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Development of a Novel Formulation that Improves Pre-clinical Bioavailability of Tenofovir Disoproxil Fumarate

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Abstract

Tenofovir disoproxil fumarate (TDF), the bisphosphonate ester prodrug of tenofovir (TFV), has poor bioavailability due to intestinal degradation and efflux transport. Reformulation using FDA-approved esterase and efflux inhibitors to increase oral bioavailability could provide lower dose alternatives and reduce costs for patients with HIV in resource-limited settings (RLS). Inhibition of mucosal and intracellular esterases was studied in human and rat intestinal extracts (S9), where TDF was protected by the carboxylesterase (CE) inhibitor bis-para-nitrophenylphosphate (BNPP), the ester mix EM1, and the generally-recognized-as-safe (GRAS) excipient propylparaben (PP). Permeability studies using Madin-Darby canine kidney (MDCK) and Caco-2 cell monolayers demonstrated that TDF was a substrate for the permeability glycoprotein (P-gp) with P-gp inhibitors reducing basolateral to apical transport of TDF. These studies also showed that transport was increased by esterase inhibitors. TDF, TFV, and tenofovir monophosphonate ester (TFV-ME) transport across Caco-2 monolayers with esterase and efflux inhibitors revealed a maximum 38.7-fold increase in apical to basolateral TDF transport with the potent non-GRAS combination of EM1 and GF120918 (GF918). Transport was increased 22.8-fold by the GRAS excipients, PP and D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS, a vitamin E derivative). TFV pharmacokinetics (PK) in rats following oral administration of TDF and GRAS esterase and efflux inhibitors confirmed enhanced bioavailability. AUC increased 1.5 to 2.1-fold with various combinations of parabens and TPGS. This significant inhibition of TDF hydrolysis and efflux *in vivo* exhibits the potential to safely increase TDF bioavailability in humans.

Introduction

Approximately 37 million people worldwide were living with HIV/AIDS in 2015, and as of June 2015, less than half of them had access to antiretroviral therapy (ART)[1]. Initiatives such as 90-90-90[2] and Test and Treat[3] have set the stage for 90% of patients with diagnosed HIV to be placed onto sustained ART by 2020. To avoid a financial crisis in the clinical management of 37 million people living with HIV/AIDS (PLWHA), the global health community is exploring every option possible to improve healthcare efficiencies.