## The pharmacological difference of TAF to TDF

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Ideally, new anti-HIV agents should provide more convenient dosing, improved resistance profiles and reduced toxicity. Furthermore, enhanced antiviral activity in various tissue compartments is desirable to reduce potential low-level viral replication and the possibility of virological failure. Moreover, a drug that provides higher concentrations in the lymphatic tissues could potentially have a positive impact on long-term treatment outcome.

Tenofovir alafenamide is a new oral prodrug of tenofovir, a nucleotide analogue that inhibits HIV-1 transcription used in combination antiretroviral therapy for the treatment of HIV-1 infection since 2001.

Tenofovir alafenamide is more stable in plasma than tenofovir disoproxil and then is specifically converted into tenofovir within cells by the cellular enzyme cathepsin A, which is highly expressed in lymphoid tissues. Tenofovir is then further metabolized intracellularly to the active metabolite, tenofovir diphosphate, that terminates the elongation of the nascent viral cDNA chain. Given the intracellular mechanism of activation of tenofovir alafenamide and potential for intracellular accumulation, lower extracellular exposures of tenofovir may be realized with the potential to reduce off-target toxicities. Specifically, lower drug exposures to kidney cells may provide for fewer renal complications as observed in a minority of patients treated with tenofovir disoproxil fumarate and the ability to dose tenofovir alafenamide in patients with renal impairment without dose adjustment.

The pharmacokinetic data indicate that the administration of tenofovir alafenamide results in brief, systemic circulation of tenofovir alafenamide that results in improved distribution of tenofovir to tissues, including peripheral blood mononuclear cells (PBMCs). Specifically, as a function of tenofovir dose, the administration of tenofovir alafenamide results in a lower tenofovir Cmax, higher apparent volume of distribution and longer elimination half-life compared with tenofovir disoproxil fumarate. The pre-clinical tissue distribution studies showed no increased accumulation of tenofovir in kidney or liver tissue.

Then, the distinct tissue distribution profile into PBMCs and the lymphatic organs after oral administration of tenofovir alafenamide relative to tenofovir disoproxil fumarate warrants a full safety use of tenofovir alafenamide in the combination antiretroviral therapy.