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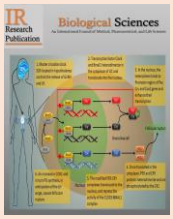

Hydroxychloroquine and Azithromycin in Treating Emerging Viral Infections: Efficacy, Safety, and Mechanisms in Monkeypox and Influenza A (H5N1)

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ABSTRACT

Due to their antiviral and immunomodulatory properties, hydroxychloroquine and azithromycin have gained attention as potential treatments for emerging viral infections, including monkeypox and Influenza A. Hydroxychloroquine has demonstrated in vitro efficacy in inhibiting viral replication, while azithromycin is primarily used as an antibiotic but has shown some promise in modulating inflammation and treating secondary infections. However, clinical evidence supporting the use of these drugs for emerging infections remains inconclusive, with existing studies often yielding mixed results. The lack of large-scale randomized controlled trials (RCTs) and long-term safety data further complicates their use in treating novel viral pathogens. This review highlights the need for comprehensive clinical trials to assess the efficacy, safety, and mechanisms of action of hydroxychloroquine and azithromycin in the treatment of emerging infections. Furthermore, it emphasizes the importance of long-term monitoring to better understand the adverse effects and the potential benefits of these drugs, particularly in high-risk populations. Future research should focus on combination therapy studies and comparative trials with other antiviral treatments to establish more effective therapeutic strategies for new viral threats.

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Introduction

Emerging viral infections have been a significant global health concern in recent years, with new pathogens posing risks to public health and economic stability. Among these, Monkeypox and Influenza A (H5N1) have attracted increasing attention due to their zoonotic origins and the potential for human-to-human transmission. Monkeypox, a disease caused by the monkeypox

virus (MPXV), was initially discovered in 1958 and largely confined to certain parts of Central and West Africa. However, in 2022, the World Health Organization (WHO) declared the outbreak a public health emergency, as it spread to non-endemic countries across multiple continents [1]. The disease caused by a member of the Orthopoxvirus genus, manifests in symptoms similar to smallpox, such as fever, rash, and swollen lymph nodes. Although monkeypox generally has a lower mortality rate than smallpox, its rapid spread and potential to cause severe illness in immunocompromised individuals have raised concerns about its impact on global health [2]. Given its recent rise in cases, particularly in previously unaffected regions, research into effective treatments and prevention strategies has become critical.

Influenza A (H5N1), an avian influenza virus, has been a recurring threat since it emerged in 1997. While primarily affecting birds, H5N1 has caused severe illness in humans and has a higher fatality rate compared to seasonal influenza [3]. H5N1 has the potential for mutation and reassortment, which could increase transmissibility between humans and lead to a pandemic [4]. The rapid mutation of the virus makes it a significant focus for surveillance and vaccine development. Although H5N1 outbreaks in humans have been relatively rare, its capacity for high mortality rates, particularly in vulnerable populations, necessitates ongoing research into effective treatments and preventative measures. Both Monkeypox and Influenza A (H5N1) represent emerging infectious diseases that require urgent attention, especially in terms of understanding their treatment options and the potential role of existing drugs.

In the face of emerging viral diseases like monkeypox and influenza A (H5N1), hydroxychloroquine and azithromycin have been widely discussed as potential therapeutic agents. These two drugs, primarily used for treating malaria and bacterial infections, respectively, have gained attention due to their reported antiviral properties, although their use remains controversial. Hydroxychloroquine is an antimalarial drug also used in the treatment of autoimmune diseases like lupus and rheumatoid arthritis. During the COVID-19 pandemic, hydroxychloroquine was touted as a potential treatment for the novel coronavirus due to its ability to interfere with the viral entry into cells and its immunomodulatory effects [5]. Despite early enthusiasm, clinical trials have provided mixed results, leading to debates over its efficacy and safety in treating viral infections [6]. Given its broad-spectrum effects, understanding the potential of hydroxychloroquine in treating emerging viral infections like monkeypox and influenza A (H5N1) is important, especially for repurposing existing drugs in the fight against new pathogens.

Azithromycin, an antibiotic known for its broad-spectrum activity against various bacterial pathogens, has also been considered for its antiviral effects, particularly in managing secondary bacterial infections in viral diseases. Azithromycin has shown some in vitro activity against respiratory viruses like influenza and Zika [7]. In combination with other drugs, azithromycin has been suggested to enhance the therapeutic efficacy in viral diseases by modulating the immune response [8]. Given its use in treating bacterial co-infections, it has been hypothesized that azithromycin could play a role in preventing bacterial complications in individuals infected with viruses like monkeypox or H5N1.

Despite their widespread use in certain contexts, the application of hydroxychloroquine and azithromycin in treating emerging viral infections is not well-established. The lack of well-controlled studies, particularly for their use in monkeypox and H5N1, constitutes a significant research gap. Evaluating these drugs in the context of emerging diseases is critical, especially when new treatments are in high demand and the development of vaccines or specific antiviral drugs may take time. Research into the mechanisms of action, efficacy, and safety profiles of these drugs in the treatment of monkeypox and influenza A (H5N1) will help guide clinical decision-making and may lead to new therapeutic strategies for managing emerging viral diseases. These evaluations will be crucial to determine whether repurposing existing treatments can provide a quick solution to global health challenges posed by emerging infections.

Mechanisms of Action of Hydroxychloroquine and Azithromycin

Hydroxychloroquine's role in viral replication and immunomodulation

Hydroxychloroquine (HCQ), a synthetic derivative of chloroquine, is primarily known for its use in treating malaria and autoimmune diseases like lupus and rheumatoid arthritis. Its role in viral replication and immunomodulation has gained significant attention, particularly for its potential effects on diseases such as COVID-19, monkeypox, and Influenza A (H5N1).

Inhibition of viral entry and replication

Hydroxychloroquine has been proposed to inhibit viral entry into host cells by altering the pH of endosomes and lysosomes, which are crucial for the fusion of the viral envelope with host cell

membranes. This mechanism has been suggested to be effective against several viruses, including SARS-CoV-2 (the virus causing COVID-19) and dengue [9]. The drug is thought to prevent the virus from utilizing the cellular machinery necessary for replication. Specifically, it can prevent the acidification of endosomes, which is required for the fusion of the viral envelope with host cell membranes [10]. This action may inhibit monkeypox and H5N1 viruses, but limited studies exist regarding its effect on these pathogens.

Modulation of immune responses

Hydroxychloroquine also modulates immune responses by inhibiting Toll-like receptors (TLRs) and reducing cytokine release, which can dampen excessive inflammation associated with viral infections. This immunomodulatory effect has made it an attractive candidate for treating autoimmune diseases and potentially severe viral infections where immune dysregulation is prominent, such as in COVID-19 [11]. Hydroxychloroquine can also reduce T-cell activation and alter cytokine profiles, helping to control the exaggerated immune responses observed in some viral infections.

Clinical and experimental findings

Despite its potential mechanisms, the clinical evidence for hydroxychloroquine's effectiveness in viral infections, especially in diseases like monkeypox and H5N1, remains mixed. For example, while COVID-19 studies showed some in vitro promise, large-scale clinical trials have failed to confirm significant therapeutic benefits [12]. Moreover, concerns regarding toxicity and adverse effects, particularly in high doses, have limited its widespread use in viral infections [13].

Azithromycin's antibacterial effects and potential in secondary infections

Azithromycin, a macrolide antibiotic, is widely used for treating a variety of bacterial infections, including respiratory tract infections, skin infections, and sexually transmitted diseases. Its mechanism of action is primarily antibacterial; however, it also has some antiviral and immunomodulatory properties that make it of interest in the context of secondary bacterial infections following viral diseases like monkeypox, influenza A (H5N1), and COVID-19.

Antibacterial mechanism

Azithromycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit and blocking the elongation of the polypeptide chain. This effect halts bacterial growth and replication. Azithromycin is effective against a wide range of pathogens, including Gram-positive and Gram-negative bacteria, making it an essential antibiotic for treating infections that may complicate viral diseases [14]. Given its broad spectrum, azithromycin has been explored for potential use in secondary bacterial infections in patients infected with viral pathogens like H5N1 and monkeypox, which can sometimes lead to pneumonia or other bacterial complications.

Antiviral properties

While primarily used as an antibiotic, azithromycin has shown some antiviral activity in preclinical studies. Research has demonstrated that it may have effects against respiratory viruses, such as influenza and Zika, by modulating host immune responses and reducing viral replication. It is thought to reduce viral cellular entry and replication by interfering with the host's cellular machinery [15]. These antiviral properties may be particularly useful in managing viral infections when secondary bacterial infections arise, complicating the clinical course.

Immunomodulation

In addition to its antibacterial activity, azithromycin has been shown to modulate immune responses. It can enhance phagocytic activity and cytokine production, improving the body's ability to fight off infections. Studies have suggested that azithromycin may enhance the innate immune response, particularly in viral infections like influenza [16]. This immunomodulatory effect is believed to be one reason azithromycin may be useful in patients suffering from viral infections, such as monkeypox, where immune system dysregulation can exacerbate disease severity.

Clinical use in viral infections

Although azithromycin has been widely prescribed for its antibacterial properties, its use in viral infections like monkeypox and H5N1 is primarily aimed at preventing or treating secondary bacterial infections, which are common in patients with compromised immune systems or those with viral pneumonia. Azithromycin is sometimes combined with other antiviral or antibacterial drugs to provide broader coverage, particularly in severe cases where secondary infections may lead to complications like sepsis or pneumonia [17].

Challenges and research gaps

Despite its potential benefits, the use of azithromycin in the treatment of emerging viral infections such as monkeypox and H5N1 remains poorly studied. There is a lack of robust clinical data

regarding its effectiveness in treating the primary viral infection. Moreover, the potential for antibiotic resistance and adverse effects requires careful consideration when prescribing azithromycin for viral diseases. Research is needed to explore the full extent of azithromycin's antiviral properties and its role in managing secondary bacterial infections in the context of emerging viral pathogens.

Efficacy of Hydroxychloroquine and Azithromycin in Viral Infections

Clinical outcomes in previous viral infections: malaria, SARS, and COVID-19

Hydroxychloroquine (HCQ) and azithromycin have been studied in various viral infections, though their clinical outcomes vary across different pathogens and treatment settings.

Hydroxychloroquine in malaria

Hydroxychloroquine is well-established as an effective treatment for malaria, specifically Plasmodium falciparum malaria. The drug works by interfering with the parasite's ability to digest hemoglobin, thereby preventing its growth. Moreso, it has immunomodulatory effects, which have been beneficial in diseases like lupus and rheumatoid arthritis. However, its role in malaria has not been challenged, as the drug has been a first-line treatment for malaria for many years. Its therapeutic efficacy in malaria has been well-established in randomized controlled trials [18].

Hydroxychloroquine in SARS

In the case of SARS-CoV (Severe Acute Respiratory Syndrome), hydroxychloroquine was tested for its potential to inhibit the virus. Early studies indicated that HCQ could reduce viral replication in vitro, but clinical trials provided mixed results. A 2005 study by [19] found that chloroquine (the parent compound) had some inhibitory effects on SARS-CoV, but these effects did not translate well into clinical settings, where other therapies were more successful [19]. Nevertheless, the drug was used during the SARS outbreak, and while it did not show a significant impact on reducing viral load or improving outcomes, it remained part of treatment protocols due to its safety profile and potential benefits.

Hydroxychloroquine and azithromycin in COVID-19

The use of hydroxychloroquine as a treatment for COVID-19 received considerable attention during the early stages of the pandemic. Studies showed some in vitro activity against SARS-CoV-2, suggesting it might block the virus's ability to enter cells by increasing the pH within the host cell's endosomes. When combined with azithromycin, a macrolide antibiotic, it was theorized that the combination could both reduce viral load and prevent secondary bacterial infections [20]. However, multiple large-scale randomized controlled trials (RCTs), including those by the World Health Organization (WHO) and the U.S. National Institutes of Health (NIH), have shown no significant benefit of HCQ or the HCQ-azithromycin combination for COVID-19 patients [21]. The recovery trial, in particular, indicated that hydroxychloroquine did not reduce mortality or improve recovery in hospitalized patients [22].

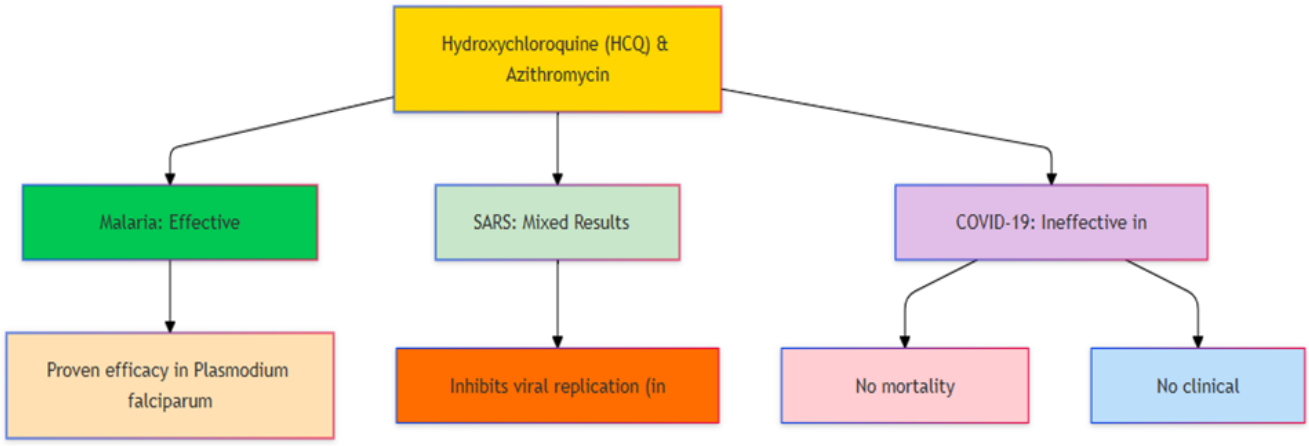

Figure1. Clinical outcomes of hydroxychloroquine and azithromycin in viral infections.

Azithromycin, while primarily an antibiotic, also has antiviral properties. During the COVID-19 pandemic, it was combined with hydroxychloroquine in an attempt to treat secondary bacterial infections and modulate immune responses. Some early studies indicated

azithromycin could have a synergistic effect with HCQ, especially in preventing bacterial pneumonia. However, subsequent clinical studies have been less supportive of its efficacy, particularly in preventing secondary infections [23]. Figure 1 below illustrates the clinical outcomes of Hydroxychloroquine (HCQ) and Azithromycin in three major viral infections: Malaria, SARS, and COVID-19. It highlights that HCQ is effective for treating malaria, showed mixed results for SARS, and was largely ineffective in clinical trials for COVID-19.

Evaluating current evidence in monkeypox and influenza A

Hydroxychloroquine and azithromycin in monkeypox

As of now, there is limited evidence supporting the use of hydroxychloroquine or azithromycin in treating monkeypox, a zoonotic viral infection caused by the monkeypox virus (MPXV). The virus primarily spreads through direct contact with infected animals or humans, causing symptoms similar to smallpox, including fever, rash, and swollen lymph nodes. No large-scale clinical trials are investigating the use of HCQ or azithromycin specifically for MPXV infections, and the standard treatment involves supportive care. Hydroxychloroquine's immunomodulatory effects might theoretically offer some benefit in modulating immune responses, but its use in monkeypox has not been proven effective. The role of azithromycin in secondary bacterial infections during monkeypox outbreaks could be significant, as secondary bacterial pneumonia or skin infections are common. However, these would require careful monitoring, as the efficacy of azithromycin would only apply to bacterial co-infections rather than directly impacting the monkeypox virus itself. Research gaps exist in exploring the full scope of using HCQ and azithromycin in the context of monkeypox.

Hydroxychloroquine and azithromycin in influenza A

Both hydroxychloroquine and azithromycin have been tested in the context of Influenza A (H5N1) infections, which cause severe respiratory illness in humans. In vitro studies on H5N1 suggest that hydroxychloroquine may have some inhibitory effects on the virus's replication by altering cellular processes involved in viral entry. However, its clinical efficacy in Influenza A has been inconsistent. While some small-scale studies showed potential benefits, larger trials did not show significant improvements in patient outcomes [24].

Azithromycin has been shown to have a modulatory effect on immune responses during viral infections. In influenza patients, azithromycin may help by modulating inflammatory responses and preventing secondary bacterial infections, such as pneumonia. However, there is still insufficient evidence to recommend azithromycin as a primary treatment for Influenza A infections [25]. Despite these promising in vitro findings, clinical studies have not provided sufficient evidence to support the widespread use of HCQ and azithromycin for treating Influenza A (H5N1). Research gaps persist in determining how these drugs might be combined with antiviral treatments to improve clinical outcomes.

Safety Profiles and Adverse Effects of Hydroxychloroquine and Azithromycin

Common and severe adverse effects of hydroxychloroquine and azithromycin

Hydroxychloroquine (HCQ) and azithromycin are commonly used drugs, with established safety profiles in various therapeutic settings. However, both medications have their own sets of adverse effects, which can be more pronounced when used outside of approved indications or in combination.

Hydroxychloroquine (HCQ) adverse effects

Hydroxychloroquine is primarily used for malaria, systemic lupus erythematosus (SLE), and rheumatoid arthritis. The common adverse effects associated with HCQ include gastrointestinal symptoms like nausea, vomiting, and diarrhea [26]. Skin reactions such as rashes, and visual disturbances, including blurred vision and retinal toxicity, are also common, especially with prolonged use. The most concerning severe adverse effect of HCQ is retinopathy, which can lead to permanent vision loss if not detected early. The risk increases with prolonged use, typically at doses greater than 5 mg/kg/day [27]. Cardiovascular effects are another serious concern, with QT interval prolongation being observed in some patients. This can predispose individuals to arrhythmias, particularly in those with preexisting heart conditions or those taking drugs that interact with HCQ [28]. CNS effects like headaches, dizziness, and confusion can also occur, and these symptoms are more common in elderly patients or those with renal impairment.

Azithromycin adverse effects

Azithromycin is an antibiotic primarily used for treating bacterial infections such as pneumonia, sinusitis, and chlamydia. Its common adverse effects are generally mild and include gastrointestinal upset (nausea, diarrhea, abdominal pain) and headaches [29]. Skin reactions, including rash and

pruritus, are also common but are typically transient. More severe adverse effects are less frequent but include QT prolongation, which can lead to life-threatening arrhythmias, particularly in individuals with underlying cardiovascular disease. Hepatic toxicity, though rare, has been reported, and azithromycin can cause liver enzyme elevations, which may progress to acute liver failure in some patients [30]. Ototoxicity, particularly high-dose therapy, is a risk, manifesting as tinnitus or hearing loss. The potential for drug interactions is another concern, especially with medications that affect the cytochrome P450 enzyme system. Azithromycin can interact with warfarin, increasing the risk of bleeding, and with statins, raising the risk of muscle toxicity.

Risk Assessment in High-Risk Populations

Both hydroxychloroquine and azithromycin require careful risk assessment, especially in high-risk populations such as the elderly, those with preexisting cardiac conditions, renal impairments, or those on multiple medications.

Hydroxychloroquine and high-risk populations

Elderly patients

The elderly are more susceptible to the adverse effects of HCQ, particularly cardiovascular and neurological side effects [31]. The risk of QT prolongation and retinopathy is elevated, and drug interactions with commonly prescribed medications in this demographic can exacerbate these effects.

Patients with Renal or Hepatic Impairment

Hydroxychloroquine is primarily excreted by the kidneys, and renal dysfunction can reduce its clearance, increasing the risk of toxicity [32]. In patients with hepatic impairment, although HCQ metabolism is not significantly altered, caution is still advised due to potential hepatotoxicity and drug interactions.

Patients with cardiovascular disease

Hydroxychloroquine can cause QT interval prolongation, which may lead to arrhythmias, especially in those with congestive heart failure or coronary artery disease. Combining HCQ with other QT-prolonging drugs (e.g., azithromycin) should be done with caution [33].

Azithromycin and high-risk populations

Patients with cardiovascular disease

The risk of QT prolongation associated with azithromycin is a significant concern for patients with underlying cardiac conditions. This risk is compounded when azithromycin is used in combination with other medications that can prolong the QT interval, such as hydroxychloroquine. Special caution is required for patients with arrhythmias, heart failure, or electrolyte disturbances [34].

Elderly Patients

Older adults are at an increased risk of side effects from azithromycin, particularly cardiovascular effects. The elderly population is also more likely to have comorbidities such as diabetes, renal dysfunction, and hepatic disease, which can exacerbate the side effects of azithromycin. Moreover, polypharmacy in this group increases the likelihood of drug-drug interactions that could lead to serious adverse events.

Patients with Hepatic or Renal Impairment

Azithromycin is mainly excreted in the bile, and while it does not require dosage adjustment in mild-to-moderate hepatic impairment, it should be used with caution in patients with severe liver dysfunction. Renal impairment does not significantly affect the pharmacokinetics of azithromycin, but caution is still advised, particularly in those with severe renal failure [35].

Both hydroxychloroquine and azithromycin should be used with caution in these high-risk populations, and careful monitoring for adverse events is essential to minimize the potential for severe side effects. Regular electrocardiogram (ECG) monitoring, liver function tests, and renal function assessments are recommended in patients receiving these drugs, especially in those with comorbid conditions.

Comparative Analysis: Hydroxychloroquine and Azithromycin vs. Other Antiviral Therapies

Existing antiviral treatments for monkeypox and influenza A (H5N1)

Monkeypox and Influenza A (H5N1) are viral infections that have been of significant concern due to their ability to cause outbreaks and potential for widespread transmission. Current antiviral therapies for these infections are quite limited, and much of the treatment involves supportive care, although some antiviral agents have been explored.

Monkeypox

The treatment for monkeypox remains primarily supportive, as there are no FDA-approved specific antiviral therapies for the disease. However, some antivirals have been used off-label or investigated for efficacy, particularly tecovirimat (TPOXX), which was approved for smallpox and has shown promise in treating monkeypox [36]. Cidofovir and brincidofovir are also considered potential treatments due to their antiviral properties against poxviruses, though they are used less frequently due to concerns over side effects [37]. In the context of the vaccinia virus, a smallpox-related virus, these antivirals may offer efficacy against monkeypox as well. However, the clinical data supporting their use specifically for monkeypox is still evolving.

Influenza A (H5N1)

Influenza A (H5N1), or avian influenza, is another virus with limited therapeutic options. The mainstay antiviral treatments for H5N1 include neuraminidase inhibitors such as oseltamivir (Tamiflu) and zanamivir, which have been shown to reduce the severity and duration of influenza symptoms when administered early in the infection [38]. Other options include amantadine and rimantadine, which inhibit viral replication by blocking the M2 ion channel. However, resistance to amantadine has emerged in H5N1 strains, limiting its use. In addition, favipiravir, an antiviral that inhibits RNA-dependent RNA polymerase, has been investigated for treating severe cases of H5N1 infection and has shown some promise in clinical trials [39].

These treatments, however, have limitations in terms of timing, efficacy, and resistance development, which highlights the need for alternative therapies.

Comparison of Hydroxychloroquine and Azithromycin with Novel Treatments

Hydroxychloroquine and azithromycin have been considered potential treatments for viral infections due to their antiviral and immunomodulatory effects, but their effectiveness, especially against monkeypox and H5N1, has been controversial.

Hydroxychloroquine and azithromycin for viral infections

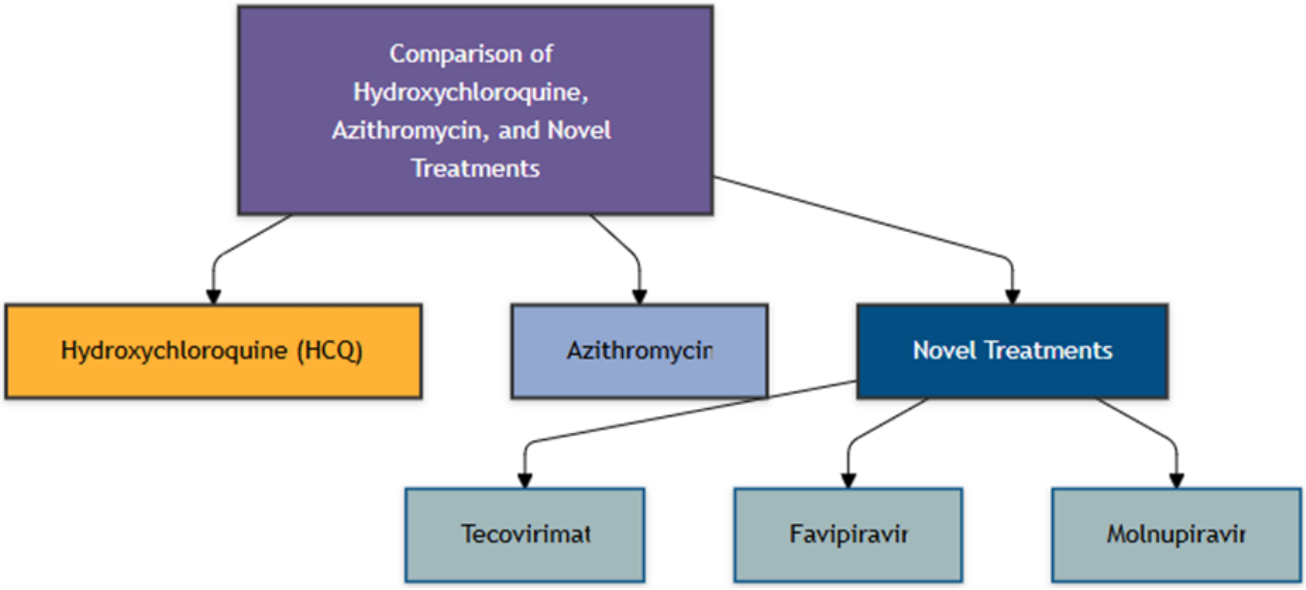

Figure 2. Comparison of hydroxychloroquine, azithromycin, and novel treatments for viral infections

Figure 2 above provides a comparative overview of Hydroxychloroquine (HCQ), Azithromycin, and novel antiviral treatments like Tecovirimat, Favipiravir, and Molnupiravir. While HCQ and Azithromycin have been used in viral infections such as COVID-19 and influenza, their effectiveness remains controversial. Novel treatments such as Tecovirimat, Favipiravir, and Molnupiravir are emerging as targeted therapies with promising results in managing infections like monkeypox and H5N1, highlighting their potential over traditional treatments. However, while hydroxychloroquine and azithromycin have shown some potential in treating viral infections, especially through their immunomodulatory and antibacterial properties, they are less effective and lack specific antiviral mechanisms when compared to newer, more targeted antivirals like tecovirimat for monkeypox or favipiravir and molnupiravir for H5N1. These newer drugs, with more specific mechanisms of action against the viruses involved, hold greater promise in managing these infections.

- Hydroxychloroquine has been studied for its antiviral effects in various contexts, particularly during the COVID-19 pandemic. It was proposed as a potential treatment for several viral infections due to its ability to alter the lysosomal pH, which could interfere with viral entry and replication. However, its efficacy in COVID-19 and other viral diseases has been challenged by clinical trials that failed to show significant benefits [40]. In the context of H5N1, while it has been suggested that HCQ may have some efficacy against influenza viruses due to its broad-spectrum antiviral properties, there is insufficient clinical evidence supporting its use as a primary treatment for H5N1 infection [41].
- Azithromycin has also been studied for its potential antiviral properties, particularly in COVID-19 and respiratory tract infections. Azithromycin has shown some anti-inflammatory effects and may assist in reducing secondary bacterial infections. However, its role in managing viral infections like monkeypox or H5N1 is less well-established. While azithromycin can help manage secondary bacterial infections in viral diseases, its use as a primary antiviral therapy for these infections remains unproven [42].

Novel treatments

Tecovirimat (TPOXX)

For monkeypox, tecovirimat is one of the most promising antiviral agents. It inhibits the VP37 protein, which is involved in the maturation of poxviruses, thereby preventing viral replication and spread [43]. This antiviral has shown efficacy in treating monkeypox in both animal models and humans, making it a more targeted approach compared to HCQ or azithromycin.

Favipiravir

As mentioned, favipiravir has been used to treat H5N1 infections and other RNA viruses, such as Ebola and COVID-19. Favipiravir inhibits the RNA-dependent RNA polymerase, which is essential for the replication of many RNA viruses, including influenza and monkeypox [44]. Early trials suggest that favipiravir may reduce the viral load and clinical symptoms of H5N1 infection, offering a promising alternative to HCQ and azithromycin.

Molnupiravir

Another novel antiviral that has been approved for use in treating COVID-19 and is under investigation for its efficacy against other viral infections, including influenza and monkeypox. It works by introducing errors into the viral RNA during replication, causing a decrease in viral replication. While its application to H5N1 and monkeypox remains experimental, its mechanism makes it a potential candidate for future treatments [45].

Research Gaps and Future Directions

Absence of randomized controlled trials for hydroxychloroquine and azithromycin in emerging infections

Significant research gap in the evaluation of hydroxychloroquine (HCQ) and azithromycin for the treatment of emerging viral infections lies in the lack of randomized controlled trials (RCTs). While both drugs have been extensively studied in the context of diseases like COVID-19, studies involving monkeypox or Influenza A (H5N1) are scarce. RCTs are the gold standard for assessing the efficacy and safety of treatments, as they reduce bias and allow for clear conclusions about causal relationships. The COVID-19 pandemic witnessed several small, non-randomized studies, which led to conflicting findings regarding the benefits of HCQ and azithromycin [46]. However, these trials were criticized for design flaws, including small sample sizes, lack of control groups, and inconsistent dosages [47]. Thus, future studies should prioritize well-powered, multicenter RCTs focused on emerging viruses to robustly establish whether these drugs are effective in treating other novel viral infections.

Lack of long-term efficacy and safety data for new viral pathogens

Another gap in research is the long-term efficacy and safety data for new viral pathogens like monkeypox and Influenza A (H5N1). While initial trials of HCQ and azithromycin have provided some insights, their long-term impact remains largely unexamined. In particular, viral diseases that emerge rapidly often receive urgent attention, but longitudinal studies that track outcomes over extended periods are often neglected. Chronic side effects or drug resistance may become significant only after extended use, which has been observed in the case of antibiotics like azithromycin [48]. Moreso, HCQ has been associated with prolonged QT interval prolongation and other cardiac issues when used for extended periods [49]. To improve patient outcomes, long-term studies assessing the safety and effectiveness of HCQ and azithromycin are needed, particularly in high-risk populations who might be treated with these drugs for prolonged periods.

Insufficient data on mechanisms of action in monkeypox and influenza A

Despite their widespread use in other diseases, there is a lack of understanding about the mechanisms of action of hydroxychloroquine and azithromycin in the context of emerging viruses like monkeypox and Influenza A (H5N1). Hydroxychloroquine's antiviral properties are thought to involve its ability to alter lysosomal pH and inhibit viral entry into host cells, but how this mechanism works in poxviruses like monkeypox or influenza viruses remains unclear. Similarly, azithromycin is believed to reduce inflammatory responses and prevent secondary bacterial infections, yet its direct action against viruses such as monkeypox or H5N1 is not fully elucidated. Molecular studies are necessary to explore the direct antiviral effects of these drugs and identify any synergistic interactions with the immune system in fighting these infections. There is also a need to better understand how these drugs interact with other viral replication pathways and immune responses in the context of new viruses [50].

Need for comparative studies between hydroxychloroquine, azithromycin, and other therapeutics

Currently, few studies compare the efficacy of HCQ and azithromycin with that of novel antiviral therapies for monkeypox and Influenza A (H5N1). As antiviral options evolve, it is essential to evaluate these older drugs for newer treatments like tecovirimat for monkeypox and favipiravir or molnupiravir for influenza [51]. While hydroxychloroquine and azithromycin have been repurposed for a wide range of viral diseases, their comparative effectiveness remains poorly documented. For example, tecovirimat, a promising antiviral for monkeypox, works by inhibiting viral maturation, offering a different mechanism of action than HCQ [52]. In Influenza A (H5N1), oseltamivir and zanamivir are standard treatments, but newer antivirals like favipiravir and molnupiravir may offer benefits in terms of reducing viral replication and viral load. Comparative studies that incorporate both traditional and novel antivirals will help inform the best therapeutic approaches for emerging viral infections.

Proposed future research: RCTs, combination therapy studies, and mechanistic investigations

Future research directions should include several key areas to address the current gaps:

RCTs

Large, multicenter randomized controlled trials are necessary to robustly evaluate the effectiveness of hydroxychloroquine and azithromycin in emerging viral infections. These trials should aim to establish optimal dosages, treatment durations, and clinical outcomes across various patient populations [53]. Moreso, studies should examine both monotherapy and combination therapy approaches to determine the most effective treatments.

Combination therapy studies

Given the broad spectrum of activity of hydroxychloroquine and azithromycin, exploring their use in combination with other antiviral or immunomodulatory agents may offer synergistic effects. For example, combining azithromycin with favipiravir or molnupiravir for influenza could provide a multi-target approach to inhibit both viral replication and inflammatory responses [54]. Similarly, pairing hydroxychloroquine with tecovirimat for monkeypox may enhance antiviral efficacy.

Mechanistic investigations

To better understand the antiviral mechanisms of hydroxychloroquine and azithromycin, future studies should focus on in vitro and in vivo models of emerging viruses. Investigating how these drugs interact with viral replication cycles, immune responses, and host cell pathways will be crucial for optimizing their use in treatment. Furthermore, understanding their impact on viral mutation rates and the potential for drug resistance is critical for ensuring long-term treatment efficacy. By addressing these gaps, future research can provide more comprehensive and targeted therapeutic strategies for the treatment of monkeypox, Influenza A (H5N1), and other emerging viral infections, thereby improving patient outcomes and informing public health responses.

Conclusion

Hydroxychloroquine and azithromycin have shown promise in treating various viral infections, including emerging ones like monkeypox and Influenza A. However, despite their in vitro antiviral properties, their clinical effectiveness for these novel pathogens remains uncertain and inconclusive. Hydroxychloroquine is believed to inhibit viral replication by altering cellular processes such as lysosomal pH and interfering with viral entry, but its success in clinical settings is inconsistent. Azithromycin, an antibiotic, plays a critical role in treating bacterial co-infections and modulating inflammation, but its antiviral potential, especially for diseases like monkeypox and Influenza A, is still

being studied. The evidence supporting these drugs' use for newer viral diseases remains limited, and existing studies often yield mixed results. The absence of large-scale randomized controlled trials (RCTs) and comprehensive long-term data further complicates the assessment of hydroxychloroquine and azithromycin's clinical efficacy for treating emerging infections. Although some studies suggest that these drugs, particularly when combined, may have a synergistic effect, there is not enough robust evidence to confirm their widespread use over more established or newer antiviral treatments. Moreso, their safety profiles, especially concerning long-term use and in vulnerable populations, remain largely underexplored. The potential for adverse effects, including cardiac complications, must be carefully considered, particularly for high-risk patients. Future research should prioritize well-designed, large-scale clinical trials, including randomized controlled trials and combination therapy studies, to evaluate the therapeutic value of hydroxychloroquine and azithromycin for emerging viral infections. These trials must include long-term follow-up to assess the efficacy and safety of these drugs in different patient populations. Further investigations into their mechanisms of action, individually and in combination, will be essential to understand how they can best treat novel viruses. Such efforts will provide critical insights to guide future treatment protocols and help optimize responses to new viral threats.

Contribution of authors

- Mustapha Abdulsalam conceptualized the study, with a particular focus on the mechanisms of action and efficacy of Hydroxychloroquine and Azithromycin in treating emerging viral infections, including Monkeypox and Influenza A (H5N1). He was responsible for drafting and revising key sections on safety profiles, efficacy comparisons, and the analysis of clinical outcomes across various viral infections.
- Musa Ojeba Innocent contributed to the comparative analysis between Hydroxychloroquine, Azithromycin, and novel antiviral therapies. His insights into the clinical outcomes and potential treatment strategies for Monkeypox and Influenza A were invaluable in shaping the discussion on future research directions.
- Miracle Uwa Livinus explored the role of Hydroxychloroquine and Azithromycin in secondary bacterial infections, specifically their potential benefits in managing co-infections in viral diseases. She provided essential input into the discussion on therapeutic strategies for controlling emerging viral infections.
- Fatimoh Abdulsalam Danjuma reviewed the safety profiles of Hydroxychloroquine and Azithromycin, particularly focusing on their adverse effects in high-risk populations. She contributed significantly to the sections on risk assessment and the identification of groups most vulnerable to the adverse impacts of these drugs.
- Idowu Afeez Temitope investigated the role of Hydroxychloroquine and Azithromycin in high-risk populations. His contributions helped identify the key safety concerns for vulnerable groups and highlighted the need for tailored therapeutic approaches in such populations.
- Ishola Jonathan Adekunle evaluated the potential for new antiviral therapies and highlighted research gaps related to the long-term efficacy and safety of Hydroxychloroquine and Azithromycin. His input on the need for randomized controlled trials (RCTs) and future research directions was essential in shaping the recommendations for novel treatments.

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Conflict of Interest

The authors declare no conflicts of interest.

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Data Availability Statements

Not Applicable

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