OPEN ACCESS Freely available online

Journal of Antivirals & Antiretrovirals

ISSN: 1948-5964

Perspective

Combination Antiviral Strategies for Drug-Resistant Viral Infections

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DESCRIPTION

The global rise in drug-resistant viral infections presents a significant challenge to public health, prompting the need for innovative therapeutic strategies that go beyond monotherapy. Combination antiviral therapy, which involves the simultaneous use of two or more antiviral agents with different mechanisms of action, has emerged as an effective approach to combat resistant strains and enhance viral suppression. This strategy not only increases the potency of antiviral effects but also reduces the likelihood of resistance development, as it becomes more difficult for the virus to simultaneously mutate against multiple pharmacologic targets. Historically, this approach has proven highly effective in the treatment of HIV and hepatitis C virus (HCV) infections and is now being explored more extensively in other viral infections where resistance is becoming problematic.

HIV therapy is the quintessential example of the success of combination antiviral strategies. Highly active antiretroviral therapy (HAART), consisting of a cocktail of drugs targeting different stages of the HIV life cycle (reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry inhibitors), has transformed HIV from a fatal illness into a manageable chronic condition. By suppressing viral replication through multiple pathways, HAART minimizes the risk of viral escape and maintains long-term viral suppression in most patients. This model has inspired similar approaches in the treatment of other persistent and mutating viral pathogens.

In hepatitis C management, the shift from interferon-based therapy to direct-acting antiviral (DAA) combinations has resulted in remarkably high cure rates. Drug regimens now typically include combinations of NS5A inhibitors, NS5B polymerase inhibitors, and protease inhibitors, tailored to the viral genotype and patient profile. This multi-pronged approach not only improves efficacy but also shortens treatment duration and reduces adverse effects. The success of such combinations has led to interest in applying the same principles to other viral pathogens that are showing signs of developing resistance, such as influenza, cytomegalovirus (CMV), and hepatitis B virus (HBV).

In influenza treatment, drug resistance—particularly to adamantanes and neuraminidase inhibitors—has been observed in circulating strains. Combination therapy using neuraminidase inhibitors (like oseltamivir) with newer agents such as baloxavir marboxil (a cap-dependent endonuclease inhibitor) is being studied to enhance treatment outcomes and prevent the emergence of resistant variants. Similarly, for CMV infections in immunocompromised patients, such as organ transplant recipients, combination therapies involving ganciclovir, foscarnet, and letermovir have shown promise in preventing breakthrough infections and managing resistant strains.

The rationale behind combination therapy lies in pharmacologic synergy—where the combined effect of drugs is greater than the sum of their individual actions. Moreover, this strategy can help lower the required doses of each drug, potentially minimizing toxicity and side effects. However, selecting the right drug combinations is complex and requires consideration of pharmacokinetics, resistance profiles, patient tolerance, and potential drug–drug interactions. Personalized medicine approaches, including resistance testing and therapeutic drug monitoring, are crucial in optimizing combination therapy protocols.

Despite its benefits, combination antiviral therapy also presents certain limitations. Cost is a significant factor, particularly in low-resource settings where access to multiple antiviral drugs may be restricted. The potential for cumulative toxicity and drug interactions, especially in patients with comorbidities or polypharmacy, also poses clinical challenges. Therefore, ongoing research is necessary to identify the most effective and safe combinations, particularly for viruses that lack an established combination therapy protocol.

In conclusion, combination antiviral strategies represent a powerful tool in the fight against drug-resistant viral infections. By targeting multiple steps in the viral replication cycle, this approach enhances therapeutic efficacy and reduces the emergence of resistance. As resistance continues to threaten the effectiveness of existing antiviral drugs, especially in the context of global pandemics and emerging pathogens, the development and optimization of combination therapies will be critical.

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Received: 03-Mar-2025, Manuscript No. JAA-25-37663; **Editor assigned:** 05-Mar-2025, PreQC No. JAA-25-37663 (PQ); **Reviewed:** 18-Mar-2025, QC No. JAA-25-37663; **Revised:** 24-Mar-2025, Manuscript No. JAA-25-37663 (R); **Published:** 01-Apr-2025, DOI: 10.35248/2572-0805-25.17.346

Citation: Teixeira M (2025). Combination Antiviral Strategies for Drug-Resistant Viral Infections. J Antivir Antiretrovir.17:346.

Through rational drug design, improved diagnostics, and strategic clinical trials, combination therapy holds the potential to redefine the standard of care in virology and safeguard the effectiveness of our antiviral arsenal for future generations.