Therapeutic Drug Monitoring of Antiretrovirals: Applications in Management and Prevention

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Scope of the lecture:
This lecture will include an overview of antiretroviral (ARV) agents employed in the management and treatment of HIV/AIDS. Benchmark therapeutic drug monitoring (TDM) studies will be discussed, as will clinical scenarios in which TDM may be appropriate. Lastly, this lecture will focus on the characterization of ARVs in HIV prevention as a pre-exposure prophylactic (PrEP) strategy.

Learning objectives:
1. Recall current drug classes used for the management of HIV, including current first line therapies in treatment naïve individuals.
2. Recognize US recommendations for TDM for the management of HIV/AIDS.
3. Identify pharmacokinetic benchmarks for PrEP adherence.

Extended abstract:

Background: Recent estimates indicate that there are 34 million individuals living with HIV/AIDS worldwide, with 2.5 million new infections occurring annually [1]. Antiretroviral therapy (ART) is the primary modality for the treatment and management of HIV/AIDS, and the advent of combinatorial therapies in the 1990s and 2000s has led to improved morbidity and mortality. Through appropriate maintenance on ART regimens, an infected individual can be longitudinally managed for the disease.

Antiretroviral Therapies Available for Management: There are currently more than 25 antiretroviral (ARV) agents approved in the United States (US) for the treatment and management of HIV, include protease inhibitors, integrase strand transfer inhibitors, cell entry inhibitors, and nucleotide and non-nucleotide reverse transcriptase inhibitors. Many of these compounds are associated with high inter-individual variability in peak (C_{max}) and trough (C_{min}) concentrations, variability in the production of active intracellular metabolites, as well as drug-associated toxicities. The need to remain above certain threshold concentrations is paramount, as the inability to maintain drug levels above mean inhibitory concentrations can lead to the generation and propagation of drug-resistant viral isolates, resulting in treatment failure. Thus, in principle, these compounds are candidates for therapeutic drug monitoring (TDM) for HIV management.

TDM Recommendations: Currently, the US Department of Health and Human Services' Panel on Antiretroviral Guidelines for Adults and Adolescents does not endorse TDM for ARVs in the routine management of HIV-infected individuals. This is largely attributed to a lack of prospective studies demonstrating that TDM-guided ART management improves clinical outcomes [2]. However, there are special populations in which drug measurements can provide critical information, including in the background of a potential drug-drug interaction, disease states that may impact drug pharmacokinetics (gastrointestinal, hepatic, renal), in pregnant women, and in ART-adherent individuals who are not virally suppressed. This lecture will discuss the current landscape of ART regimens, and the nuances where

TDM is appropriate.

ARVs for Prevention: A growing area of pharmacological interest is the use of ARVs for the prevention of HIV in high risk populations. Currently, the fixed dose formulation of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (also known as PrEP) is approved by the FDA for HIV prevention in high risk populations. To date, pharmacological therapies have shown the most promise for the sustained protection against viral acquisition. However, while the efficacy of PrEP has been demonstrated for HIV prevention, major barriers include cost, uptake, and adherence. Lack of adherence may lead to increased risk of seroconversion and the propagation of drug-resistant virus, thereby limiting regimens that can be used for management. Thus, directly observed therapeutic administration studies have been performed to characterize adherence and establish PrEP benchmarks in HIV-uninfected individuals [3]. In this context, TDM and ARV PK may be critical in understanding PrEP uptake, as well as in the objective assessment of adherence practices, and elucidation of treatment failure and viral infection in a non-adherent individual. This lecture will discuss the pharmacokinetic studies used for the characterization of PrEP in the background of varying dose frequencies, and in the context of concentrations required to prevent viral infection.

References:

1. Global report: UNAIDS report on the global AIDS epidemic 2012, http://www.unaids .org/en/resources/publications/2012; 2012 [accessed 08.14.17]
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. Updated April 8th, 2015. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGI.pdf; 2015 [accessed 08.14.17]
3. Hendrix CW, Andrade A, Bumpus NN, Kashuba AD, Marzinke MA, Moore A, Anderson PL, Bushman LR, Fuchs EJ, Wiggins I, Radebaugh C, Prince HA, Bakshi RP, Wang R, Richardson P, Shieh E, McKinstry L, Li X, Donnell D, Elharrar V, Mayer KH, Patterson KB. Dose Frequency Ranging Pharmacokinetic Study of Tenofovir-Emtricitabine After Directly Observed Dosing in Healthy Volunteers to Establish Adherence Benchmarks (HPTN 066). AIDS Res Hum Retroviruses. 2016 Jan;32(1):32-43.