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Commentary

Mechanisms of Drug Resistance in Antiretroviral Therapy Clinical Implications

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DESCRIPTION

The success of antiretroviral therapy (ART) in transforming HIV infection into a manageable chronic condition is one of the most significant achievements in modern medicine. However, the emergence and persistence of drug-resistant HIV strains continue to pose serious clinical challenges. Drug resistance occurs when mutations in the HIV genome reduce the efficacy of antiretroviral agents, either by altering drug targets or enhancing viral replication in the presence of therapy. The primary mechanisms behind this resistance include point mutations in viral enzymes such as reverse transcriptase, integrase, and protease, which compromise the binding affinity of antiretroviral drugs. In particular, mutations such as M184V/I, K103N, and Y181C have been widely studied due to their role in resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The high mutation rate of HIV, driven by its error-prone reverse transcriptase and rapid replication cycle, makes the virus especially prone to developing resistance. Monotherapy or suboptimal adherence to ART regimens provides the ideal environment for resistance selection, as incomplete viral suppression allows resistant variants to proliferate. This has led to the global standard of using combination ART (cART), which includes drugs from multiple classes to minimize the risk of resistance and improve virologic control. Nonetheless, even in combination regimens, resistance can develop, particularly in resource-limited settings where access to routine viral load monitoring and resistance testing may be limited. Moreover, Transmitted Drug Resistance (TDR), where individuals acquire resistant HIV strains prior to initiating therapy, is an increasing concern and complicates the selection of effective first-line regimens.

The clinical implications of drug resistance in ART are profound. Resistance reduces the effectiveness of available treatment options, increases the likelihood of virologic failure, and necessitates the use of more complex, expensive, and potentially toxic second or third line regimens. In addition, resistant strains can be transmitted within populations, contributing to community level resistance patterns and limiting public health efforts aimed at controlling the epidemic. Integrase strand transfer inhibitors (INSTIs), once considered less prone to resistance, are also beginning to show resistance associated mutations such as G118R and Q148H/K/R in treatment-experienced patients, especially those with incomplete adherence or long-standing virologic failure.

Surveillance and resistance testing are essential tools in managing ART-related drug resistance. Genotypic resistance testing, conducted before initiating therapy and in cases of virologic failure, allows clinicians to tailor treatment regimens based on the resistance profile of the virus. Phenotypic testing, although less commonly used due to its cost and complexity, provides additional insight into the degree of drug susceptibility. Resistance data also inform national and global HIV treatment guidelines, ensuring that commonly used regimens remain effective across populations. Additionally, therapeutic drug monitoring and adherence support strategies, such as counseling, fixed-dose combinations, and long-acting injectables, play a vital role in reducing resistance development by ensuring adequate drug exposure and consistent adherence.

Despite the challenges posed by resistance, research into next-generation antiretrovirals continues to yield promising results. Agents with higher genetic barriers to resistance, such as dolutegravir and bictegravir, have become cornerstone drugs in modern regimens. These agents are less likely to be rendered ineffective by single mutations and offer a higher level of durability in treatment-naive and treatment-experienced populations. Furthermore, therapeutic strategies such as treatment simplification, two-drug regimens, and structured treatment interruptions are being explored to reduce the long-term toxicities and selection pressure associated with lifelong ART.

In conclusion, drug resistance remains a major obstacle in the long-term management of HIV infection. Understanding the molecular mechanisms of resistance and incorporating that knowledge into clinical practice is essential for optimizing treatment outcomes. Prevention of resistance requires a multifaceted approach that includes promoting adherence,

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ensuring access to effective drug combinations, conducting regular resistance surveillance, and continuing to invest in the development of innovative therapies. With sustained effort and global coordination, it is possible to mitigate the impact of resistance on ART programs and move closer to achieving durable viral suppression for all individuals living with HIV.