared that both treatments did not affect immune cell responses or cytokine expression (Duraffour, journal.pone., 2011)

- Cidofovir was found to generate, on single-dose administration, a long-lasting protective efficacy against a lethal cowpox challenge in mice. (De Clercq, Clin Microbiol Rev., 2001)

- *Non-Human Primate data (monkeypox virus)*:

  - Cynomolgus monkeys infected with monkeypox virus were treated with either post-exposure smallpox vaccination or cidofovir. Initiation of antiviral treatment 24h post infection resulted in significantly reduced mortality and reduced number of cutaneous lesions. No significant reduction in mortality was observed with the smallpox vaccine. (Stittelaar, nature, 2006)

  - Monkeys that were challenged with a lethal dose of monkeypox virus and received cidofovir treatment were pox-antigen negative and all three NHPs survived. (Song, journal.pone., 2013)

  - Monkeys who received a lethal dose of monkeypox virus and were treated with Cidofovir survived. The main differences in clinical signs between CDV-treated and untreated animals were skin lesion development and viremia. Treatment with CDV delayed lesion appearance and peak by 2 days and reduced skin lesion numbers by 5-to 10-fold compared to that for the untreated survivor. Similar to a previous study, CDV treatment delayed viremia by 6 days and reduced peak virus load. CDV treatment reduced viral load by 2.4 log10 in comparison to that observed in untreated animals. (Dyall, J Virol, 2017)

- *Human data in orthopox viruses:*
  - Case report of a persistent corneal cowpox infection treated with cidofovir. (Graef, JAMA Ophthalmol. 2013)
  - In humans, cidofovir has so far been used in the treatment of only two varieties of poxvirus infections, namely Molluscum contagiosum and Orf (ecthyma infectiosum). (De Clercq, Trends Pharmacol. Sci, 2002).

C) Brincidofovir (CMX001) (Temexa®)

- *Summary:*

There is evidence for the efficacy of Brincidofovir in Monkeypox disease *in vivo* non-human studies. In animal studies, Brincidofovir given in conjunction with the vaccine has been shown to reduce side effects from the vaccine, whilst not impacting the efficacy of the vaccine. There are no human clinical trials investigating the effectiveness of Brincidofovir for Monkeypox virus infections. There are 3 case studies in which Brincidofovir therapy in humans needed to be stopped due to elevated liver enzymes.

Status, security profile and availability: Approved by FDA against smallpox in adults and pediatric patients, including neonates (under agency's animal rule). Not approved in EU nor Switzerland.

PO drug (prodrug of cidofovir), safe (indirect data obtained from other indications), increase of liver enzymes, gastro-intestinal side effects, increased risk of death in CMV infected patients. Embryofoetal toxicity (?)

Tablets, 100mg. 200mg dose 1 day 1 and second dose 200mg day 8.

Not available in Switzerland, not delivered by the manufacturer.

- *Human data (monkeypox virus)*
    - Case series of 3 patients who were treated by brincidofovir PO -> elevation of liver enzymes resulting in cessation of therapy
- *Animal models (monkeypox virus)*
    - Mouse model using a lethal monkeypox intranasal infection to assess efficacy of pre-exposure MVA vaccination and post-exposure (day 0) treatment with Brincidofovir or Tecovirimat. All 3 treatment groups were effective. Mice were re-challenged 38 days post infection- 20% died in both Brincidofovir and Tecovirimat group, (Stabenow, J. Virol., 2010)
- Animal models (orthopoxviruses other than monkeypox virus)
    - Normal and immune deficient mice were infected with vaccinia virus. Brincidofovir treatment was initiated either day 1 or day 2 post challenge. Initiating BCV treatment earlier was more efficient in reducing viral loads and in providing protection from pox lesion development. In immune-deficient mice, BCV protected animals from lethality and reduced viral loads while animals were on the drug. Viral recrudescence occurred within 4 to 9 days, and mice succumbed ~10 to 20 days after treatment termination (Zaitseva, J. Virol., 2015)
    - Intranasal mousepox model, in which mice were vaccination with either Dryvax or ACAM2000. Co-treatment with Brincidofovir reduced the severity of vaccination-associated lesion development. Although the immune response to vaccination was quantifiably attenuated, vaccination combined with BCV treatment did not alter the development of full protective immunity, even when administered two days following ectromelia challenge. (Parker, Antivir. Res., 2014)
- Case reports of use in conjunction with other treatments (see below)

D) Other treatments:

- **Vaccinia immune globulin**

Used in treatment of smallpox vaccine complications. No data in treatment of MPX complication.

- Lit. review: Studies that provide information on VIG treatment of established vaccine complications generally report efficacy with respect to morbidity or mortality rates for specific complications: generalized vaccinia, vaccinia encephalitis, eczema vaccinatum, progressive vaccinia, and accidental infection (usually ocular). None of these studies are formal controlled trials. (Hopkins, Clin. Infect. Dis., 2004)

- Mice were EC sensitised with ovalbumin, then inoculated with VV Western Reserve strain. VIG at days -1 and +1, but not +3, developed significantly smaller primary lesions and lower numbers of satellite lesions compared with controls. (Oyoshi, J. Invest. Dermatol. 2012)

- **Modified vaccinia Ankara (Imvanex)**

  - Mice study with a lethal respiratory challenge with VACV Western Reserve. Post-exposure immunization with MVA failed to protect animals, but immunization 2 days prior to challenge was fully protective. On the day immunization prevented death but not onset of severe respiratory symptoms. (Staib, J. Gen. Virol., 2006)

  - Mice infected with ectromelia virus were fully protected by an IV immunization of MVA 3 days post-exposure. (Lauterbach, journal.pone, 2010)

  - Healthcare worker received Imvanex on day 5 post exposure with monkeypox. This did not prevent development of monkeypox disease. (Vaughan, Emerg Infect Dis., 2018)

  - 30 people (7 pre-exposure, 23 post-exposure) received small pox vaccine (type unknown), 3 people went on to devlop rash. 1 confirmed monkeypox virus. (State and local health departments. Monkeypox investigation team, CDC., 2003).

  - Case reports of use in conjunction with antivirals (see below)

4. Treatment combinations

Evidence for the following treatment combinations:

Tecovirimat, Brincidofovir and Vaccinia immunoglobulin:

- Case description of a patient with progressive vaccinia who required treatment with vaccinia immune globulin and who received 2 investigational agents, ST-246 and CMX001. Despite development of resistance to ST-246 during treatment, the patient had resolution of PV. (Lederman, J. Infect. Dis., 2012)

Tecovirimat and Brincidofovir:

- Combinations of ST-246 and CMX001 are synergistic both in vitro and in vivo, therefore combination therapy (ST-246 and CMX001) for treatment of orthopoxvirus disease in humans may provide an additional benefit over monotherapy. (Quenelle, AAC, 2007 Nov)

Tecovirimat in conjunction with the smallpox vaccine:

- ST-246 did not compromise protective immunity elicited by the vaccine. Can be considered for treating adverse events due to vaccination (Grosenbach, Vaccine, 2008)

- Tecovirimat reduced the severity of vaccination lesions in all mice except those lacking both CD4- and CD8- T cells. Similar survival rates to mice with vaccination alone were observed, indicating that tecovirimat does not impair development of short or long-term protective immunity (Berhanu, Vaccine, 2010)

Cidofovir in combination with vaccine:

- A single post exposure CDV treatment is sufficient for protection depending on the initiation time and dose (2.5 – 100 mg/kg) of treatment. The combination of CDV and vaccination provided no additional protection over CDV alone. Yet, combining CDV and vaccination maintained vaccination efficacy. (Israely, Virol. J., 2012)

- The single-dose coadministration of cidofovir and Dryvax effectively controlled vaccination side effects but significantly compromised vaccine-elicited immune responses and vaccine-induced immunity to monkeypox. (Wei, Virol. J., 2009)

Cidofovir with vaccinia immune globulin:

- Treatment of progressive cutaneous Vaccinia Virus infections in immunosuppressed hairless mice. The greatest efficacy was achieved by triple therapy (topical CDV, parenteral CDV, and VIG). In humans, this regimen should translate to a faster cure rate, thus sparing the amount of VIG used for treatment. (Smee, AAC, 2014)

5. Existing recommendations/target population

- Existing recommendations from other health authorities:

- CDC guidelines for tecovirimat:
  - People with severe disease: Extensive or hemorrhagic lesions, sepsis, pneumonia, encephalitis
  - People at risk for severe disease: Immunocompromised hosts, children (in particular if < 8 years old), pregnant or breast-feeding women (cave no data in pregnancy, no teratogenicity in animal models), active skin exfoliation lesion incl atopic dermatitis, when complication occurs.
  - Everyone with an "aberrant lesion" incl, into mouth, eye genital/peri-anal lesion
- CDC guidelines for cidofovir/brincidofovir: "It is unknown whether or not a person with severe monkeypox infection will benefit from treatment with Cidofovir, although its use may be considered in such instances. Brincidofovir may have an improved safety profile over Cidofovir."

- WHO: "In patients with MPX, it is preferable to use antivirals under randomized clinical trials (RCTs) with collection of standardized clinical and outcome data to rapidly increase evidence generation on efficacy and safety and, when not possible, antivirals may be used under expanded access protocols, such as MEURI (Monitored Emergency Use of Unregistered and Investigational Interventions)." (https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1)

- France Haute Autorité de Santé: tecovirimat: first line of treatment (after multidisciplinary assessment)

- France, Belgium, Italy, UK, USA: use of the vaccine as PEP for high-risk exposure and/or PrEP.