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Perspective

Pharmacokinetics and Safety Profiles of Novel Antiretroviral Agents

Leila Moradi*

Department of Clinical Pharmacology, Tehran Institute for Infectious Diseases Research, Tehran, Iran

DESCRIPTION

The development of novel antiretroviral agents has significantly advanced the treatment landscape of HIV, providing improved viral suppression, better tolerability, and simplified dosing regimens. As resistance to traditional regimens emerges and the need for long-term therapy grows, the pharmacokinetic (PK) properties and safety profiles of new agents are crucial in determining their clinical utility. Contemporary drug discovery efforts focus on optimizing Absorption, Distribution, Metabolism and Excretion (ADME) characteristics to ensure consistent plasma concentrations, reduced dosing frequency, and minimal toxicity.

One of the primary objectives in designing next-generation antiretrovirals is extending the drug half-life to allow for weekly or even monthly dosing. Agents such as cabotegravir and rilpivirine exemplify this goal, offering injectable formulations with sustained plasma levels. These agents achieve their extended duration through slow-release depot formulations and favorable PK profiles, with a slow absorption rate and long terminal half-life. Such characteristics reduce pill burden and enhance adherence, which is critical in maintaining viral suppression.

Another important factor in PK evaluation is bioavailability. Oral formulations like Tenofovir Alafenamide (TAF) have been engineered for improved bioavailability compared to their predecessors, such as Tenofovir Disoproxil Fumarate (TDF), allowing for lower dosing and reduced renal and bone toxicity. TAF's targeted intracellular delivery results in high concentrations of the active metabolite in lymphoid cells with minimal systemic exposure, demonstrating how PK improvements can directly correlate with safety enhancements.

The metabolism of new antiretrovirals is also under intense scrutiny, particularly regarding cytochrome P450 enzyme interactions. Minimizing drug-drug interactions (DDIs) is essential for patients co-infected with hepatitis or tuberculosis or those on chronic medications for non-communicable diseases. Agents such as doravirine show a reduced propensity for CYP450-related DDIs, which expands their utility in complex patient populations. This characteristic makes doravirine particularly attractive for aging HIV populations who are often polymedicated.

In terms of safety, the newer integrase strand transfer inhibitors (INSTIs) like bictegravir have demonstrated favorable profiles. Bictegravir, in particular, exhibits minimal renal clearance and does not require pharmacokinetic boosters, which are often associated with gastrointestinal side effects and metabolic disturbances. Clinical trials have shown a low incidence of adverse events, with the most common being mild headache and diarrhea. Importantly, bictegravir has not shown significant weight gain in contrast to earlier concerns surrounding other INSTIs.

Long-acting injectables, while promising, have raised questions about local site reactions and potential for resistance in the context of missed doses. However, studies have indicated that most injection-site reactions are mild to moderate and decrease over time. Moreover, the long pharmacologic tail of these agents may offer a window of protection even if doses are missed, though careful monitoring remains necessary.

In pediatric populations and pregnant women, PK and safety evaluations are even more critical due to physiological differences affecting drug metabolism and distribution. Trials involving dolutegravir and other newer agents in these groups have shown reassuring data, with no significant teratogenic effects and effective viral suppression. Nonetheless, ongoing surveillance is vital to confirm these findings across diverse populations.

As the field moves toward personalized medicine, pharmacogenomic data is beginning to influence ARV selection. Variations in genes encoding drug-metabolizing enzymes, transporters, or receptors can impact drug exposure and side effects. For instance, polymorphisms in UGT1A1 may predispose some patients to hyperbilirubinemia when using certain protease inhibitors or INSTIs. Understanding these genetic influences will allow for more individualized and safer prescribing practices in the future.

Correspondence to: Department of Molecular Virology, Colombo Institute of Biomedical Research, Sri Lanka, E-mail: l.moradi@tidr-iran.org

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Overall, the pharmacokinetic and safety profiles of novel antiretroviral agents support their growing role in modern HIV treatment strategies. With innovations in drug formulation and delivery, clinicians now have access to agents that not only maintain virologic control but also reduce adverse effects and improve adherence. The transition to long-acting, well-tolerated therapies is likely to enhance the quality of life for people living with HIV and may play a key role in achieving the UNAIDS 95-95-95 targets. As ongoing research provides more real-world data and post-marketing surveillance continues, these agents are expected to become standard components in the next era of HIV care.