

**Session 4: Chemotherapy and Discovery of Anti-HIV Agents****Pharmacogenomics and Pharmacokinetics in Anti-HIV Agent Development****Tim R. Cressey<sup>1,2</sup>**

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**Abstract**

HIV-infected immunocompromised patients require life-long antiretroviral therapy. To date, 26 antiretroviral drugs are approved by the US Food and Drug Administration for the treatment of HIV. Highly Active Antiretroviral Therapy (HAART), normally a combination of three antiretroviral drugs, has dramatically improved the prognosis of HIV/AIDS. However, viral replication under therapy can lead to the selection of drug resistant viruses and subsequent virologic failure. While poor adherence is likely to be the main cause of treatment failure, individual pharmacokinetic variability can also play an important role. Drug-drug interactions, drug-food interactions, sex, age, renal/hepatic function and pregnancy are all sources of pharmacokinetic variability.

In recent years, host genetic polymorphisms have also been shown to explain part of this variability and several pharmacogenetics studies have demonstrated that host genetic polymorphisms can influence antiretroviral drug exposure, toxicity and response to treatment. During antiretroviral drug development, drug hypersensitivity reactions have been reported for several agents. Based on pharmacogenetic research data antiretroviral treatment decisions based on host genetics to prevent the risk of hypersensitivity reactions are now part clinical practice. Specifically, it is now recommended that patients initiating abacavir are screened for the presence of the HLA-B\*5701 allele as it is strongly associated with an immunologically mediated hypersensitivity reaction to abacavir, which in rare cases can be fatal.

Antiretroviral drugs within the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs) drug class are commonly used within first-line HAART regimens. Substantial evidence exists that polymorphisms in the *CYP2B6* drug metabolizing enzyme gene are associated with higher NNRTI drug exposure, and in some studies with early drug toxicity (mainly efavirenz related neuropsychological toxicity). The bulk of evidence concerns the *CYP2B6 516G>T* polymorphism, primarily within the variant *CYP2B6\*6* allele that also includes the *785A>G* polymorphism, which has been shown to be associated with higher efavirenz plasma exposure but not with time to virologic or toxicity-related failure. To date, in the absence of drug toxicity, it is unclear the benefit of a clinical intervention for patients identified with high NNRTI plasma drug concentrations or who are carriers of a genotype associated with high drug concentrations.

Some antiretroviral drug toxicities do not appear until after months of treatment and clinical and pharmacogenomics data could be combined to individualize antiretroviral treatment. Strong evidence supports the existence of host genetic polymorphisms that predict a higher risk of unconjugated hyperbilirubinemia in patients receiving atazanavir. Perhaps patients with risk alleles for hyperbilirubinemia should not necessarily avoid atazanavir use but may require closer laboratory monitoring. Similarly, the genetics of tenofovir associated nephrotoxicity may become increasingly important as tenofovir slowly replaces zidovudine in HAART regimens throughout the world.

To date, pharmacogenetics analyses of antiretroviral drugs have identified several host genetic polymorphisms associated with antiretroviral drug toxicity and

pharmacokinetics. Understanding the contribution of specific polymorphisms on antiretroviral drug efficacy and/or toxicity may lead to simple yet critical interventions to further optimize these life-saving treatments.

**Keywords:** Pharmacogenomics, HIV, antiretroviral, HLA-B\*5701, *CYP2B6*, efavirenz, hypersensitivity reactions