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HIV treatment outcomes in Uganda: The impact of baseline characteristics and variability in pharmacokinetics and pharmacogenetics of antiretroviral drugs

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Guidelines specify criteria for initiation and monitoring of antiretroviral treatment (ART), including options for first line regimens. Immunological progress remains a widely used form of HIV/ART monitoring and efavirenz a preferred first line antiretroviral drug. CD4 cell values vary among HIV seronegative populations and among HIV patients starting ART. Variations in pharmacokinetics and pharmacogenetics of efavirenz are widely documented. This thesis explores the role of variability in relevant baseline immunological characteristics in HIV negative and positive populations and how variations in the pharmacokinetics and pharmacogenetics of efavirenz can affect HIV/ART response in Ugandan populations.

We conducted three sub-studies of HIV seronegative and seropositive Ugandans to address these issues. **Sub-study I; Paper 1:** 206 HIV seronegative Ugandans were recruited for a cross-sectional study of variations in CD4 reference ranges. We observed a CD4 reference range of 418-2105 cells/μL for this population, wider than ranges reported from other settings. Socio-economic status, altitude and prevalent tropical illnesses influenced CD4 reference values. **Sub-study II; Paper 2:** Using records for 426 HIV infected Ugandans treated between 2002 and 2007, we found that patients who started therapy at low baseline CD4 cell levels were less likely to achieve complete immunological recovery. **Sub-study III; Papers 3-6:** A total of 263 HIV positive, ART naïve Ugandans, of which 157 were TB co-infected, were recruited and followed up to 8 months after starting ART. Data from these 263 patients, and from 105 healthy volunteers, were used to describe efavirenz pharmacokinetics for the population, and to study the effect of HIV infection, pharmacogenetics and antituberculous treatment on the pharmacokinetics of efavirenz. Variations in efavirenz pharmacokinetics were observed, and 95% of the patients reached steady state maximum plasma concentrations (C_{max}) above the recommended range of 1-4μg/dl (3.2-12.6 μmol/L). Efavirenz–related central nervous system (CNS) toxicity was observed in 40 (69%) of 58 patients who were evaluated, and 38 (95%) of the patients with CNS toxicity had efavirenz plasma concentrations that were above the recommended range. HIV patients displayed a 30% lower relative bioavailability of efavirenz compared to healthy volunteers while CYP2B6*6/*6 genotype had lower apparent oral clearance and higher plasma concentrations of efavirenz. Regardless of rifampicin co-treatment, efavirenz autoinduction was prominent in CYP2B6*1/*1 genotypes, and surprisingly, long-term efavirenz clearance was higher among patients receiving efavirenz-based HAART alone compared to those who were co-treated with rifampicin-based therapies. Population pharmacokinetic modelling of data from 99 of the HIV only patients showed that the efavirenz exposure was twice as high among patients homogenous for the CYP2B6*6/*6 mutation compared to those without the mutation. It was found that a daily dose of 450 mg efavirenz in the general Ugandan population and a dose of 300 mg in CYP2B6*6/*6 population gave adequate drug exposure.

Population characteristics, including immunological and genetic variations, affect the response to antiretroviral treatment, and population based CD4 cell values and pharmacogenetic-based dose modifications of antiretroviral therapies may improve HIV/ART outcomes.

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