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Therapeutic synergy: Combining antivirals with immunomodulators.

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Introduction

The treatment of viral infections has traditionally relied on direct-acting antivirals (DAAs) that inhibit viral replication. While effective, these agents often face limitations such as resistance development, limited efficacy in immunocompromised patients, and inability to address virus-induced immune dysregulation. In recent years, a new paradigm has emerged—therapeutic synergy through the combination of antivirals with immunomodulators. This approach not only targets the virus but also modulates the host immune response, offering a more holistic and potentially more effective strategy for managing viral diseases [1].

Viruses are adept at evading and manipulating host immune responses. Some suppress immune signaling to avoid detection, while others trigger hyperinflammatory states that contribute to disease severity. Antivirals can reduce viral load, but they do not directly address these immune imbalances. Immunomodulators, on the other hand, can restore immune homeostasis, enhance antiviral immunity, or dampen harmful inflammation [2].

Combining these two therapeutic classes can yield synergistic effects—where the combined outcome is greater than the sum of individual effects. This synergy can improve clinical outcomes, reduce drug resistance, and expand treatment options for severe or chronic infections. A nucleotide analog that inhibits RNA-dependent RNA polymerase, used in COVID-19 treatment. A neuraminidase inhibitor for influenza [3].

Targets herpesvirus DNA polymerase. Used in hepatitis C therapy, targeting viral RNA polymerase. These drugs are most effective when administered early, before extensive viral replication and immune dysregulation occur. Immunomodulators encompass a broad range of agents that influence immune function. They can be categorized as: Boost antiviral immunity, e.g., interferons, toll-like receptor (TLR) agonists. Reduce harmful inflammation, e.g., corticosteroids, IL-6 inhibitors. Balance immune responses, e.g., JAK inhibitors, PD-1 blockers. For instance, dexamethasone has been shown to reduce mortality in severe COVID-19 by suppressing cytokine storms, while interferon-alpha enhances antiviral defenses in hepatitis B and C [4].

The COVID-19 pandemic highlighted the potential of combination therapy. Early in the pandemic, remdesivir was used to inhibit viral replication. However, many patients progressed to severe disease due to hyperinflammation. The addition of dexamethasone, an immunosuppressive corticosteroid, significantly improved survival in hospitalized patients requiring oxygen. A JAK inhibitor that reduces inflammatory signaling, showing improved recovery times. Enhancing innate immunity in early-stage disease. These examples underscore the importance of timing and patient stratification in combination therapy. HIV treatment has long relied on combination antiretroviral therapy (cART), which uses multiple DAAs to suppress viral replication. More recently, immunomodulatory strategies have been explored to enhance immune control and reduce latent reservoirs [5].

Conclusion

Combining antivirals with immunomodulators represents a powerful strategy to combat viral infections. In chronic hepatitis B, the virus persists despite antiviral therapy due to immune tolerance

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and exhaustion. Combining antivirals like tenofovir with immunomodulators such as TLR agonists or checkpoint inhibitors may restore immune control. For hepatitis C, the advent of DAAs has revolutionized treatment. However, in patients with advanced liver disease or co-infections, immunomodulators may help manage inflammation and fibrosis. For emerging viruses like Ebola, Nipah, or Zika, combination therapy offers a flexible and adaptive strategy. Immunomodulators can be rapidly repurposed to manage immune responses while antivirals are developed. By addressing both the pathogen and the host response, this approach offers improved efficacy, reduced resistance, and broader applicability. As our understanding of host-pathogen interactions deepens, therapeutic synergy will become a cornerstone of personalized and resilient antiviral therapy.

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