UJEMI PERSPECTIVES

# Biological and societal impacts of combination antiviral therapy for SARS-CoV-2 variants of concern

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**SUMMARY** The development of vaccines targeting SARS-CoV-2 has been heavily studied since the start of COVID-19 and its declaration by WHO as a pandemic in March of 2020. However, with the emerging variants of concern (VoCs), such as Omicron and Delta, research into antiviral therapy in addition to vaccines is essential to help combat current and future VoCs. Recent studies have shown that multidrug therapy combining a variety of antivirals targeting different aspects of the SARS-CoV-2 lifecycle could be more effective at suppressing the virus, and could potentially reduce the risk of developing viral resistance. However, with these benefits also come concerns surrounding the feasibility and safety of administering a combination of drugs. This article will discuss the current state of knowledge pertaining to combination antiviral therapy against SARS-CoV-2 to determine the benefits and disadvantages from a health and molecular biology perspective. Additionally, this article will look into the societal perceptions and ramifications of antivirals against SARS-CoV-2, and whether there is less hesitancy in taking antivirals as compared to getting vaccinated. With 2 million unvaccinated young children in Canada, as well as patients suffering with various immunological disorders, it is even more important to explore different options of protection against SARS-CoV-2 for those who are unable to get vaccinated. When designing these therapies, it will be essential to consider the social accessibility of the drug in addition to its biological effectiveness. In an increasingly globalized world, interdisciplinary work will be critical to having a more complete understanding of an area of research, particularly in the field of health and medicine. By exploring the two topics above, this article will aim to unite the social and biological perspectives on combination antiviral therapy in relation to the COVID-19 pandemic.

## INTRODUCTION

From its onset in early 2020, the global health crisis caused by the coronavirus disease 2019, or COVID-19, pandemic has claimed the lives of millions of people worldwide, and has exacerbated a host of social issues including inequality, exclusion and discrimination (1,2). From an alternative perspective, the COVID-19 pandemic has also been a period of growth across multiple disciplines, where scientists have worked alongside public health experts, policy makers, educators, and others to reduce the negative impact of the pandemic (3). Together they developed vaccines targeting COVID-19's causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), communicated the importance of the vaccine, and began its distribution in under a year. With the vaccine and the implementation of public health measures like social distancing and wearing masks, the number of new COVID-19 cases declined until the emergence of SARS-CoV-2 variants of concern (VoCs) (2).

VoCs for SARS-CoV-2 are viral copies that have acquired specific mutations in their genetic information (+ssRNA) which may have affected its transmissibility (spread), virulence (severity of the disease), and/or vaccine effectiveness (4). Mutations in VoCs are often found in key components of the SARS-CoV-2 viral structure and lifecycle. These components include the spike protein embedded in the viral envelope, which is important for host cell receptor (angiotensin converting enzyme-2, or ACE2) recognition during viral

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attachment (Figure 1a). Serine protease TMPRSS2 and cysteine protease Cathepsin L have both been identified as potential players in viral entry, through pH independent and pH dependent pathways, respectively (Figure 1b). Viral replication involves viral cysteine proteases such as papain-like protease (PLpro) and 3C-like protease (3CLpro), as well as RNA dependent RNA polymerase (RdRP) (Figure 1c). In the maturation step, it is possible that furin-like proteases cleave the spike protein at the S1-S2 cleavage site, which in turn interferes with the fusion capability of the S protein and syncytia formation (Figure 1d). These key components are important for the development of COVID-19 treatment strategies.

Antiviral therapy and monoclonal antibodies (mAb) are two examples of such therapies, and are designed to suppress SARS-CoV-2 viral replication in the body by inactivating key components of the life cycle (antivirals) or by binding to and tagging viral particles for destruction by host immune cells (mAb) (5,6). These treatments along with others can be incorporated into multidrug therapy regimens (MDT) for SARS-CoV-2, which utilizes a combination of drugs to suppress viral infections (7,8). Combination antiviral therapy (CAT) is a subset of MDT that specifically uses several antivirals in combination to combat an infection, and will be the focus for this paper (5).

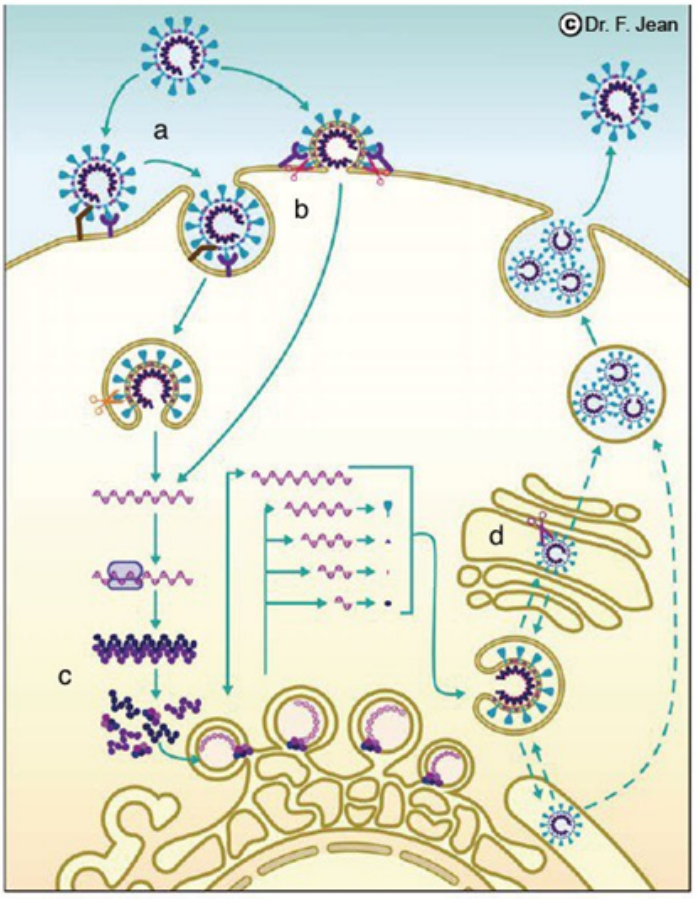


**FIG. 1 Key players in the viral life cycle of SARS-CoV-2.** a) Attachment of viral spike protein to ACE2 receptor on host cells. b) Viral entry using either serine protease TMPRSS2 and cysteine protease Cathepsin L. c) Viral replication involving PLpro, 3CLpro, and RdRP. d) Maturation step involving furin-like proteases that cleave the spike protein. Figure was used with permission from Dr. François Jean (33).

## PROPOSED RESEARCH QUESTIONS

To date, numerous studies have been published on potential antivirals for the treatment of COVID-19 (5, 9-13). From this research, the 3Clpro inhibitor PAXLOVID (nirmatrelvir and ritonavir) and RdRP inhibitor Velkury (Remdesivir) both passed clinical trials and were recently approved by Health Canada (14-15). However, with HIV and influenza virus infection, MDT and CAT have been shown to be more effective at suppressing viruses than singular antivirals, which may also be true for SARS-CoV-2 infection (16-17). It is also important from a social perspective to consider which treatments would be most effective and acceptable to the target unvaccinated population, including young children, immunocompromised individuals, and the vaccine hesitant. Therefore, with the potential for

emergence of new and harmful (highly virulent and transmissible) VoCs, and reduced vaccine efficacy, it is important to expand treatment strategies beyond singular antivirals and explore the potential of CAT against SARS-CoV-2 VoCs. This paper will address these knowledge gaps by discussing both the benefits and concerns surrounding CAT from first a biological perspective, and then from a social perspective.

## PROPOSED PROJECT NARRATIVE

**What are the benefits and risks of MDT and CAT for SARS-CoV-2 infection from a biological perspective?** CAT for COVID-19 treatment is a topic of research for SARS-CoV-2 that is beginning to be explored. VoCs have been found to carry mutations in key components of the viral life cycle in ways that allow them to bypass certain treatments and possibly evade vaccine induced immunity (18). If a harmful VoC emerges in the future, having a working CAT treatment option would be highly beneficial for several reasons. Firstly, targeting multiple key proteins in the SARS-CoV-2 viral life cycle instead of only one could be more effective at suppressing the virus (19). For example, if a mutation allows the virus to bypass a viral entry inhibitor, another inhibitor can prevent it from replicating at a later step. This effect can be strengthened by targeting multifunctional proteins such as furin and 3CLpro, as these proteins could be essential at multiple parts of the pathway. CAT could also reduce the chance of the virus developing resistance to treatment (20). With the synergy of multiple antivirals, if a virus becomes resistant to one of the antivirals, it is unlikely to pass this resistance down to viral progeny because other antivirals in the CAT treatment would prevent it from replicating. The reduced dosage of each drug in CAT could also prevent viral resistance.

Despite these benefits, concerns arise around the safety and potential side effects of CAT, such as the gastrointestinal issues noted in Xie et al.'s study (10). This leads us to question the factors that contribute to the emergence of side effects in CAT. Developing antivirals that are highly specific to their targets is essential, as it reduces the chance that host proteins uninvolved in the viral life cycle will be targeted (21). Additionally, choosing treatments that are administered over a shorter duration of time and at a lower dosage could also prevent side effects due to the lower quantities of the drug being used. Another potential issue lies in the feasibility of administering CAT. Pills are a convenient way to administer drugs as they usually can be easily self-administered (22). However, when combining multiple drugs, they might not all operate effectively using the same route of entry. For example, some drugs are made as nasal sprays, while others, such as mAbs, need to be injected (6, 23). For this reason, the route of entry is a point to consider when selecting antivirals.

As MDT and CAT for SARS-CoV-2 is still an emerging topic, few studies have been published. In the beginning of the pandemic, various MDT therapies were used to treat ambulatory SARS-CoV-2 patients. One particular study used TNR4 treatment (Ivermectin, Azithromycin, Montelukast, Aspirin) and found that the likelihood of recovery within 14 days was 3.4 times greater among patients receiving the treatment (24). Patients also had a 75% reduced chance of being hospitalized, and a 81% reduced chance of death (24). More recently in March 2022, a different study performed in silico screening of 9870 pairs of 140 potential targets, and identified 9 possible combinations of drugs for MDT (13). Of these, Camostat and Apilimod were predicted to be the most promising combination for suppressing viral replication in the early stages of infection (13). Looking more specifically into CAT, another March 2022 study found that SARS-CoV-2 has an exonuclease-based proofreader which could reduce the efficacy of drugs like remdesivir (12). To overcome this, they suggest using a combination of antivirals that target both the viral RNA-dependent RNA polymerase and the exonuclease (12).

**What are the benefits and considerations of MDT for SARS-CoV-2 from a social perspective?** Although the SARS-CoV-2 vaccine has been available for over a year, a subset of the population remains unvaccinated for different reasons, including personal beliefs, fear of authorities, age, and medical history (25). Having an effective CAT treatment available to treat these individuals will be beneficial, particularly if a harmful VoC was to emerge. It is possible that those who are vaccine hesitant may be more psychologically open to receiving antivirals than vaccines. Although this hypothesis has yet to be formally studied, a number of

detailed opinion pieces and media articles believe that some of the fears of side effects and ulterior motives linked to the vaccines may dissipate when confronted with an actual COVID-19 diagnosis (26). In other words, some individuals may be more open to using CAT to treat an infection that they already have instead of taking a vaccine as a preventative measure. Another point to consider is the route of administration for treatment. Society has been conditioned to believe that taking pills is normal and accepted, as it is required to treat many different medical conditions (27). For example, some vaccine hesitant individuals believe that taking vitamin C tablets is important for preventing COVID-19 (27). But receiving an injection is not an everyday experience; it signals something different and exceptional, and requires a medical professional to administer the treatment. Therefore, the psychological ease of taking antiviral treatment is another benefit of developing CAT for SARS-CoV-2.

In contrast, the unjust policies for drug production and distribution is a concern for MDT from a social perspective (28). For example, when the first COVID-19 vaccine was first approved and made available for distribution, it was in high demand. These vaccines were more often given to the countries who were able to pay for them, rather than to countries that would benefit from them the most (28). It is possible that when an effective antiviral treatment method such as Pfizer's PAXLOVID or a future CAT treatment becomes available on the market, that the same issue will resurface. While many systematic changes will need to be made in order to make this process more just, raising this concern is an important first step.

## POTENTIAL IMPACT/CONCLUSIONS

The COVID-19 pandemic has devastated the world, leaving lasting health, social and economic consequences (1). However, emerging from this pandemic, we are now better prepared to fight future waves of virulent VoCs or a new pandemic involving a different virus. CAT has the potential to be a significant player in these future battles, but there are a number of challenges to consider from the biological perspective. The combination of drugs selected should not only be effective at suppressing the virus, but should also be administered in low doses over short periods of time in ways that are easy to administer (7,8). Additionally, when designing CAT it is important to consider the target recipients, including young children and those with conflicting medical conditions who both cannot be vaccinated (29).

In addition to its health consequences, the pandemic has also exacerbated social inequalities on a global level (1). Information on COVID-19 treatments and vaccines has been communicated by health authorities both inadequately and in ways that aren't socially and culturally understood by low-income communities (30). Even if the information is conveyed, the inaccessibility of antivirals due to cost or lack of availability serves as another roadblock (31). Furthermore, low-income workers may be unable to take sick leave from work, or leave family unattended to get treated, particularly for those living in rural or remote areas that have to travel longer distances (32). Therefore, when designing MDT for SARS-CoV-2 and future viruses, it will be important to consider both the biological effectiveness and social accessibility, and determine which policy changes need to be made to help balance inequalities. More broadly, we must consider how we can adapt our approach to the pandemic to better serve all populations. As communication improves and the world becomes more globalized, interdisciplinary work will likely become integral to all areas of research.

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