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Perspective

The Role of Pharmacogenetics in Tenofovir Plasma and Urine Exposure Variability

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DESCRIPTION

Tenofovir, a Nucleotide Reverse Transcriptase Inhibitor (NRTI), is a method in the treatment and prevention of HIV infection. It is widely used in combination Antiretroviral Therapy (ART) for managing HIV and as a main component of Pre-Exposure Prophylaxis (PrEP) regimens. Despite its efficacy, tenofovir's pharmacokinetics the way it is absorbed, distributed, metabolized and excreted can vary significantly between individuals. These differences can influence drug efficacy, the likelihood of side effects and long-term outcomes. Pharmacogenetics, the study of how genetic variations affect drug response, plays a critical role in understanding how tenofovir exposure in plasma and urine is modulated by genetic factors. This article describes the relationship between pharmacogenetics and tenofovir plasma and urine exposures, explains how genetic variability can influence treatment outcomes and drug safety.

Tenofovir pharmacokinetics

Tenofovir is administered as a prodrug, either Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide (TAF). Once absorbed, it is converted into its active form, tenofovir diphosphate, which inhibits the replication of HIV by blocking reverse transcriptase. TDF and TAF differ in their pharmacokinetics. TDF is primarily absorbed and converted into tenofovir in the bloodstream, leading to higher plasma concentrations, while TAF is metabolized within cells, resulting in lower systemic tenofovir levels but higher intracellular concentrations. Both forms are eventually excreted unchanged in the urine.

While tenofovir is effective in suppressing HIV, prolonged exposure, particularly at high plasma concentrations, can lead to adverse effects such as kidney damage (nephrotoxicity) and bone mineral loss. Understanding the pharmacokinetic factors that contribute to these outcomes is essential for optimizing therapy, especially since genetic variations can influence how tenofovir is processed in the body.

Pharmacogenetics and tenofovir plasma exposure

Pharmacogenetic factors are known to impact drug absorption, metabolism and excretion, all of which influence plasma exposure to tenofovir. One of the most critical genetic factors involved in tenofovir pharmacokinetics is the ATP-Binding Cassette subfamily B member 1 (*ABCB1* gene, which encodes P-glycoprotein, a transporter protein involved in drug efflux.

P-glycoprotein plays an important role in regulating the absorption and distribution of drugs by pumping them out of cells. Polymorphisms in the *ABCB1* gene can affect the function and expression of this transporter, potentially altering tenofovir plasma levels. For example, individuals with certain variants of the *ABCB1* gene may have reduced P-glycoprotein activity, leading to higher plasma concentrations of tenofovir. This can increase the risk of drug-related toxicities, including kidney damage.

Another gene of interest is the solute carrier family 22 member 6 (*SLC22A6* gene, which encodes organic anion transporter 1 (OAT1. OAT1 is primarily expressed in the kidneys and is responsible for the renal uptake and excretion of tenofovir. Polymorphisms in *SLC22A6* can affect the renal clearance of tenofovir, leading to increased plasma exposure and a heightened risk of nephrotoxicity.

In addition to these transporter genes, genetic variations in the Cytochrome P450 (CYP family of enzymes can indirectly influence tenofovir exposure by affecting the metabolism of other co-administered drugs that may interact with tenofovir. For instance, individuals with certain *CYP2B6* polymorphisms may experience altered metabolism of efavirenz, a drug often co-prescribed with tenofovir, which in turn can impact tenofovir plasma levels.

Pharmacogenetics and tenofovir urine exposure

The excretion of tenofovir primarily occurs through the kidneys, with a significant portion of the drug being eliminated unchanged in the urine. Genetic variations that affect renal

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function can therefore have a direct impact on tenofovir urine exposure and overall drug clearance. The same transporter genes that influence plasma exposure also play a major role in renal excretion, particularly *ABCB1* and *SLC22A6*.

Polymorphisms in these genes can result in altered drug handling by the kidneys, leading to variations in tenofovir concentrations in urine. For example, reduced activity of P-glycoprotein due to *ABCB1* polymorphisms can lead to lower efflux of tenofovir from renal cells into the urine, causing increased retention of the drug in the body. This may result in higher systemic exposure and potentially greater toxicity risks.

In contrast, increased activity of renal transporters like OAT1 due to *SLC22A6* polymorphisms could enhance tenofovir excretion into the urine, potentially reducing plasma levels and diminishing the drug's antiviral efficacy. Therefore, understanding genetic variations that affect renal drug transport is critical for optimizing tenofovir dosing, particularly in individuals at risk for kidney-related side effects.

Clinical implications of pharmacogenetic variability in tenofovir exposure

The influence of pharmacogenetics on tenofovir exposure has significant clinical implications for the management of HIV and PrEP. Patients with genetic variations that increase tenofovir plasma concentrations may be at higher risk for nephrotoxicity and bone mineral loss, necessitating more frequent monitoring of kidney function and bone density. In some cases, clinicians may opt for TAF, which has a more favorable renal and bone safety profile, for patients with these genetic risk factors.

Conversely, individuals with genetic variants that lead to increased renal excretion of tenofovir may require higher doses to achieve therapeutic drug levels. This is particularly important for preventing HIV transmission in PrEP users, where suboptimal drug levels could reduce the efficacy of the regimen.

CONCLUSION

Pharmacogenetics plays an important role in determining individual variations in tenofovir plasma and urine exposures. Genetic polymorphisms in drug transporter and metabolizing genes such as *ABCB1* and *SLC22A6* can significantly influence tenofovir pharmacokinetics, impacting drug efficacy, safety and patient outcomes. By incorporating pharmacogenetic testing into clinical practice, healthcare providers can personalize tenofovir-based treatment regimens, optimizing drug exposure and minimizing the risk of adverse effects. As research in this field continues to evolve, pharmacogenetics holds great potential for enhancing the precision of HIV therapy and prevention strategies.