

## *CYP2B6*\*6 Screening; Potential Benefits and Challenges in HIV Therapy in Sub-Saharan Africa

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### Abstract

*CYP2B6*\*6 genotyping appears to be a promising approach towards the prediction of efavirenz toxicity and risk of developing resistant mutations to nevirapine. The use of cost-effective technologies to screen for the allele may therefore become part of routine clinical practice, for which benefits in terms of cost reduction for governments and patients are evident. However, pharmacogenomics has not yet lived up to its hype and benefits in both the developed and developing worlds in particular sub-Saharan Africa where access to basic healthcare services is limited. Although numerous reports have advocated for the implementation of *CYP2B6*\*6-guided drug therapy in HIV patients receiving efavirenz or nevirapine, this has not been effected yet. The reasons require both practical and clinical considerations.

**Keywords:** *CYP2B6*\*6; Efavirenz; Nevirapine; Clinical pharmacogenetics; Sub-Saharan Africa

### Introduction

Potent highly active antiretroviral therapy (HAART) has now been available to HIV-infected patients for over a decade, resulting in a significant decline in disease-related morbidity and mortality [1]. However, a number of HIV-infected individuals fail to experience the full benefit of their HAART, while others lack a robust virologic response, and others experience drug related adverse reactions. A number of factors may contribute to these variable drug responses including virologic, immunologic, pharmacologic, pharmacokinetic and pharmacogenetic differences [2]. Pharmacogenetic studies of antiretroviral drug therapy have explored the influence of single nucleotide polymorphisms in genes responsible for key proteins involved in antiretroviral drug metabolism [3]. This has offered the possibility of optimizing virologic response and minimizing drug toxicity by individualizing anti-HIV pharmacotherapy [4]. *CYP2B6* is an important pharmacogene and a member of the cytochrome P450 family. It makes up approximately 2–10% of the total hepatic CYP content [5], and is also expressed in the brain. *CYP2B6* is responsible for the metabolism of 4% of the top 200 drugs [6] and is highly inducible by several drugs and other xenobiotics [7]. Among these drugs are the non-nucleoside reverse transcriptase inhibitors (NNRTIs); efavirenz and nevirapine. With the increasing use of NNRTIs in African countries, due to high prevalence of HIV/AIDS, it has become crucial to provide information on pharmacogenetic factors influencing drug efficacy and safety [8]. The *CYP2B6* gene exhibits extensive polymorphism reflected currently by over 40 allelic variants [9]. Of these, the most common allele, *CYP2B6*\*6 which contains the 516G>T and 785A>G polymorphisms, is found at high frequencies in all major ethnic groups ranging from 15% in Asians to almost 50% in Blacks and African Americans [10-12].

The impact of genotype-guided efavirenz dosing has been a subject of interest in many studies worldwide. Schackman et al. reported that

dosing of efavirenz in the treatment of HIV/AIDS, based on *CYP2B6*\*6 genotyping is cost-effective compared with standard care in the USA. In addition, there is decreased early treatment-limiting efavirenz toxicity [13]. Although concerns have been raised regarding the possibility of virologic failure with lower efavirenz doses, this would be unlikely if medication adherence and drug monitoring of lower dose regimens is maintained in the patients. A comprehensive genetic analysis of *CYP2B6* polymorphisms and their association with EFV concentrations in the largest Chinese HIV-infected patient cohort suggested that personalization of medical care may be feasible if these genomic markers are validated and incorporated in EFV-containing treatments [14].

Likewise, studies have also been done in African populations to evaluate the clinical implications of the *CYP2B6*\*6 allele in the use of efavirenz [15-18], and nevirapine [19-21]. *CYP2B6*\*6 has been associated with higher efavirenz plasma concentrations due to lower clearance rates, which may lead to CNS side effects [22,23]. These correlations have led to recommendations to reduce the EFV dosage in order to prevent occurrence of the adverse drug effects [18,24]. Individuals with the *CYP2B6*\*6 allele have also been shown to have a significant increase in nevirapine plasma concentrations, which has been associated with immunologic response [19]. The use of single-dose NVP to prevent perinatal vertical transmission has been reported to have pro-longed exposures in women with the *CYP2B6*\*6 allele, which greatly increases the risk of developing resistance mutations to NVP [25]. Given this background *CYP2B6*\*6 may be the ideal genetic marker for detecting predisposed patients to efavirenz induced side effects and possible resistance to nevirapine. The economic and health benefits to the patients are undeniable.

Notwithstanding the benefits of pharmacogenetic testing for *CYP2B6*\*6 in HIV therapy, several barriers impede its translation into clinical practice. Despite several replication studies in African populations that have confirmed the role of *CYP2B6*\*6 in efavirenz and nevirapine efficacy and safety, not much has been done to translate this into routine clinical practice. One of the main challenges

particularly in sub-Saharan Africa is the limited access to basic healthcare services. As a result, implementation of pharmacogenomics into routine clinical practice seems like a far off step. Most patients are struggling to afford costs for basic tests and a genotype test would add on to this burden. The availability of necessary facilities, infrastructure and expertise poses another challenge. While some laboratories in sub-Saharan Africa have adequate and high tech equipment required to carry out the tests, availability for routine clinical use is impeded by expensive running costs. Most of these technologies are finding more use in research.

The current WHO HIV treatment guidelines (2016), recommend a “treat-all” strategy which means that more people in Africa will start ART earlier. This in turn means that there will be increased risk of efavirenz-associated side effects due to high plasma concentrations as well as nevirapine drug resistance due to prolonged high exposures. The economic and health benefits associated with screening for patients that are predisposed to these outcomes greatly outweigh the challenges of the genotyping costs. The screening provides an opportunity to improving the quality of life of those patients carrying the allele either by switching them to alternative regimens or putting them on reduced dosages. There is also a larger cost-effective impact by decreasing the quantity of active pharmaceutical ingredients required to cover the need of EFV containing ART regimens.

As the HIV epidemic continues to develop, countries in sub-Saharan Africa continue to face the challenge of limited resources in their health care systems. The emerging interests by developed countries to conduct more clinical trials in the region may serve as an opportunity to improve the current treatment strategies and slowly start to implement pharmacogenomics in drug use. As governments in the region continue to make improvements in treatment delivery, e.g introducing access to routine viral load testing, serious considerations should also be made towards implementation of pharmacogenetic testing before therapy is initiated. In the long-term this will improve treatment quality and individual health outcomes for people living with HIV/AIDS in the region.

## References

1. Panos G, Samonis G, Alexiou VG, Kavarnou GA, Charatsis G, et al. (2008) Mortality and morbidity of HIV infected patients receiving HAART: a cohort study. *Curr HIV Res* 6: 257-260.
2. Owen A, Pirmohamed M, Khoo SH, Back DJ (2006) Pharmacogenetics of HIV therapy. *Pharmacogenet Genomics* 16: 693-703.
3. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C (2007) Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoeconomic and clinical aspects. *Pharmacol Ther* 116: 496-526.
4. Quirk E, McLeod H, Powderly W (2004) The pharmacogenetics of antiretroviral therapy: a review of studies to date. *Clin Infect Dis* 39: 98-106.
5. Wang H, Tompkins LM (2008) CYP2B6: new insights into a historically overlooked cytochrome P450 isozyme. *Curr Drug Metab* 9: 598-610.
6. Zanger UM, Turpeinen M, Klein K, Schwab M (2008) Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem* 392: 1093-1108.
7. Code EL (1997) Human cytochrome P4502B6: interindividual hepatic expression, substrate specificity, and role in procarcinogen activation. *Drug Metab Dispos* 25: 985-993.
8. Rotger M (2005) Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics* 15: 1-5.
9. Ramachandran G, Hemanth AK, Rajasekaran S, Kumar P, Ramesh K, et al. (2009) CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South India. *Antimicrob Agents Chemother* 3: 863-868.
10. Rotger M, Tegude H, Colombo S, Cavassini M, Furrer H, et al. (2007) Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther* 81: 557-566.
11. Haas DW, Ribaud HJ, Kim RB, Tierney C, Wilkinson GR, et al. (2004) Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 18: 2391-2400.
12. Schackman BR, Haas DW, Park SS, Li XC, Freedberg KA, et al. (2015) Cost-effectiveness of CYP2B6 genotyping to optimize efavirenz dosing in HIV clinical practice. *Pharmacogenomics* 16: 2007-2018.
13. Meng X, Yin K, Wang J, Dong P, Liu L, et al. (2015) Effect of CYP2B6 Gene Polymorphisms on Efavirenz Plasma Concentrations in Chinese Patients with HIV Infection. *PLoS One* 10: e0130583.
14. Nyakutira C, Röshammar D, Chigutsa E, Chonzi P, Ashton M, et al. (2008) High prevalence of the CYP2B6 516G-->T(\*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol* 64: 357-365.
15. Kwara A, Lartey M, Sagoe KW, Kenu E, Court MH (2009) CYP2B6, CYP2A6 and UGT2B7 genetic polymorphisms are predictors of efavirenz mid-dose concentration in HIV-infected patients. *AIDS* 23: 2101-2106.
16. Mukonzo JK, Röshammar D, Waako P, Andersson M, Fukasawa T et al. (2009) A novel polymorphism in ABCB1 gene, CYP2B6\*6 and sex predict single-dose efavirenz population pharmacokinetics in Ugandans. *Br J Clin Pharmacol* 5: 690-699.
17. Dhoro M, Zvada S, Ngara B, Nhachi C, Kadzirange G, et al. (2015) CYP2B6\*6, CYP2B6\*18, Body weight and sex are predictors of efavirenz pharmacokinetics and treatment response: population pharmacokinetic modeling in an HIV/AIDS and TB cohort in Zimbabwe. *BMC Pharmacol Toxicol*: 16.
18. Oluka MN, Okalebo FA, Guantai AN, McClelland RS, Graham SM, et al. (2015) Cytochrome P450 2B6 genetic variants are associated with plasma nevirapine levels and clinical response in HIV-1 infected Kenyan women: a prospective cohort study. *AIDS Res Ther* 12.
19. Dickinson L (2014) Population Pharmacokinetic and Pharmacogenetic Analysis of Nevirapine in Hypersensitive and Tolerant HIV-Infected Patients from Malawi. *Antimicrob Agents Chemother* 58: 706-712.
20. Mhandire D, Lacerda M, Castel S, Mhandire K, Zhou D, et al. (2015) Effects of CYP2B6 and CYP1A2 Genetic Variation on Nevirapine Plasma Concentration and Pharmacodynamics as Measured by CD4 Cell Count in Zimbabwean HIV-Infected Patients. *OMICS* 19: 553-562.
21. Rodriguez-Nóvoa S, Barreiro P (2005) Influence of 515G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. *Clin Infect Dis* 40: 1358-1361.
22. Tsuchiya K, Gatanaga H, Tachikawa N, Teruya K, Kikuchi Y, et al. (2004) Homozygous CYP2B6 \*6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. *Biochem Biophys Res Commun* 319: 1322-1326.
23. Puls R (2013) Encore1 Study Group. A daily dose of 400 mg efavirenz (EFV) is non-inferior to the standard 600 mg dose: week 48 data from the ENCORE1 study, a randomised, double-blind, placebo controlled, non-inferiority trial. in 7<sup>th</sup> IAS Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur.
24. Chantarangsu S, Cressey TR, Mahasirimongkol S, Capparelli E, Tawon Y, et al. (2009) Influence of CYP2B6 polymorphisms on the persistence of plasma nevirapine concentrations following a single intra-partum dose for the prevention of mother to child transmission in HIV-infected Thai women. *J Antimicrob Chemother* 64: 1265-1273.

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