The Clinical Manifestation of Monkeypox (MPOX) Infection, with a Focus on People Living with HIV (PLWH): A Literature Review

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ABSTRACT

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This review aims to provide an overview of the current knowledge regarding the co-infection of Monkeypox (MPOX) and HIV, with a specific emphasis on the significance of immune status and effective antiretroviral therapy (ART) on the course of MPOX infection among people living with HIV (PLWH). Typically, MPOX symptoms include skin lesions, fever, and malaise. The clinical manifestations of Monkeypox infection in PLWH can vary, depending mainly on the depletion of CD4+ lymphocytes. Patients with severe immunodeficiency caused by HIV are at a higher risk of developing health complications. Conversely, PLWH with high CD4+ lymphocyte levels tend to exhibit clinical features similar to those without HIV infection. Nevertheless, the hospitalization rate among MPOX-infected patients is observed to be lower in individuals without HIV infection compared to PLWH. Regarding treatment, ART may interact with MPOX antiviral medications, necessitating careful management. Prophylaxis, including vaccines like JYNNEOS and ACAM2000, is available for preventing orthopoxvirus infections in the general population. For immunocompromised individuals, including PLWH, pre- and post-exposure prophylaxis (PrEP, PEP) with monkeypox vaccination is also advisable. In this context, JYNNEOS vaccination is recommended, while the use of ACAM2000 is contraindicated.

Keywords: *co-infection, Monkeypox, HIV, antiretroviral therapy, ART*

STRESZCZENIE

Kliniczna manifestacja zakażenia małpią ospą (MPOX) ze szczególnym uwzględnieniem osób żyjących z wirusem HIV (PLWH): Przegląd literatury

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Niniejszy artykuł ma na celu przedstawienie aktualnej wiedzy na temat koinfekcji wirusa małpiej ospy (MPOX) i HIV, ze szczególnym uwzględnieniem znaczenia statusu immunologicznego oraz skutecznej terapii antyretrowirusowej (ART) na przebieg zakażenia MPOX wśród osób żyjących z HIV (PLWH). Typowe objawy MPOX obejmują zmiany skórne, gorączkę i złe samopoczucie. Kliniczne objawy zakażenia wirusem małpiej ospy u PLWH mogą się różnić, głównie w zależności od stopnia zmniejszenia liczby limfocytów CD4+. Pacjenci z ciężkim niedoborem odporności spowodowanym przez HIV są bardziej narażeni na rozwój powikłań zdrowotnych. Natomiast PLWH z wysokim poziomem limfocytów CD4+ mają tendencję do wykazywania objawów klinicznych podobnych do tych, które występują u osób bez zakażenia HIV. Niemniej jednak, obserwuje się niższy wskaźnik hospitalizacji wśród pacjentów zakażonych MPOX bez HIV w porównaniu do PLWH. Jeśli chodzi o leczenie, ART może wchodzić w interakcje z lekami przeciwwirusowymi stosowanymi w terapii MPOX, co wymaga szczególnej uwagi. Profilaktyka, w tym szczepionki takie jak JYNNEOS i ACAM2000, jest dostępna w celu zapobiegania zakażeniom ortopoksywirusami w populacji ogólnej. Dla osób z obniżoną odpornością, w tym PLWH, zaleca się stosowanie profilaktyki przedekspozycyjnej (PrEP) i poekspozycyjnej (PEP) poprzez szczepienie przeciw małpiej ospie. W tym kontekście zaleca się szczepienie JYNNEOS, podczas gdy stosowanie ACAM2000 jest przeciwwskazane.

Słowa kluczowe: *koinfekcja, wirus małpiej ospy, HIV, terapia antyretrowirusowa, ART*

1. Introduction

Over the past five decades, the global community faced significant challenges associated with two distinct viruses that originated from animals and transitioned to humans: human immunodeficiency virus (HIV) and Monkeypox virus (MPXV) [1]. Acquired Immune Deficiency Syndrome (AIDS) was identified in 1981 as a rising number of men who have sex with men (MSM) began presenting with rare infections and malignancies. HIV, a member of the Retroviridae family, transitioned from wild chimpanzees to humans [2]. Among people, its transmission, mainly through sexual contact and bodily fluids such as blood and breast milk, causes persistent infection. Combined antiretroviral therapy (ART) is highly effective in the management of HIV infection. Over time, in PLWH without ART, HIV infection results in immune deficiency and eventual death, mainly due to opportunistic infections and neoplasms [3]. It has also been well documented that PLWH are at an increased risk of other viral infections. A compromised immune system can facilitate a more severe disease course, especially during co-infections that elicit a strong immune response, such as Monkeypox.

Monkeypox, caused by the MPXV, is an increasing public health concern. This virus belongs to the orthopoxvirus genus, sharing its group with variola, cowpox, and vaccinia viruses. Two main strains of this virus have been identified in Central and West Africa; the strain originating from Central Africa is linked to a more severe form of the infection [4]. The first case of MPOX in Poland was reported in June 2022. By the end of 2022, there were 213 cases, while only three new cases were reported in 2023 [5]. The symptoms of this disease are similar to smallpox, including rash, prodromal symptoms such as fever, flu-like symptoms, and lymphadenopathy [6]. Transmission occurs through direct contact with infectious lesions and shared items [7]. Notably, the significant frequency of detecting MPXV in rectal swabs suggests sexual transmission of this infection [8]. Moreover, sexual transmission has also been observed in many cases during the current wave of infections, particularly among MSM [9,10]. It has been demonstrated that the presence of primary genital and oral mucosal lesions can potentially serve as points of entry for the infection [11]. Nevertheless, further research is required to ascertain whether transmission results solely from close skin-to-skin contact or if there is a potential role of local inoculation from skin lesions or bodily fluids during penetrative sexual intercourse. Regarding MPOX, treatments with tecovirimat (TPOXX) are available, and vaccines such as JYNNEOS and ACAM2000 offer preventive measures [12]. Vaccinations against Monkeypox in Poland are administered with the JYNNEOS vaccine both pre-exposure and post-exposure in groups of at-risk individuals [13].

Considering that MPXV significantly weakens the immune system, an essential question arises: Are patients infected with HIV more susceptible to complications from other viral infections, such as Monkeypox? The main objective of this study is to determine whether PLWH exhibit a more severe course of Monkeypox disease. Moreover, during this review, we will also place special emphasis on the potential impact of effective ART on the severity of MPOX.

2. Clinical Manifestation of MPOX

It is noteworthy that the majority of MPOX cases tend to be mild and self-limited, without serious complications. The clinical course of Monkeypox can be characterized by the development of a monophasic vesiculopustular rash after a prodromal period of systemic symptoms (fever, malaise, headache). However, the prodromal phase is sometimes absent, with a mucocutaneous rash as the first manifestation. The rash could be multiphasic, with lesions in various stages; it tends to develop more often in the genital area and is often accompanied by lymphadenopathy [8].

2.1. Clinical Manifestation of Human MPOX Infection in the General Population

The presence of rash or skin lesions consistently emerges as the predominant symptom in several studies. These lesions may manifest on the whole body or on the face, with the genital region being the most frequently affected site [9,10,11,14,15]. Patients with MPOX typically experience systemic symptoms such as fever, lethargy, myalgia, headache, and lymphadenopathy before the rash appears [9,11].

In a comprehensive international study that investigated all clinical presentations resulting from human MPOX infection, researchers explored a diverse range of clinical features. The findings indicated that common clinical manifestations, observed in over 60% of cases, included the presence of a rash, chills, and fever. Intermediate presentations, documented in 20% to 60% of cases, included symptoms such as lymphadenopathy, lethargy, pruritus, myalgia, headache, skin ulcers, abdominal symptoms, and pharyngitis. Rare presentations, occurring in less than 20% of cases, included symptoms such as respiratory issues, nausea or vomiting, scrotal or penile edema, conjunctivitis, and fatalities. Furthermore, researchers categorized patients with rashes into two groups based on the number of skin lesions: those with mild cases (<25) and those with moderate to severe cases (≥25). The prevalence of mild cases was 67.1%, while that of

moderate to severe cases was 27.3%. The distribution of skin lesions by location was as follows: anogenital area (38.4%), trunk or limbs (32.4%), face (20.4%), and palms or soles (15.6%) [15].

Additionally, pruritus, defined as an intense itching sensation in the anogenital area, has been reported as a frequent symptom. While specific data concerning pruritus were not routinely collected for cases that did not necessitate hospitalization, it was noted that most of the patients requiring hospital admission reported experiencing intense pruritus at the onset of the eruptive phase [10].

2.2. Monkeypox in PLWH

Certain clinical characteristics may differ between HIV-infected and non-infected individuals. HIV-negative patients typically present with a febrile illness and generalized skin rashes, whereas PLWH with Monkeypox exhibit an elevated likelihood of developing skin rash in the genital or perianal areas [14,16]. PLWH with Monkeypox co-infection demonstrate an increased probability of experiencing proctitis, tenesmus, rectal bleeding, and purulent or bloody stools, and they are more predisposed to experiencing diarrhea [8,16,17]. For a range of other symptoms, such as fever, lymphadenopathy, myalgia, fatigue, arthralgia, headache, pruritus, chills or sweats, odynophagia, sore throat, oral ulceration or pharyngitis, and chest or back pain, no statistically significant differences in occurrence have been observed between HIV-positive and HIV-negative Monkeypox patients [16].

Monkeypox can develop in PLWH independently of CD4+ count. However, the CD4+ count can influence the manifestation of symptoms of MPOX in PLWH [14].

2.2a. Patients with Normal CD4+ Count

PLWH with normal CD4+ cell count exhibit clinical features similar to those without HIV infection [11,14]. Most patients with undetectable plasma HIV viral loads can experience prodromic symptoms, such as fever, general malaise, lymphadenopathy, followed by skin lesions, pharyngitis, and proctitis [8]. Furthermore, the clinical presentation and complications associated with MPOX remain strikingly similar among patients with well-controlled HIV infection and those without HIV infection [8,10,11,18].

2.2b. Patients with Low CD4+ Count

PLWH with unsuppressed HIV infection were found to be more prone to experiencing symptoms like lymphadenopathy, generalized pruritus, rectal bleeding, and purulent or bloody stools compared to those with suppressed HIV viral loads. Moreover, those with CD4 counts less than 350/μL are more likely to experience fever and generalized pruritus [17]. Data from Nigeria, where most patients were not treated with ART, suggest that advanced or uncontrolled HIV infection may lead to more severe MPOX progression, which is consistent with WHO observations [8,19]. This condition is characterized by more advanced skin lesions, a longer duration of the disease, and a higher frequency of complications such as genital ulceration and secondary bacterial skin infections, compared to HIV-negative patients [19].

3. Hospitalization Rates in Human Monkeypox Infection

The hospitalization rate among MPOX patients is notably low, as evidenced by multiple studies [9,10,11]. Moreover, it is lower in individuals without HIV infection compared to PLWH [17]. In a cohort of 954 individuals, only 8% required hospital admission due to illness severity [9]. Similarly, in another cohort, 9% of the 54 subjects required hospitalization. This was primarily due to the progression of genital or perianal lesions into coalescing ulcerations, often complicated by cellulitis, necessitating antibiotic treatment and pain management with analgesics [10]. Hospitalization was also necessary for various other reasons, including severe anorectal pain, pharyngitis, and difficulties with oral intake. Less frequent reasons included eye lesions, acute kidney injury, myocarditis, and the need to control the spread of infection [11].

4. Mortality Rates in Monkeypox Infection

The mortality rate among individuals infected with MPOX is estimated to be low, as evidenced by multiple studies [9,10,11], which reported no fatalities in their cohorts. Conversely, in a comprehensive summary study comprising 27 cases, the mortality rate among individuals co-infected with HIV was found to be increased. Specifically, those with a low CD4+ count were at a significantly heightened risk of developing severe disease and experiencing adverse outcomes [14].

5. Treatment Options for MPOX and Their Interactions with Antiretroviral Therapy (ART)

5.1. Treatment

Antiretroviral therapy is a critical component of HIV management, involving the use of specific medication combinations to effectively control HIV replication and prevent the development of drug resistance and im-

munodeficiency. Preferred ART regimens typically include one of the following combinations:

1. Two nucleotide reverse transcriptase inhibitors (NRTIs) along with one non-nucleoside reverse transcriptase inhibitor (NNRTI),
2. Two NRTIs in combination with one protease inhibitor (PI),
3. Two NRTIs supplemented by one integrase inhibitor (INI) [20].

At present, there are no FDA-approved treatments specifically designated for Monkeypox. Nevertheless, drugs that have obtained FDA approval for the treatment of smallpox and cytomegalovirus infections may potentially demonstrate efficacy against the Monkeypox virus [21]. The treatment options available for managing MPOX include tecovirimat, brincidofovir, and vaccinia immune globulin. Tecovirimat is the first drug of choice for MPOX treatment, while cidofovir and brincidofovir serve as alternative options [21,22]. Treatment for MPOX is currently unavailable in Poland [13]. Consequently, it is crucial to consider pharmacokinetic drug interactions between ART medications and MPOX antivirals if the need for MPOX treatment arises in PLWH due to specific risk factors.

5.2. Drug Interactions

5.2a. Tecovirimat

Tecovirimat, available in oral and intravenous formulations, is the only antiviral medication approved by the European Medicines Agency (EMA) for the treatment of MPOX in the EU. Considering the mechanism of action of tecovirimat, it is important to note that it has a limited impact on CYP3A enzyme activity, making it a relatively weak inducer. It is essential to highlight that no clinically significant drug interactions are expected when tecovirimat is used alongside NRTIs and INIs. Given the infrequency of anticipated and confirmed adverse interactions with ART, there should be no hindrance to the simultaneous use of tecovirimat and ART [21]. Nevertheless, there is a possibility of interactions leading to decreased levels of certain antiretroviral medications.

For ART-naïve individuals prescribed tecovirimat, it is advisable to delay the initiation of an ART regimen containing rilpivirine by two weeks after completing the tecovirimat course. In treatment-experienced individuals, there is no need for adjustments to treatment. In the context of treating multidrug-resistant HIV-1 infection with attachment inhibitor fostemsavir (FTR) or capsid inhibitor lenacapavir (LEN), both metabolized by CYP3A4, it is important to be aware that tecovirimat could potentially lower serum concentrations due to its ability to induce CYP3A4 [20].

5.2b. Cidofovir

Cidofovir, another drug used in treating MPOX, primarily manages cytomegalovirus retinitis in adults with acquired immunodeficiency syndrome (AIDS) [20]. It has also demonstrated effectiveness against Orthopoxviruses in both in vitro and in vivo studies [21]. Due to its low oral bioavailability, cidofovir should be administered intravenously using a controlled-infusion pump [20]. However, it should be avoided in individuals with pre-existing kidney conditions, as it can potentially cause kidney damage. When combined with other substances that have the potential to cause acute kidney injury, there is a risk of developing renal insufficiency, proximal renal tubulopathy, or Fanconi syndrome [20]. The likelihood of drug interactions is low when cidofovir is administered alongside an antiretroviral drug from a different class than NRTI [20]. Therefore, it is advisable to avoid co-administering cidofovir with the NRTI tenofovir disoproxil fumarate (TDF). The likelihood of kidney damage is reduced when using the formulation of tenofovir alafenamide [20].

5.2c. Brincidofovir

Another medication to consider is brincidofovir, which offers enhanced renal safety compared to cidofovir, with its primary side effects related to the gastrointestinal system [20,23]. The likelihood of drug interactions between brincidofovir and NRTI, NNRTI, INI, maraviroc, and lenacapavir is quite low. Nonetheless, caution is necessary when co-administering brincidofovir with TDF and ZDV, as it is advisable to monitor for potential kidney and blood disorders [20,21].

6. Prophylaxis and Other Preventive Methods

6.1. Vaccine Prophylaxis

6.1a. Pre-Exposure Prophylaxis (PrEP)

There are two FDA-approved vaccines currently available for pre-exposure prophylaxis to protect individuals at risk of orthopoxvirus infections: ACAM2000 and JYNNEOS [24]. JYNNEOS is a live virus vaccine utilizing non-replicating modified vaccinia Ankara (MVA) and is licensed for the prevention of smallpox and monkeypox in adults aged 18 years or older. In contrast, ACAM2000, a replication-competent live vaccinia virus, is licensed for the prevention of smallpox [21,24]. JYNNEOS presents fewer contraindications, eliminates the risk of inadvertent inoculation and auto-inoculation, and is associated with fewer serious adverse events when compared to ACAM2000 [24]. Importantly, JYNNEOS vaccination is considered safe

for PLWH [21]. As ACAM2000 contains a modified vaccinia virus capable of replication, it poses a risk of severe localized or systemic complications, particularly in individuals with compromised immune systems, such as PLWH. Therefore, in accordance with current ACIP recommendations, the administration of ACAM2000 in PLWH is contraindicated [24].

6.1b. Post-Exposure Prophylaxis (PEP)

For post-exposure prophylaxis (PEP), vaccination against monkeypox should be considered for immunocompromised individuals, including those with HIV infection. While the use of smallpox vaccines for PEP during monkeypox outbreaks has not been extensively studied, it has been demonstrated that early vaccination (within four days of exposure) may be effective in preventing monkeypox. Even if administered later (five days or more after exposure), it might still reduce the severity of the disease, especially in severely immunocompromised individuals with a known high-risk exposure. In cases where the risk of severe monkeypox is significant, the benefits of vaccination even more than 14 days after exposure might outweigh the potential risks [25].

6.2. Other Preventive Measures

When dealing with confirmed or suspected cases of monkeypox, especially in individuals with advanced immunosuppression, alternative post-exposure prophylaxis options including tecovirimat and vaccinia immune globulin intravenous (VIGIV) can be considered. Nevertheless, it is crucial to emphasize that the effectiveness of these medications in monkeypox post-exposure prophylaxis has not been definitively established [21].

7. Summary

Monkeypox is characterized by the presence of skin lesions, often in the genital region, accompanied by symptoms such as fever, lymphadenopathy, skin ulcers, and pharyngitis. Non-specific prodromal symptoms are observed before the rash becomes apparent. The impact of HIV on monkeypox manifestations varies depending on the severity of immunosuppression caused by HIV infection. Individuals with a high CD4+ cell count exhibit clinical features similar to those without HIV infection, while those with AIDS can experience severe monkeypox manifestations. Notable differences include a higher prevalence of skin rash, proctitis, diarrhea, tenesmus, rectal bleeding, and purulent or bloody stools.

Hospitalization rates for MPOX patients are generally low, with less than 10 percent requiring hospital admission due to the severity of their illness. Fatality rates are also low. Reasons for hospitalization include the need for treatment of soft-tissue superinfections, pharyngitis and difficulties in oral fluid intake, as well as eye lesions, acute kidney injury, myocarditis, and pain management.

Effective management of HIV with ART is essential. Tecovirimat is the treatment of choice for MPOX, and cidofovir and brincidofovir serve as alternative options. The simultaneous use of tecovirimat and ART is generally well-tolerated, with minimal anticipated drug interactions.

For preventive measures, two vaccines, ACAM2000 and JYNNEOS, are recommended for pre-exposure prophylaxis against orthopoxviral infections. Post-exposure prophylaxis (PEP) with monkeypox vaccination should be considered for immunocompromised individuals, including those with HIV. Notably, ACAM2000 is contraindicated for PLWH, while JYNNEOS vaccination is considered safe and effective in this population.

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The authors declare no conflict of interest.

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