Supplement to:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2B6* and Efavirenz-containing Antiretroviral Therapy

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GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2B6* and efavirenz therapy is published in full on the CPIC website (https://cpicpgx.org/guidelines/cpic-guideline-for-efavirenz-based-on-cyp2b6-genotype/) (1). Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

The PubMed® database (1966 to August 2017) was searched for the following keywords: (CYP2B6 OR cytochrome P450 2B6) AND efavirenz. Using these search terms, 282 publications were identified. Study inclusion criteria included publications that incorporated analyses for the association between *CYP2B6* genotypes and efavirenz pharmacokinetic parameters or efavirenz-related clinical outcomes (e.g., CNS toxicity, viral load, CD4+ T lymphocyte count, treatment discontinuation). Non-English manuscripts were excluded. Following the application of these inclusion and exclusion criteria, 150 publications were reviewed and included in the evidence table (**Table S1**).

The **CYP2B6 Frequency Table** (1) was made by searching the PubMed® database (1966 to May 2018) for the following keywords: (CYP2B6 OR cytochrome P450 2B6) AND (allele OR haplotype OR frequency OR population OR ethnic OR race OR racial OR ethnicity) with filter limits to retrieve "English" literature. Studies were considered for inclusion in the **CYP2B6 Frequency Table** if (1) the ancestry of the population was clearly indicated; (2) either allele

frequencies or genotype frequencies were reported; and (3) the method by which variants were genotyped was indicated. Given the limited information on *CYP2B6* allele frequency from the PubMed search, allele frequencies reported in the gnomAD browser (http://gnomad.broadinstitute.org/ - exomes and genomes) and ensembl (grch37.ensembl.org - exomes or genomes) were also included for several population groups.

GENETIC TEST INTERPRETATION

The haplotype, or star (*) allele name, is determined by a specific SNP or a combination of SNPs that are interrogated in the genotyping analysis. In addition, structural variants such as the *CYP2B6* breakpoint to a 529-bp intron 4 region with high homology to *CYP2B7P1*, resulting in the *CYP2B6*29* partial deletion allele (2) and *CYP2B6/2B7P1* duplicated fusion allele (*CYP2B6*30*) (3) have been identified. The frequency of the *CYP2B6*29* and *CYP2B6*30* alleles is very low in the population tested (~0.005% in African Americans and Asians, respectively) and are identified in other population studies as evidenced by entries in the Data Base of Genomic Variants (DGV) for this region. Although little is generally known about structural variants of the *CYP2B6* gene, these findings highlight that the *CYP2B6* gene can undergo rearrangements.

The genotypes that constitute the haplotype, or star (*) alleles for *CYP2B6*, and the rs# for each of the specific genomic nucleotide alterations that define the alleles, are described in the **CYP2B6 Allele Definition Table** online. The genotype results are generally reported as a diplotype, which includes one maternal and one paternal star allele (e.g., **1/*6*). The CYP2B6

function associated with each of the common star alleles is summarized in the **CYP2B6 Allele Functionality Table** online.

AVAILABLE GENETIC TEST OPTIONS

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at: http://www.ncbi.nlm.nih.gov/gtr. Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (4). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (**CYP2B6 Allele Definition Table**, **CYP2B6 Allele Functionality Table**, and **CYP2B6 Allele Frequency Table**) may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles.

Because the genomic structure of the *CYP2B6* gene is complex, there are several factors that cause potential uncertainty in the genotyping results and phenotype predictions. 1) Since it is impractical to test for every variation in the *CYP2B6* gene, patients with rare variants may be assigned a default genotype; this can happen when a patient's one or two rare allele(s) are not included in the genotype test used. Several variants of the *CYP2B6* gene with potential functional consequences are rare (MAF <1%) in most populations, and thus sequencing-based approaches are recommended if patients receiving efavirenz develop CNS toxicity. 2) In some cases, there

are gene units involved in duplication (*CYP2B6*30*) and partial deletion (*CYP2B6*29*). These two variants have potential functional impact and detecting structural variants like *CYP2B6*29* and **30* may have significant pharmacogenetic implications when accurately interpreting the metabolizer phenotype. For example, if just assessing copy number of exons 1 through 4, **30* could be misclassified as *CYP2B6*1x2*, which predicts an ultrarapid metabolizer phenotype. Both the two TaqMan qPCR assays (one in exon 4 and a second located 12.6 kb downstream of the *CYP2B6* gene) and a long-range PCR-based sequence strategy is needed to interrogate and correctly assign the breakpoint regions of the identified *CYP2B6*29* deletion and *CYP2B6*30* duplication fusion alleles (3). If the specific gene units involved in duplication and deletion or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate. Currently, these variants are rare across different populations. This along with the difficulty of the genotyping assays of these variants to incorporate into currently existing *CYP2B6* genotyping test platforms may limit the utility of genetic tests of structural variants. 3) Some SNPs exist on multiple alleles (e.g., c.516G>T is found in combination with other variants in 11 other *CYP2B6* alleles [**6, *7, *13, *19, *20, *26, *29, *34, *36, *37, *38*]. If testing indicates heterozygosity for multiple SNPs, it may be difficult to accurately assign a specific genotype. For example, an individual heterozygous for the c.516G>T, c.785A>G, and c.1459C>T variants in the *CYP2B6* gene could be classified as *CYP2B6*1/*7* or **5/*6* unless PCR-based haplotype determination or cloning methods is developed to distinguish between these two genotypes (5). 4) Allele frequencies may vary considerably among patients of different populations and ethnic backgrounds. For example, *CYP2B6*18* and other rare variants are relatively common in black populations and have a considerably lower prevalence, or are even absent, in other ethnic groups such as Caucasians of European ancestry. Thus, the alleles that should be tested for a given

population may vary considerably. 5) As described above, both *CYP2B6*29* (partial deletion) and *CYP2B6*30* (duplication representing CYP2B7/CYP2B6 hybrid [crossover in intron 4] require complementary assays including sequencing to distinguish between the two variants. 6) The possibility that rare SNPs or pseudogenes may interfere with PCR amplification and/or detection on a particular platform or assay cannot be ruled out. For example, testing for c.785A>G is challenging using the commercially available TaqMan assay (6). This SNP is located in a region that is identical *CYP2B7*, a nonfunctional pseudogene. Small *CYP2B6*-specific PCR amplicons bracketing c.785A>G cannot be reliably generated. Thus, the genotype assay is often performed in two steps where exon 5 is first amplified with primer sand then a pre-amplified *CYP2B6*-specific long-range PCR amplicon is used as a template for a custom TaqMan genotyping assay.

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Table S1** is graded on a scale of high, moderate, and weak (7) based upon the level of evidence:

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or the indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type/reference or variant-containing CYP2B6, *in vitro* CYP2B6 enzyme activity from tissues isolated from individuals of known *CYP2B6* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (8):

- **Strong** recommendation for the statement: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (9-14). See https://cpicpgx.org/guidelines/cpic-guideline-for-efavirenz-based-on-cyp2b6-genotype/ for resources to support the adoption of CPIC guidelines within an EHR (15). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *CYP2B6* genotype results in an EHR to guide efavirenz use.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (16). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript; *CYP2B6* Diplotype to Phenotype Table** (1)). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient's summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Efavirenz Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts;

https://cpicpgx.org/guidelines/cpic-guideline-for-efavirenz-based-on-cyp2b6-genotype/) (17, 18). The CDS alerts for *CYP2B6*/efavirenz apply for adult patients and for children > 40 kg.

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2B6* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see https://cpicpgx.org/guidelines/cpic-guideline-for-efavirenz-based-on-cyp2b6-genotype/) (19). Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (see https://cpicpgx.org/guidelines/cpic-guideline-for-efavirenz-based-on-cyp2b6-genotype/).

TABLE S1. EVIDENCE LINKING CYP2B6 TO EFAVIRENZ PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
In vitro	CYP2B6 is the major metabolizing enzyme for efavirenz.	Ward, *et al*. 2003 (20) Ogburn, *et al.* 2010 (21)	High
In vitro	No association found between *CYP2B6*4* (c.785 A>G) and catalytic activity of CYP2B6 or metabolism of efavirenz.	**Supports statement:** Zhang, *et al.* 2011 (22) **Does not support statement:** Ariyoshi, *et al.* 2011 (23)	Weak
In vitro	*CYP2B6*5* (c.1459 C>T) is associated with increased catalytic activity of CYP2B6 and increased efavirenz metabolism.	**Supports statement:** Zhang, *et al.* 2011 (22) **Does not support statement:** Desta, *et al*. 2007 (24)	Weak
In vitro	*CYP2B6*6* (c.516 G>T and c.785 A>G) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Zhang, *et al.* 2011 (22) Ariyoshi, *et al.* 2011 (23) Xu, *et al.* 2012 (25) Desta, *et al*. 2007 (24)	High
In vitro	*CYP2B6*7* (c.516 G>T, c.785 A>G, c.1459 C>T) is associated with increased catalytic activity of CYP2B6 and increased efavirenz metabolism.	Zhang, *et al.* 2011 (22)	Weak
In vitro	*CYP2B6*8* (c.415 A>G) is associated with abolished catalytic activity of CYP2B6 and no efavirenz metabolism.	Zhang, *et al.* 2011 (22)	Weak
In vitro	*CYP2B6*9* (c.516 G>T) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Zhang, *et al.* 2011 (22)	Weak
In vitro	*CYP2B6*13* (c.415 A>G, c.516 G>T, c.785 A>G) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Desta, *et al*. 2007 (24)	Weak
In vitro	*CYP2B6*14* (c.419 G>A) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Desta, *et al*. 2007 (24)	Weak

In vitro	*CYP2B6*15* (c.1172 T>A) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Desta, *et al*. 2007 (24)	Weak
Clinical	*CYP2B6* c.516 G>T is associated with increased efavirenz plasma, cerebrospinal fluid, breast milk, and/or hair concentrations.	Abdelhady, *et al.* 2016 (26) Rohrich, *et al.* 2016 (27) Abdelhady, *et al.* 2014 (28) Sanchez Martin, *et al.* 2013 (29) Swart, *et al.* 2013 (30) Sukasem, *et al.* 2013 (31) Jiang, *et al*. 2013 (32) Heil, *et al.* 2012 (33) Ngaimisi, *et al.* 2010 (34) Mukonzo, *et al.* 2009 (35) Kwara, *et al*. 2008 (36) Gatanaga, *et al.* 2007 (37) Rotger, *et al.* 2007 (38) Tsuchiya, *et al*. 2004 (39) Anagnostopoulos, *et al*. 2013 (40) Gallien, *et al.* 2017 (41) Sanchez-Martin, *et al*. 2016 (42) Sandkovsky, *et al.* 2017 (43) Orrell, *et al*. 2016 (44) Nightingale, *et al.* 2016 (45) Mukonzo, *et al*. 2016 (46) Bienczak, *et al.* 2016 (47) Pinillos, *et al.* 2016 (48) Swart, *et al.* 2016 (49) Cusato, *et al.* 2016 (50) Meng, *et al.* 2015 (51) Dickinson, *et al.* 2015 (52) Abdissa, *et al*. 2015 (53) Maganda, *et al.* 2016 (54) Dhoro, *et al.* 2015 (55) Olagunju, *et al.* 2015 (56) Habtewold, *et al.* 2015 (57) Olagunju, *et al*. 2015 (58)	High

		Sinxadi, *et al*. 2015 (59) Winston, *et al*. 2015 (60) Mukonzo, *et al*. 2014 (61) Olagunju, *et al.* 2014 (62) Lee, *et al.* 2014 (63) Ramachandran, *et al.* 2013 (64) Mukonzo, *et al.* 2014 (65) Bienvenu, *et al.* 2014 (66) Naftalin, *et al.* 2014 (67) Salem, *et al*. 2014 (68) Sarfo, *et al*. 2014 (69) Bertrand, *et al.* 2014 (70) Lee, *et al.* 2014 (71) Ngaimisi, *et al.* 2013 (72) Swart, *et al.* 2013 (30) Mukonzo, *et al*. 2013 (73) Sukasem, *et al.* 2013 (31) Manosuthi, *et al.* 2013 (74) Cortes, *et al*. 2013 (75) Holzinger, *et al.* 2012 (76) Gandhi, *et al.* 2012 (77) Mutwa, *et al*. 2012 (78) Sukasem, *et al*. 2012 (79) Heil, *et al.* 2012 (33) Viljoen, *et al*. 2012 (80) Maimbo, *et al*. 2012 (81) Sanchez, *et al*. 2011 (82) Habtewold, *et al.* 2011 (83) Ngaimisi, *et al*. 2011 (84) Strehlau, *et al.* 2011 (85) Kwara, *et al*. 2011 (86) Elens, *et al.* 2010 (87) Lindfelt, *et al*. 2010 (88) Gounden, *et al*. 2010 (89) Cabrera Figueroa, *et al.* 2010 (90)	

		Chen, *et al.* 2010 (91) Cabrera Figueroa, *et al*. 2010 (92) Uttayamakul, *et al.* 2010 (93) Kwara, *et al.* 2009 (94) Cohen, *et al.* 2009 (95) Leger, *et al.* 2009 (96) To, *et al*. 2009 (97) Mahungu, *et al.* 2009 (98) Cabrera, *et al.* 2009 (99) Kwara, *et al.* 2009 (100) Ramachandran, *et al.* 2009 (101) Ramachandran, *et al*. 2009 (102) Gupta, *et al.* 2008 (103) Kwara, *et al*. 2008 (36) Wyen, *et al*. 2008 (104) Nyakutira, *et al*. 2008 (105) Lowenhaupt, *et al*. 2007 (106) Saitoh, *et al*. 2007 (107) Motsinger, *et al*. 2006 (108) Wang, *et al*. 2006 (109) Ribaudo, *et al*. 2006 (110) Haas, *et al.* 2005 (111) Rodriguez-Novoa, *et al.* 2005 (112) Hasse, *et al.* 2005 (113) Liu, *et al.* 2017 (114) Haas, *et al*. 2004 (115) Rotger, *et al*. 2005 (116) Mathiesen, *et al.* 2006 (117) ter Heine, *et al*. 2008 (118) Puthanakit, *et al.* 2009 (119) Habtewold, *et al*. 2017 (120) Nemaura, *et al*. 2012 (121) Gengiah, *et al.* 2015 (122) Duarte*, et al.* 2017 (123) Aurpibul, *et al.* 2012 (124)	

		Nijhawan, *et al*. 2008 (125) Luo, *et al.* 2016 (126) Reay, *et al.* 2017 (127)	
Clinical	*CYP2B6* c.516 G>T is associated with increased efficacy (decreased viral load, increased T-cell count) of efavirenz therapy.	**Supports statement:** Vujkovic, *et al.* 2017 (128) Ramachandran, *et al.* 2013 (64) Sarfo, *et al.* 2014 (69) Frasco, *et al.* 2012 (129) Habtewold, *et al.* 2011 (83) **Does not support statement:** Muller, *et al.* 2017 (130) Queiroz, *et al.* 2017 (131) Orrell, *et al.* 2016 (44) Dickinson, *et al.* 2016 (132) Dickinson, *et al.* 2015 (52) Bienvenu, *et al.* 2014 (66) Naftalin, *et al.* 2014 (67) Ngaimisi, *et al.* 2013 (72) Glass, *et al.* 2012 (133) Gounden, *et al.* 2010 (89) Uttayamakul, *et al.* 2010 (93) Saitoh, *et al.* 2007 (107) Haas, *et al.* 2005 (111) Haas, *et al.* 2004 (115) Puthanakit, *et al.* 2009 (119) Rohrich, *et al.* 2016 (27)	Weak
Clinical	*CYP2B6* c.516 G>T is associated with increased toxicity (CNS side effects) of efavirenz therapy.	**Supports statement:** Gallien, *et al.* 2017 (41) Pinillos, *et al.* 2016 (48) Lee, *et al.* 2014 (71) Mukonzo, *et al.* 2013 (73) Strehlau, *et al.* 2011 (85) Cabrera Figueroa, *et al.* 2010 (90) Lowenhaupt, *et al.* 2007 (106)	Moderate

		Hasse, *et al*. 2005 (113) Haas, *et al.* 2004 (115) Rotger, *et al.* 2005 (116) Mathiesen, *et al.* 2006 (117) Torno, *et al.* 2008 (134) Nijhawan, *et al.* 2008 (125) Dhoro, *et al.* 2013 (135) Sanchez Martin, *et al.* 2013 (29) Anagnostopoulos, *et al.* 2013 (40) **Does not support statement:** Muller, *et al.* 2017 (130) Sandkovsky, *et al.* 2017 (43) Abdissa, *et al.* 2015 (53) Dhoro, *et al.* 2015 (55) Sarfo, *et al.* 2014 (69) Gounden, *et al.* 2010 (89) Ramachandran, *et al.* 2009 (101) Saitoh, *et al.* 2007 (107) Aurpibul, *et al.* 2012 (124)	
Clinical	*CYP2B6* c.516 G>T is associated with increased toxicity (hepatic injury) of efavirenz therapy.	**Supports statement:** Elsharkawy, *et al.* 2013 (136) Mugusi, *et al.* 2012 (137) Yimer, *et al*. 2011 (138) Yimer, *et al.* 2012 (139) Manosuthi, *et al.* 2014 (140) **Does not support statement:** Queiroz, *et al.* 2017 (131)	Moderate
Clinical	*CYP2B6* c.516 G>T is associated with increased toxicity (QTc prolongation) of efavirenz therapy.	Abdelhady, *et al.* 2016 (26)	Weak
Clinical	*CYP2B6* c.516 G>T is associated with discontinuation of efavirenz therapy.	**Supports statement:** Dickinson, *et al.* 2016 (132) Dickinson, *et al.* 2015 (52) Wyen, *et al*. 2011 (141)	Moderate

		Does not support statement: Powers, *et al.* 2009 (142) Haas, *et al.* 2004 (115)	
Clinical	No association found between *CYP2B6*2* (c.64 C>T) and efavirenz plasma and/or hair concentrations.	Sukasem, *et al.* 2013 (31) Manosuthi, *et al.* 2013 (74) Sukasem, *et al*. 2012 (79) Rohrich, *et al.* 2016 (27) Sanchez*, et al.* 2011 (82)	Weak
Clinical	*CYP2B6*2* (c.64 C>T) is associated with increased toxicity (CNS side effects) of efavirenz therapy.	Usami, *et al.* 2007 (143)	Weak
Clinical	*CYP2B6*4* (c.785 A>G) is associated with increased efavirenz plasma concentrations.[b]	**Supports statement:** Meng, *et al.* 2015 (51) Sukasem, *et al.* 2013 (31) Manosuthi, *et al.* 2013 (74) Mutwa, *et al*. 2012 (78) Sukasem, *et al*. 2012 (79) Heil, *et al.* 2012 (33) Maimbo, *et al.* 2012 (81) Sanchez*, et al.* 2011 (82) Lindfelt, *et al.* 2010 (88) Duarte, *et al*. 2017 (123) **Does not support statement:** Ribaudo, *et al.* 2010 (144) Chen, *et al*. 2010 (91) Wang, *et al*. 2006 (109) Rotger, *et al*. 2007 (38) Reay, *et al.* 2017 (127)	Weak
Clinical	No association found between *CYP2B6*5* (c.1459 C>T) and efavirenz plasma and/or hair concentrations.	Bertrand, *et al.* 2014 (70) Sanchez*, et al.* 2011 (82) Sukasem, *et al.* 2013 (31) Manosuthi, *et al.* 2013 (74) Heil, *et al.* 2012 (33) Lindfelt, *et al.* 2010 (88)	High

		Ribaudo, *et al.* 2010 (144) Wyen, *et al*. 2008 (104) Rotger, *et al*. 2007 (38) Burger, *et al*. 2006 (145) Haas, *et al.* 2005 (111) Rohrich, *et al.* 2016 (27) Haas, *et al.* 2004 (115)	
Clinical	*CYP2B6*11* (c.136 A>G) is associated with increased efavirenz plasma concentrations.	**Supports statement:** Mukonzo, *et al.* 2016 (46) Mukonzo, *et al.* 2014 (61) Mukonzo, *et al.* 2013 (73) Mukonzo, *et al.* 2009 (35) **Does not support statement:** Swart, *et al*. 2016 (49) Mukonzo, *et al.* 2014 (65) Swart, *et al*. 2013 (30) Sanchez*, et al.* 2011 (82)	Weak
Clinical	No association found between *CYP2B6*11* (c.136 A>G) and increased toxicity (CNS side effects) of efavirenz therapy.	Mukonzo, *et al.* 2013 (73)	Weak
Clinical	*CYP2B6*16* (c.785 A>G and c.983 T>C) is associated with increased efavirenz plasma concentrations.	Wang, *et al.* 2006 (109)	Moderate
Clinical	No association found between *CYP2B6*17* and efavirenz hair concentrations.[c]	Rohrich, *et al.* 2016 (27)	Weak
Clinical	*CYP2B6*18* (c.983 T>C) is associated with increased efavirenz plasma and/or hair concentrations.	**Supports statement:** Orrell, *et al.* 2016 (44) Bienczak, *et al.* 2016 (47) Swart, *et al*. 2016 (49) Rohrich, *et al.* 2016 (27) Dickinson, *et al.* 2015 (52) Dhoro, *et al.* 2015 (55) Sinxadi, *et al.* 2015 (59) Sarfo, *et al.* 2014 (69) Swart, *et al*. 2013 (30) Holzinger, *et al*. 2012 (76)	High

		Gandhi, *et al.* 2012 (77) Mutwa, *et al*. 2012 (78) Heil, *et al.* 2012 (33) Maimbo, *et al.* 2012 (81) Elens, *et al*. 2010 (87) Wyen, *et al*. 2008 (104) Gengiah, *et al.* 2015 (122) Reay, *et al.* 2017 (127) **Does not support statement:** Maganda, *et al*. 2016 (54) Olagunju, *et al*. 2015 (56) Olagunju, *et al*. 2015 (58) Bienvenu, *et al.* 2014 (66) Kwara, *et al*. 2009 (94) Kwara, *et al*. 2009 (100) Duarte, *et al*. 2017 (123)	
Clinical	No association found between *CYP2B6*18* (c.983 T>C) and increased efficacy (decreased viral load, increased T-cell count) of efavirenz therapy.	Orrell, *et al.* 2016 (44) Dickinson, *et al.* 2016 (132) Rohrich, *et al.* 2016 (27) Dickinson, *et al.* 2015 (52) Bienvenu, *et al.* 2014 (66) Frasco, *et al.* 2012 (129)	High
Clinical	*CYP2B6*18* (c.983 T>C) is associated with decreased toxicity (CNS side effects) of efavirenz therapy.	**Supports statement:** Dickinson, *et al.* 2016 (132) Dhoro, *et al.* 2013 (135) **Does not support statement:** Dhoro, *et al.* 2015 (55) Sarfo, *et al.* 2014 (69)	Weak
Clinical	No association found between *CYP2B6*18* (c.983 T>C) and discontinuation of efavirenz therapy.	Dickinson, *et al.* 2016 (132) Dickinson, *et al.* 2015 (52)	Moderate
Clinical	*CYP2B6* g.15582 C>T is associated with increased efavirenz plasma concentrations.	**Supports statement:** Sinxadi, *et al.* 2015 (59) Holzinger, *et al*. 2012 (76)	Weak

		Does not support statement: Evans, *et al.* 2015 (146) Dickinson, *et al.* 2015 (52)	
Clinical	No association found between *CYP2B6* g.15582 C>T and increased efficacy (decreased viral load) of efavirenz therapy.	Dickinson, *et al.* 2016 (132) Dickinson, *et al.* 2015 (52)	Moderate
Clinical	*CYP2B6* g.15582 C>T is associated with increased toxicity (CNS side effects) of efavirenz therapy.	Dickinson, *et al.* 2016 (132)	Weak
Clinical	No association found between *CYP2B6* g.15582 C>T and discontinuation of efavirenz therapy.	Dickinson, *et al.* 2016 (132) Dickinson, *et al.* 2015 (52)	Moderate
Clinical	*CYP2B6* g.18492 T>C is associated with decreased efavirenz plasma concentrations.	Manosuthi, *et al.* 2014 (147) Sukasem, *et al*. 2014 (148) Sukasem, *et al*. 2014 (149) Manosuthi, *et al.* 2013 (74) Sukasem, *et al*. 2012 (79)	Moderate
Clinical	*CYP2B6* g.21563 C>T is associated with increased efavirenz plasma concentrations.	Sukasem, *et al*. 2012 (79) Manosuthi, *et al.* 2013 (74)	Weak
Clinical	CYP2B6 poor metabolizers have decreased metabolite-to-efavirenz plasma concentration ratios.	Aouri, *et al*. 2016 (150)	Moderate
Clinical	CYP2B6 poor metabolizers have increased efavirenz plasma concentrations.	Luetkemeyer, *et al*. 2015 (151) Sinxadi, *et al.* 2015 (59) Dooley, *et al*. 2015 (152) McIlleron, *et al*. 2013 (153) Dooley, *et al*. 2012 (154) Ribaudo, *et al.* 2010 (144) Leger, *et al*. 2009 (96) Haas, *et al*. 2009 (155) Arab-Alameddine, *et al.* 2009 (156) Rotger, *et al*. 2007 (38) Gross, *et al*. 2017 (157) Robarge, *et al.* 2016 (158) Fayet Mello, *et al*. 2011 (159)	High
Clinical	CYP2B6 intermediate metabolizers have increased efavirenz plasma concentrations.	Dooley, *et al*. 2015 (152) McIlleron, *et al*. 2013 (153) Dooley, *et al*. 2012 (154)	High

		Robarge, *et al.* 2016 (158)	
Clinical	CYP2B6 poor metabolizers are at an increased risk of discontinuing efavirenz therapy.	Cummins, *et al*. 2015 (160) Leger, *et al*. 2016 (161)	Moderate
Clinical	No association found between CYP2B6 intermediate metabolizers and discontinuation of efavirenz therapy.	Leger, *et al*. 2016 (161)	Moderate
Clinical	CYP2B6 poor metabolizers have increased efavirenz toxicity (CNS side effects).	**Supports statement:** Johnson, *et al*. 2013 (162) Ribaudo, *et al.* 2010 (144) Mollan, *et al*. 2017 (163) **Does not support statement:** Gross, *et al*. 2017 (157)	Moderate
Clinical	CYP2B6 intermediate metabolizers have increased efavirenz toxicity (CNS side effects).	**Supports statement:** Mollan, *et al*. 2017 (163) **Does not support statement:** Johnson, *et al*. 2013 (162) Ribaudo, *et al.* 2010 (144) Gross, *et al*. 2017 (157)	Weak
Clinical	CYP2B6 poor metabolizers have increased efavirenz efficacy (decreased viral load, increased T-cell count).	**Supports statement:** Frasco, *et al.* 2012 (129) Ribaudo, *et al.* 2010 (144) **Does not support statement:** Gross, *et al*. 2017 (157) Haas, *et al.* 2014 (164)	Weak
Clinical	CYP2B6 intermediate metabolizers have increased efavirenz efficacy (decreased viral load, increased T-cell count).	**Supports statement:** Frasco, *et al.* 2012 (129) **Does not support statement:** Ribaudo, *et al.* 2010 (144) Gross, *et al*. 2017 (157) Haas, *et al.* 2014 (164)	Weak
Clinical	Efavirenz dosing based on *CYP2B6* genotype (e.g., c.516 G>T) is associated with therapeutic efavirenz plasma concentrations.	Bolton Moore, *et al*. 2017 (165) Hui, *et al*. 2016 (166)	High

		Damronglerd, *et al*. 2015 (167) Martin, *et al.* 2014 (168) Mukonzo, *et al.* 2014 (61) Sanchez*, et al.* 2011 (82) Cabrera Figueroa, *et al*. 2010 (90) Cabrera Figueroa, *et al*. 2010 (92) Nyakutira, *et al*. 2008 (105) Gatanaga, *et al.* 2007 (37) Mathiesen, *et al.* 2006 (117) ter Heine, *et al.* 2008 (118) Nemaura, *et al*. 2012 (121)	
Clinical	Efavirenz dosing based on *CYP2B6* genotype (e.g., c.516 G>T) maintains efficacy (as indicated by viral load and/or CD4+ T lymphocyte count).	Damronglerd, *et al*. 2015 (167) Martin, *et al.* 2014 (168) Gatanaga, *et al.* 2007 (37)	Moderate
Clinical	Efavirenz dosing based on *CYP2B6* genotype (e.g., c.516 G>T) is associated with decreased toxicity (CNS side effects).	**Supports statement:** Bushyakanist, *et al*. 2015 (169) Martin, *et al.* 2014 (168) Cabrera Figueroa, *et al.* 2010 (92) Gatanaga, *et al.* 2007 (37) Mathiesen, *et al.* 2006 (117) Torno, *et al.* 2008 (134) **Does not support statement:** Damronglerd, *et al*. 2015 (167)	Moderate
Clinical	Efavirenz dose reduction in patients with elevated efavirenz plasma concentrations (e.g., CYP2B6 poor metabolizers) yields therapeutic efavirenz plasma concentrations, decreases toxicity (CNS side effects), and maintains efficacy (as indicated by viral load).	Fayet Mello, *et al.* 2011 (159)	High

[a]Rating scheme described in the **Supplemental Material**

[b]The *CYP2B6*4* (c.785 A>G) functional assignment is "increased function." However, *CYP2B6*4* has frequently been associated with increased efavirenz plasma concentrations in clinical studies, likely due to the fact that it is often inherited with c.516 G>T, a SNP associated with decreased CYP2B6 function. Together, 785 A>G and 516 G>T comprise the *CYP2B6*6* haplotype.

[c]Decreased efavirenz concentrations in hair samples were associated with *CYP2B6*17* in the South African Black cohort only.

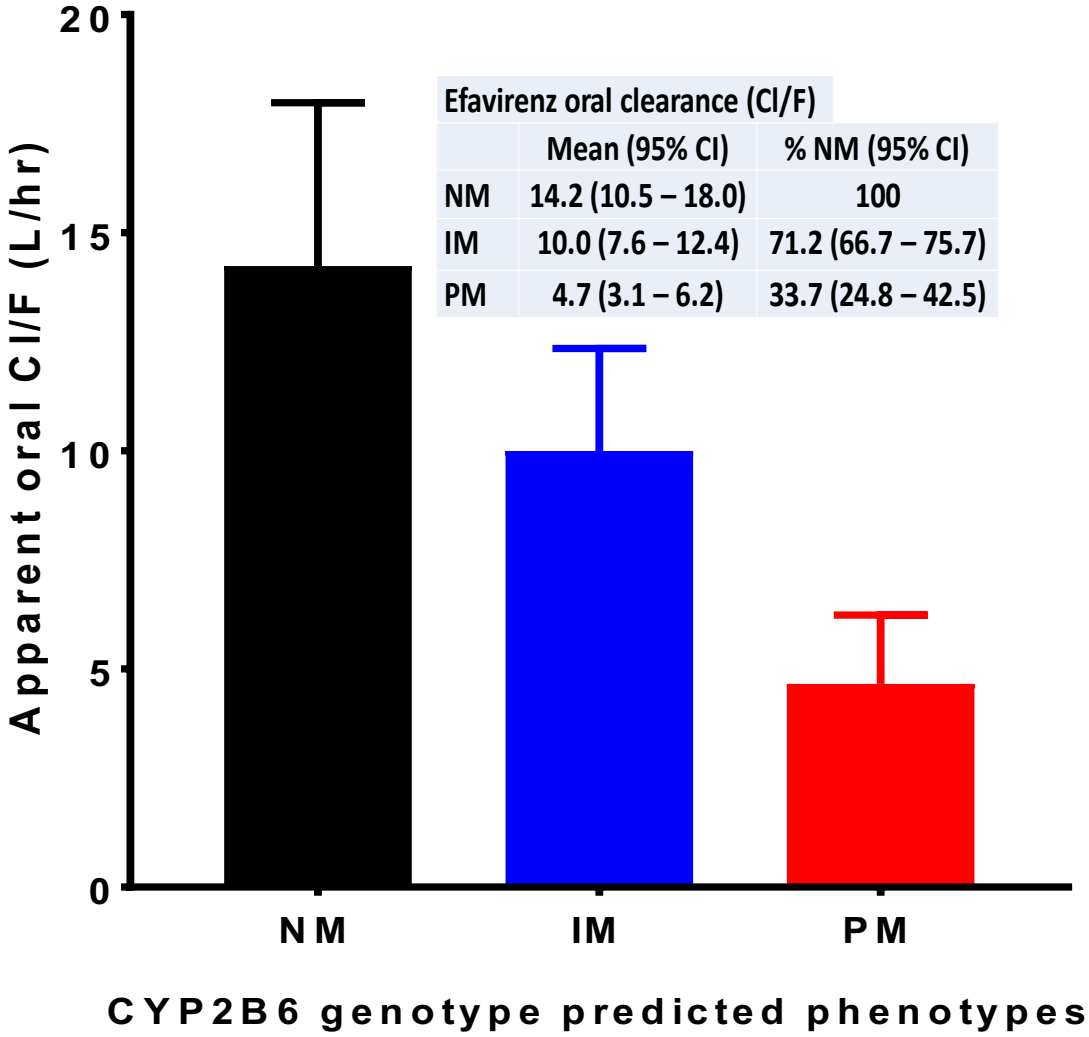

FIGURE S1. APPARENT ORAL CLEARANCE (CL/F) OF EFAVIRENZ (600 MG/DAY) IN HIV-POSITIVE INDIVIDUALS GENOTYPED FOR *CYP2B6* VARIANTS. Genotype predicted phenotypes were based on *CYP2B6*6* and **18* alleles as described in Table 1 (main manuscript). The data were derived from 10 independent clinical studies (65, 70, 90, 99, 105, 120, 123, 156, 166, 170).

REFERENCES

(1) CPIC. *CPIC Guideline for Efavirenz based on CYP2B6 genotype*. < https://cpicpgx.org/guidelines/cpic-guideline-for-efavirenz-based-on-cyp2b6-genotype> (2018).

(2) Rotger, M. *et al.* Partial deletion of CYP2B6 owing to unequal crossover with CYP2B7. *Pharmacogenet Genomics* **17**, 885-90 (2007).

(3) Martis, S., Mei, H., Vijzelaar, R., Edelmann, L., Desnick, R.J. & Scott, S.A. Multi-ethnic cytochrome-P450 copy number profiling: novel pharmacogenetic alleles and mechanism of copy number variation formation. *Pharmacogenomics J* **13**, 558-66 (2013).

(4) Kalman, L.V. *et al.* Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. *Clin Pharmacol Ther* **99**, 172-85 (2016).

(5) Futatsugawa, Y., Kubota, T., Ishiguro, A., Suzuki, H., Ishikawa, H. & Iga, T. PCR-based haplotype determination to distinguish CYP2B6*1/*7 and *5/*6. *Clin Chem* **50**, 1472-3 (2004).

(6) Twist, G.P., Gaedigk, R., Leeder, J.S. & Gaedigk, A. High-resolution melt analysis to detect sequence variations in highly homologous gene regions: application to CYP2B6. *Pharmacogenomics* **14**, 913-22 (2013).

(7) Valdes R, P.D., Linder MW. Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice. In: *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* (Washington, DC, 2010).

(8) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf> (2018). Accessed June 18 2018.

(9) Shuldiner, A.R. *et al.* The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. *Clin Pharmacol Ther* **94**, 207-10 (2013).

(10) Wilke, R.A. *et al.* The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther* **89**, 379-86 (2011).

(11) Peterson, J.F. *et al.* Electronic health record design and implementation for pharmacogenomics: a local perspective. *Genet Med* **15**, 833-41 (2013).

(12) Gottesman, O. *et al.* The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genet Med* **15**, 761-71 (2013).

(13) Kullo, I.J., Jarvik, G.P., Manolio, T.A., Williams, M.S. & Roden, D.M. Leveraging the electronic health record to implement genomic medicine. *Genet Med* **15**, 270-1 (2013).

(14) Hicks, J.K., Dunnenberger, H.M., Gumpper, K.F., Haidar, C.E. & Hoffman, J.M. Integrating pharmacogenomics into electronic health records with clinical decision support. *Am J Health Syst Pharm* **73**, 1967-76 (2016).

(15) Hoffman, J.M. *et al.* Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *J Am Med Inform Assoc* **23**, 796-801 (2016).

(16) Hicks, J.K. *et al.* A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. *Clin Pharmacol Ther* **92**, 563-6 (2012).

(17) Bell, G.C. *et al.* Development and use of active clinical decision support for preemptive pharmacogenomics. *J Am Med Inform Assoc* **21**, e93-9 (2014).

(18) Pulley, J.M. *et al.* Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clin Pharmacol Ther* **92**, 87-95 (2012).
(19) Caudle, K.E. *et al.* Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genet Med* **19**, 215-23 (2017).
(20) Ward, B.A., Gorski, J.C., Jones, D.R., Hall, S.D., Flockhart, D.A. & Desta, Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. *J Pharmacol Exp Ther* **306**, 287-300 (2003).
(21) Ogburn, E.T., Jones, D.R., Masters, A.R., Xu, C., Guo, Y. & Desta, Z. Efavirenz primary and secondary metabolism in vitro and in vivo: identification of novel metabolic pathways and cytochrome P450 2A6 as the principal catalyst of efavirenz 7-hydroxylation. *Drug Metab Dispos* **38**, 1218-29 (2010).
(22) Zhang, H., Sridar, C., Kenaan, C., Amunugama, H., Ballou, D.P. & Hollenberg, P.F. Polymorphic variants of cytochrome P450 2B6 (CYP2B6.4-CYP2B6.9) exhibit altered rates of metabolism for bupropion and efavirenz: a charge-reversal mutation in the K139E variant (CYP2B6.8) impairs formation of a functional cytochrome p450-reductase complex. *J Pharmacol Exp Ther* **338**, 803-9 (2011).
(23) Ariyoshi, N. *et al.* Q172H replacement overcomes effects on the metabolism of cyclophosphamide and efavirenz caused by CYP2B6 variant with Arg262. *Drug Metab Dispos* **39**, 2045-8 (2011).
(24) Desta, Z. *et al.* Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. *Pharmacogenomics* **8**, 547-58 (2007).
(25) Xu, C., Ogburn, E.T., Guo, Y. & Desta, Z. Effects of the CYP2B6*6 allele on catalytic properties and inhibition of CYP2B6 in vitro: implication for the mechanism of reduced efavirenz metabolism and other CYP2B6 substrates in vivo. *Drug Metab Dispos* **40**, 717-25 (2012).
(26) Abdelhady, A.M. *et al.* Efavirenz Inhibits the Human Ether-A-Go-Go Related Current (hERG) and Induces QT Interval Prolongation in CYP2B6*6*6 Allele Carriers. *J Cardiovasc Electrophysiol* **27**, 1206-13 (2016).
(27) Rohrich, C.R. *et al.* CYP2B6*6 and CYP2B6*18 Predict Long-Term Efavirenz Exposure Measured in Hair Samples in HIV-Positive South African Women. *AIDS Res Hum Retroviruses* **32**, 529-38 (2016).
(28) Abdelhady, A.M., Desta, Z., Jiang, F., Yeo, C.W., Shin, J.G. & Overholser, B.R. Population pharmacogenetic-based pharmacokinetic modeling of efavirenz, 7-hydroxy- and 8-hydroxyefavirenz. *J Clin Pharmacol* **54**, 87-96 (2014).
(29) Sanchez Martin, A., Cabrera Figueroa, S., Cruz Guerrero, R., Hurtado, L.P., Hurle, A.D. & Carracedo Alvarez, A. Impact of pharmacogenetics on CNS side effects related to efavirenz. *Pharmacogenomics* **14**, 1167-78 (2013).
(30) Swart, M., Skelton, M., Ren, Y., Smith, P., Takuva, S. & Dandara, C. High predictive value of CYP2B6 SNPs for steady-state plasma efavirenz levels in South African HIV/AIDS patients. *Pharmacogenet Genomics* **23**, 415-27 (2013).
(31) Sukasem, C. *et al.* High plasma efavirenz concentration and CYP2B6 polymorphisms in Thai HIV-1 infections. *Drug Metab Pharmacokinet* **28**, 391-7 (2013).

(32) Jiang, F. *et al.* Effects of clopidogrel and itraconazole on the disposition of efavirenz and its hydroxyl metabolites: exploration of a novel CYP2B6 phenotyping index. *Br J Clin Pharmacol* **75**, 244-53 (2013).
(33) Heil, S.G. *et al.* Associations between ABCB1, CYP2A6, CYP2B6, CYP2D6, and CYP3A5 alleles in relation to efavirenz and nevirapine pharmacokinetics in HIV-infected individuals. *Ther Drug Monit* **34**, 153-9 (2012).
(34) Ngaimisi, E. *et al.* Long-term efavirenz autoinduction and its effect on plasma exposure in HIV patients. *Clin Pharmacol Ther* **88**, 676-84 (2010).
(35) Mukonzo, J.K. *et al.* A novel polymorphism in ABCB1 gene, CYP2B6*6 and sex predict single-dose efavirenz population pharmacokinetics in Ugandans. *Br J Clin Pharmacol* **68**, 690-9 (2009).
(36) Kwara, A. *et al.* Pharmacokinetics of efavirenz when co-administered with rifampin in TB/HIV co-infected patients: pharmacogenetic effect of CYP2B6 variation. *J Clin Pharmacol* **48**, 1032-40 (2008).
(37) Gatanaga, H. *et al.* Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis* **45**, 1230-7 (2007).
(38) Rotger, M. *et al.* Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther* **81**, 557-66 (2007).
(39) Tsuchiya, K. *et al.* 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**, 1322-6 (2004).
(40) Anagnostopoulos, A. *et al.* Efavirenz intoxication due to a new CYP2B6 constellation. *Antivir Ther* **18**, 739-43 (2013).
(41) Gallien, S. *et al.* Cytochrome 2B6 polymorphism and efavirenz-induced central nervous system symptoms : a substudy of the ANRS ALIZE trial. *HIV Med* **18**, 537-45 (2017).
(42) Sanchez-Martin, A. *et al.* Gene-gene interactions between DRD3, MRP4 and CYP2B6 polymorphisms and its influence on the pharmacokinetic parameters of efavirenz in HIV infected patients. *Drug Metab Pharmacokinet* **31**, 349-55 (2016).
(43) Sandkovsky, U. *et al.* Impact of efavirenz pharmacokinetics and pharmacogenomics on neuropsychological performance in older HIV-infected patients. *J Antimicrob Chemother* **72**, 200-4 (2017).
(44) Orrell, C. *et al.* Effect of mid-dose efavirenz concentrations and CYP2B6 genotype on viral suppression in patients on first-line antiretroviral therapy. *Int J Antimicrob Agents* **47**, 466-72 (2016).
(45) Nightingale, S. *et al.* Efavirenz and Metabolites in Cerebrospinal Fluid: Relationship with CYP2B6 c.516G-->T Genotype and Perturbed Blood-Brain Barrier Due to Tuberculous Meningitis. *Antimicrob Agents Chemother* **60**, 4511-8 (2016).
(46) Mukonzo, J.K., Bisaso, R.K., Ogwal-Okeng, J., Gustafsson, L.L., Owen, J.S. & Aklillu, E. CYP2B6 genotype-based efavirenz dose recommendations during rifampicin-based antituberculosis cotreatment for a sub-Saharan Africa population. *Pharmacogenomics* **17**, 603-13 (2016).
(47) Bienczak, A. *et al.* The impact of genetic polymorphisms on the pharmacokinetics of efavirenz in African children. *Br J Clin Pharmacol* **82**, 185-98 (2016).

(48) Pinillos, F. *et al.* Case report: Severe central nervous system manifestations associated with aberrant efavirenz metabolism in children: the role of CYP2B6 genetic variation. *BMC Infect Dis* **16**, 56 (2016).
(49) Swart, M. *et al.* An Expanded Analysis of Pharmacogenetics Determinants of Efavirenz Response that Includes 3'-UTR Single Nucleotide Polymorphisms among Black South African HIV/AIDS Patients. *Front Genet* **6**, 356 (2015).
(50) Cusato, J. *et al.* Efavirenz pharmacogenetics in a cohort of Italian patients. *Int J Antimicrob Agents* **47**, 117-23 (2016).
(51) Meng, X. *et al.* Effect of CYP2B6 Gene Polymorphisms on Efavirenz Plasma Concentrations in Chinese Patients with HIV Infection. *PLoS One* **10**, e0130583 (2015).
(52) Dickinson, L. *et al.* Pharmacokinetic and Pharmacodynamic Comparison of Once-Daily Efavirenz (400 mg vs. 600 mg) in Treatment-Naive HIV-Infected Patients: Results of the ENCORE1 Study. *Clin Pharmacol Ther* **98**, 406-16 (2015).
(53) Abdissa, A. *et al.* Lipid-based nutrient supplements do not affect efavirenz but lower plasma nevirapine concentrations in Ethiopian adult HIV patients. *HIV Med* **16**, 403-11 (2015).
(54) Maganda, B.A., Minzi, O.M., Ngaimisi, E., Kamuhabwa, A.A. & Aklillu, E. CYP2B6*6 genotype and high efavirenz plasma concentration but not nevirapine are associated with low lumefantrine plasma exposure and poor treatment response in HIV-malaria-coinfected patients. *Pharmacogenomics J* **16**, 88-95 (2016).
(55) Dhoro, M. *et al.* 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**, 4 (2015).
(56) Olagunju, A. *et al.* Breast milk pharmacokinetics of efavirenz and breastfed infants' exposure in genetically defined subgroups of mother-infant pairs: an observational study. *Clin Infect Dis* **61**, 453-63 (2015).
(57) Habtewold, A. *et al.* Is there a need to increase the dose of efavirenz during concomitant rifampicin-based antituberculosis therapy in sub-Saharan Africa? The HIV-TB pharmagene study. *Pharmacogenomics* **16**, 1047-64 (2015).
(58) Olagunju, A. *et al.* Pharmacogenetics of pregnancy-induced changes in efavirenz pharmacokinetics. *Clin Pharmacol Ther* **97**, 298-306 (2015).
(59) Sinxadi, P.Z. *et al.* Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. *Br J Clin Pharmacol* **80**, 146-56 (2015).
(60) Winston, A. *et al.* Cerebrospinal fluid exposure of efavirenz and its major metabolites when dosed at 400 mg and 600 mg once daily: a randomized controlled trial. *Clin Infect Dis* **60**, 1026-32 (2015).
(61) Mukonzo, J.K., Nanzigu, S., Waako, P., Ogwal-Okeng, J., Gustafson, L.L. & Aklillu, E. CYP2B6 genotype, but not rifampicin-based anti-TB cotreatments, explains variability in long-term efavirenz plasma exposure. *Pharmacogenomics* **15**, 1423-35 (2014).
(62) Olagunju, A. *et al.* CYP2B6 516G>T (rs3745274) and smoking status are associated with efavirenz plasma concentration in a Serbian cohort of HIV patients. *Ther Drug Monit* **36**, 734-8 (2014).
(63) Lee, K.Y. *et al.* Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. *PLoS One* **9**, e88497 (2014).

(64) Ramachandran, G. *et al.* Lack of association between plasma levels of non-nucleoside reverse transcriptase inhibitors & virological outcomes during rifampicin co-administration in HIV-infected TB patients. *Indian J Med Res* **138**, 955-61 (2013).
(65) Mukonzo, J.K. *et al.* Pharmacogenetic-based efavirenz dose modification: suggestions for an African population and the different CYP2B6 genotypes. *PLoS One* **9**, e86919 (2014).
(66) Bienvenu, E., Swart, M., Dandara, C. & Ashton, M. The role of genetic polymorphisms in cytochrome P450 and effects of tuberculosis co-treatment on the predictive value of CYP2B6 SNPs and on efavirenz plasma levels in adult HIV patients. *Antiviral Res* **102**, 44-53 (2014).
(67) Naftalin, C.M., Chan, K.C., Wong, K.H., Cheung, S.W., Chan, R.C. & Lee, S.S. CYP2B6-G516T genotype influences plasma efavirenz concentration in a Hong Kong population, allowing potential individualization of therapy. *HIV Med* **15**, 63-4 (2014).
(68) Salem, A.H., Fletcher, C.V. & Brundage, R.C. Pharmacometric characterization of efavirenz developmental pharmacokinetics and pharmacogenetics in HIV-infected children. *Antimicrob Agents Chemother* **58**, 136-43 (2014).
(69) Sarfo, F.S. *et al.* Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients. *J Antimicrob Chemother* **69**, 491-9 (2014).
(70) Bertrand, J. *et al.* Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. *J Infect Dis* **209**, 399-408 (2014).
(71) Lee, S.S. *et al.* Sleep quality in efavirenz-treated Chinese HIV patients - comparing between GT and GG genotype of CYP2B6-516 G/T polymorphisms. *Int J STD AIDS* **25**, 193-200 (2014).
(72) Ngaimisi, E. *et al.* Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. *PLoS One* **8**, e67946 (2013).
(73) Mukonzo, J.K. *et al.* Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: a prospective cohort study. *BMC Infect Dis* **13**, 261 (2013).
(74) Manosuthi, W. *et al.* Impact of pharmacogenetic markers of CYP2B6, clinical factors, and drug-drug interaction on efavirenz concentrations in HIV/tuberculosis-coinfected patients. *Antimicrob Agents Chemother* **57**, 1019-24 (2013).
(75) Cortes, C.P., Siccardi, M., Chaikan, A., Owen, A., Zhang, G. & la Porte, C.J. Correlates of efavirenz exposure in Chilean patients affected with human immunodeficiency virus reveals a novel association with a polymorphism in the constitutive androstane receptor. *Ther Drug Monit* **35**, 78-83 (2013).
(76) Holzinger, E.R. *et al.* Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several CYP2B6 variants. *Pharmacogenet Genomics* **22**, 858-67 (2012).
(77) Gandhi, M. *et al.* A single-nucleotide polymorphism in CYP2B6 leads to >3-fold increases in efavirenz concentrations in plasma and hair among HIV-infected women. *J Infect Dis* **206**, 1453-61 (2012).
(78) Mutwa, P.R. *et al.* Mid-dosing interval efavirenz plasma concentrations in HIV-1-infected children in Rwanda: treatment efficacy, tolerability, adherence, and the influence of CYP2B6 polymorphisms. *J Acquir Immune Defic Syndr* **60**, 400-4 (2012).

(79) Sukasem, C. *et al.* Pharmacogenetic markers of CYP2B6 associated with efavirenz plasma concentrations in HIV-1 infected Thai adults. *Br J Clin Pharmacol* **74**, 1005-12 (2012).
(80) Viljoen, M., Karlsson, M.O., Meyers, T.M., Gous, H., Dandara, C. & Rheeders, M. Influence of CYP2B6 516G>T polymorphism and interoccasion variability (IOV) on the population pharmacokinetics of efavirenz in HIV-infected South African children. *Eur J Clin Pharmacol* **68**, 339-47 (2012).
(81) Maimbo, M., Kiyotani, K., Mushiroda, T., Masimirembwa, C. & Nakamura, Y. CYP2B6 genotype is a strong predictor of systemic exposure to efavirenz in HIV-infected Zimbabweans. *Eur J Clin Pharmacol* **68**, 267-71 (2012).
(82) Sanchez, A. *et al.* Population pharmacokinetic/pharmacogenetic model for optimization of efavirenz therapy in Caucasian HIV-infected patients. *Antimicrob Agents Chemother* **55**, 5314-24 (2011).
(83) Habtewold, A. *et al.* Long-term effect of efavirenz autoinduction on plasma/peripheral blood mononuclear cell drug exposure and CD4 count is influenced by UGT2B7 and CYP2B6 genotypes among HIV patients. *J Antimicrob Chemother* **66**, 2350-61 (2011).
(84) Ngaimisi, E. *et al.* Effect of rifampicin and CYP2B6 genotype on long-term efavirenz autoinduction and plasma exposure in HIV patients with or without tuberculosis. *Clin Pharmacol Ther* **90**, 406-13 (2011).
(85) Strehlau, R. *et al.* Absence seizures associated with efavirenz initiation. *Pediatr Infect Dis J* **30**, 1001-3 (2011).
(86) Kwara, A., Lartey, M., Sagoe, K.W. & Court, M.H. Paradoxically elevated efavirenz concentrations in HIV/tuberculosis-coinfected patients with CYP2B6 516TT genotype on rifampin-containing antituberculous therapy. *AIDS* **25**, 388-90 (2011).
(87) Elens, L., Vandercam, B., Yombi, J.C., Lison, D., Wallemacq, P. & Haufroid, V. Influence of host genetic factors on efavirenz plasma and intracellular pharmacokinetics in HIV-1-infected patients. *Pharmacogenomics* **11**, 1223-34 (2010).
(88) Lindfelt, T., O'Brien, J., Song, J.C., Patel, R. & Winslow, D.L. Efavirenz plasma concentrations and cytochrome 2B6 polymorphisms. *Ann Pharmacother* **44**, 1572-8 (2010).
(89) Gounden, V., van Niekerk, C., Snyman, T. & George, J.A. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther* **7**, 32 (2010).
(90) Cabrera Figueroa, S. *et al.* The convergence of therapeutic drug monitoring and pharmacogenetic testing to optimize efavirenz therapy. *Ther Drug Monit* **32**, 579-85 (2010).
(91) Chen, J. *et al.* CYP2B6 polymorphism and nonnucleoside reverse transcriptase inhibitor plasma concentrations in Chinese HIV-infected patients. *Ther Drug Monit* **32**, 573-8 (2010).
(92) Cabrera Figueroa, S., Iglesias Gomez, A., Sanchez Martin, A., de la Paz Valverde Merino, M., Dominguez-Gil Hurle, A. & Cordero Sanchez, M. Long-term efficacy and safety of efavirenz dose reduction to 200 mg once daily in a Caucasian patient with HIV. *Clin Drug Investig* **30**, 405-11 (2010).

(93) Uttayamakul, S. *et al.* Effects of CYP2B6 G516T polymorphisms on plasma efavirenz and nevirapine levels when co-administered with rifampicin in HIV/TB co-infected Thai adults. *AIDS Res Ther* **7**, 8 (2010).
(94) Kwara, A., Lartey, M., Sagoe, K.W., Kenu, E. & Court, M.H. CYP2B6, CYP2A6 and UGT2B7 genetic polymorphisms are predictors of efavirenz mid-dose concentration in HIV-infected patients. *AIDS* **23**, 2101-6 (2009).
(95) Cohen, K. *et al.* Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther* **14**, 687-95 (2009).
(96) Leger, P. *et al.* CYP2B6 variants and plasma efavirenz concentrations during antiretroviral therapy in Port-au-Prince, Haiti. *J Infect Dis* **200**, 955-64 (2009).
(97) To, K.W., Liu, S.T., Cheung, S.W., Chan, D.P., Chan, R.C. & Lee, S.S. Pharmacokinetics of plasma efavirenz and CYP2B6 polymorphism in southern Chinese. *Ther Drug Monit* **31**, 527-30 (2009).
(98) Mahungu, T.W. *et al.* The relationships of ABCB1 3435C>T and CYP2B6 516G>T with high-density lipoprotein cholesterol in HIV-infected patients receiving Efavirenz. *Clin Pharmacol Ther* **86**, 204-11 (2009).
(99) Cabrera, S.E. *et al.* Influence of the cytochrome P450 2B6 genotype on population pharmacokinetics of efavirenz in human immunodeficiency virus patients. *Antimicrob Agents Chemother* **53**, 2791-8 (2009).
(100) Kwara, A., Lartey, M., Sagoe, K.W., Rzek, N.L. & Court, M.H. CYP2B6 (c.516G-->T) and CYP2A6 (*9B and/or *17) polymorphisms are independent predictors of efavirenz plasma concentrations in HIV-infected patients. *Br J Clin Pharmacol* **67**, 427-36 (2009).
(101) Ramachandran, G. *et al.* Association of high T allele frequency of CYP2B6 G516T polymorphism among ethnic south Indian HIV-infected patients with elevated plasma efavirenz and nevirapine. *J Antimicrob Chemother* **63**, 841-3 (2009).
(102) Ramachandran, G. *et al.* 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* **53**, 863-8 (2009).
(103) Gupta, S.K. *et al.* The pharmacokinetics and pharmacogenomics of efavirenz and lopinavir/ritonavir in HIV-infected persons requiring hemodialysis. *AIDS* **22**, 1919-27 (2008).
(104) Wyen, C. *et al.* Impact of CYP2B6 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. *J Antimicrob Chemother* **61**, 914-8 (2008).
(105) Nyakutira, C. *et al.* 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**, 357-65 (2008).
(106) Lowenhaupt, E.A., Matson, K., Qureishi, B., Saitoh, A. & Pugatch, D. Psychosis in a 12-year-old HIV-positive girl with an increased serum concentration of efavirenz. *Clin Infect Dis* **45**, e128-30 (2007).
(107) Saitoh, A. *et al.* Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr* **45**, 280-5 (2007).

(108) Motsinger, A.A. *et al.* Multilocus genetic interactions and response to efavirenz-containing regimens: an adult AIDS clinical trials group study. *Pharmacogenet Genomics* **16**, 837-45 (2006).
(109) Wang, J. *et al.* Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. *Pharmacogenet Genomics* **16**, 191-8 (2006).
(110) Ribaudo, H.J. *et al.* Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis* **42**, 401-7 (2006).
(111) Haas, D.W. *et al.* Pharmacogenetics of long-term responses to antiretroviral regimens containing Efavirenz and/or Nelfinavir: an Adult Aids Clinical Trials Group Study. *J Infect Dis* **192**, 1931-42 (2005).
(112) Rodriguez-Novoa, S., Barreiro, P., Rendon, A., Jimenez-Nacher, I., Gonzalez-Lahoz, J. & Soriano, V. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. *Clin Infect Dis* **40**, 1358-61 (2005).
(113) Hasse, B., Gunthard, H.F., Bleiber, G. & Krause, M. Efavirenz intoxication due to slow hepatic metabolism. *Clin Infect Dis* **40**, e22-3 (2005).
(114) Liu, X. *et al.* Impact of Single Nucleotide Polymorphisms on Plasma Concentrations of Efavirenz and Lopinavir/Ritonavir in Chinese Children Infected with the Human Immunodeficiency Virus. *Pharmacotherapy* **37**, 1073-80 (2017).
(115) Haas, D.W. *et al.* Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* **18**, 2391-400 (2004).
(116) Rotger, M. *et al.* Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics* **15**, 1-5 (2005).
(117) Mathiesen, S., Justesen, U.S., Von Luttichau, H.R. & Hansen, A.B. Genotyping of CYP2B6 and therapeutic drug monitoring in an HIV-infected patient with high efavirenz plasma concentrations and severe CNS side-effects. *Scand J Infect Dis* **38**, 733-5 (2006).
(118) ter Heine, R. *et al.* A pharmacokinetic and pharmacogenetic study of efavirenz in children: dosing guidelines can result in subtherapeutic concentrations. *Antivir Ther* **13**, 779-87 (2008).
(119) Puthanakit, T., Tanpaiboon, P., Aurpibul, L., Cressey, T.R. & Sirisanthana, V. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther* **14**, 315-20 (2009).
(120) Habtewold, A. *et al.* Population Pharmacokinetic Model Linking Plasma and Peripheral Blood Mononuclear Cell Concentrations of Efavirenz and Its Metabolite, 8-Hydroxy-Efavirenz, in HIV Patients. *Antimicrob Agents Chemother* **61**, (2017).
(121) Nemaura T, N.C., Masimirembwa C. Impact of gender, weight and CYP2B6 genotype on efavirenz exposure in patients on HIV/AIDS and TB treatment: Implications for individualising therapy. *African Journal of Pharmacy and Pharmacology* **6**, 2188-93 (2012).
(122) Gengiah, T.N., Botha, J.H., Yende-Zuma, N., Naidoo, K. & Abdool Karim, S.S. Efavirenz dosing: influence of drug metabolizing enzyme polymorphisms and concurrent tuberculosis treatment. *Antivir Ther* **20**, 297-306 (2015).

(123) Duarte, H. *et al.* Population Approach to Efavirenz Therapy. *J Pharm Sci* **106**, 3161-6 (2017).
(124) Aurpibul, L. *et al.* Correlation of CYP2B6-516G > T Polymorphism with Plasma Efavirenz Concentration and Depression in HIV-Infected Adults in Northern Thailand. *Curr HIV Res* **10**, 653-60 (2012).
(125) Nijhawan, A.E., Zachary, K.C., Kwara, A. & Venna, N. Status epilepticus resulting from severe efavirenz toxicity in an HIV-infected patient. *AIDS Read* **18**, 386-8, C3 (2008).
(126) Luo, M. *et al.* Population Pharmacokinetics Analysis To Inform Efavirenz Dosing Recommendations in Pediatric HIV Patients Aged 3 Months to 3 Years. *Antimicrob Agents Chemother* **60**, 3676-86 (2016).
(127) Reay, R., Dandara, C., Viljoen, M. & Rheeders, M. CYP2B6 Haplotype Predicts Efavirenz Plasma Concentration in Black South African HIV-1-Infected Children: A Longitudinal Pediatric Pharmacogenomic Study. *OMICS* **21**, 465-73 (2017).
(128) Vujkovic, M. *et al.* Brief Report: CYP2B6 516G>T Minor Allele Protective of Late Virologic Failure in Efavirenz-Treated HIV-Infected Patients in Botswana. *J Acquir Immune Defic Syndr* **75**, 488-91 (2017).
(129) Frasco, M.A. *et al.* Underlying genetic structure impacts the association between CYP2B6 polymorphisms and response to efavirenz and nevirapine. *AIDS* **26**, 2097-106 (2012).
(130) Muller, T.E., Ellwanger, J.H., Michita, R.T., Matte, M.C.C. & Renner, J.D.P. CYP2B6 516 G>T polymorphism and side effects of the central nervous system in HIV-positive individuals under Efavirenz treatment: Study of a sample from southern Brazil. *An Acad Bras Cienc* **89**, 497-504 (2017).
(131) Queiroz, M.A.F. *et al.* The CYP2B6 G516T polymorphism influences CD4(+) T-cell counts in HIV-positive patients receiving antiretroviral therapy in an ethnically diverse region of the Amazon. *Int J Infect Dis* **55**, 4-10 (2017).
(132) Dickinson, L. *et al.* Comprehensive Pharmacokinetic, Pharmacodynamic and Pharmacogenetic Evaluation of Once-Daily Efavirenz 400 and 600 mg in Treatment-Naive HIV-Infected Patients at 96 Weeks: Results of the ENCORE1 Study. *Clin Pharmacokinet* **55**, 861-73 (2016).
(133) Glass, T.R. *et al.* Determinants of sustained viral suppression in HIV-infected patients with self-reported poor adherence to antiretroviral therapy. *PLoS One* **7**, e29186 (2012).
(134) Torno, M.S., Witt, M.D., Saitoh, A. & Fletcher, C.V. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: case report and review of the literature. *Pharmacotherapy* **28**, 782-7 (2008).
(135) Dhoro, M., Ngara, B., Kadzirange, G., Nhachi, C. & Masimirembwa, C. Genetic variants of drug metabolizing enzymes and drug transporter (ABCB1) as possible biomarkers for adverse drug reactions in an HIV/AIDS cohort in Zimbabwe. *Curr HIV Res* **11**, 481-90 (2013).
(136) Elsharkawy, A.M. *et al.* Efavirenz induced acute liver failure requiring liver transplantation in a slow drug metaboliser. *J Clin Virol* **58**, 331-3 (2013).
(137) Mugusi, S. *et al.* Liver enzyme abnormalities and associated risk factors in HIV patients on efavirenz-based HAART with or without tuberculosis co-infection in Tanzania. *PLoS One* **7**, e40180 (2012).

(138) Yimer, G. *et al.* Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. *PLoS One* **6**, e27810 (2011).
(139) Yimer, G. *et al.* High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naive HIV patients from Ethiopia: a prospective cohort study. *Pharmacogenomics J* **12**, 499-506 (2012).
(140) Manosuthi, W. *et al.* CYP2B6 haplotype and biological factors responsible for hepatotoxicity in HIV-infected patients receiving efavirenz-based antiretroviral therapy. *Int J Antimicrob Agents* **43**, 292-6 (2014).
(141) Wyen, C. *et al.* Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. *J Antimicrob Chemother* **66**, 2092-8 (2011).
(142) Powers, V., Ward, J. & Gompels, M. CYP2B6 G516T genotyping in a UK cohort of HIV-positive patients: polymorphism frequency and influence on efavirenz discontinuation. *HIV Med* **10**, 520-3 (2009).
(143) Usami, O. *et al.* Efavirenz-induced neurological symptoms in rare homozygote CYP2B6 *2/*2 (C64T). *Int J STD AIDS* **18**, 575-6 (2007).
(144) Ribaudo, H.J. *et al.* Effect of CYP2B6, ABCB1, and CYP3A5 polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. *J Infect Dis* **202**, 717-22 (2010).
(145) Burger, D. *et al.* Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* **61**, 148-54 (2006).
(146) Evans, J., Swart, M., Soko, N., Wonkam, A., Huzair, F. & Dandara, C. A Global Health Diagnostic for Personalized Medicine in Resource-Constrained World Settings: A Simple PCR-RFLP Method for Genotyping CYP2B6 g.15582C>T and Science and Policy Relevance for Optimal Use of Antiretroviral Drug Efavirenz. *OMICS* **19**, 332-8 (2015).
(147) Manosuthi, W., Sukasem, C., Thongyen, S., Nilkamhang, S., Manosuthi, S. & Sungkanuparph, S. CYP2B6 18492T->C polymorphism compromises efavirenz concentration in coinfected HIV and tuberculosis patients carrying CYP2B6 haplotype *1/*1. *Antimicrob Agents Chemother* **58**, 2268-73 (2014).
(148) Sukasem, C. *et al.* Pharmacogenetics and clinical biomarkers for subtherapeutic plasma efavirenz concentration in HIV-1 infected Thai adults. *Drug Metab Pharmacokinet* **29**, 289-95 (2014).
(149) Sukasem, C. *et al.* Low level of efavirenz in HIV-1-infected Thai adults is associated with the CYP2B6 polymorphism. *Infection* **42**, 469-74 (2014).
(150) Aouri, M. *et al.* In Vivo Profiling and Distribution of Known and Novel Phase I and Phase II Metabolites of Efavirenz in Plasma, Urine, and Cerebrospinal Fluid. *Drug Metab Dispos* **44**, 151-61 (2016).
(151) Luetkemeyer, A.F. *et al.* Combined effect of CYP2B6 and NAT2 genotype on plasma efavirenz exposure during rifampin-based antituberculosis therapy in the STRIDE study. *Clin Infect Dis* **60**, 1860-3 (2015).
(152) Dooley, K.E. *et al.* Pharmacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis coinfection. *J Infect Dis* **211**, 197-205 (2015).

(153) McIlleron, H.M. *et al.* Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. *AIDS* **27**, 1933-40 (2013).
(154) Dooley, K.E. *et al.* Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. *J Acquir Immune Defic Syndr* **59**, 455-62 (2012).
(155) Haas, D.W. *et al.* Associations between CYP2B6 polymorphisms and pharmacokinetics after a single dose of nevirapine or efavirenz in African americans. *J Infect Dis* **199**, 872-80 (2009).
(156) Arab-Alameddine, M. *et al.* Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther* **85**, 485-94 (2009).
(157) Gross, R. *et al.* CYP2B6 genotypes and early efavirenz-based HIV treatment outcomes in Botswana. *AIDS* **31**, 2107-13 (2017).
(158) Robarge, J.D. *et al.* Population Pharmacokinetic Modeling To Estimate the Contributions of Genetic and Nongenetic Factors to Efavirenz Disposition. *Antimicrob Agents Chemother* **61**, (2017).
(159) Fayet Mello, A. *et al.* Successful efavirenz dose reduction guided by therapeutic drug monitoring. *Antivir Ther* **16**, 189-97 (2011).
(160) Cummins, N.W. *et al.* Investigation of Efavirenz Discontinuation in Multi-ethnic Populations of HIV-positive Individuals by Genetic Analysis. *EBioMedicine* **2**, 706-12 (2015).
(161) Leger, P. *et al.* Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. *Pharmacogenet Genomics* **26**, 473-80 (2016).
(162) Johnson, D.H. *et al.* Neuropsychometric correlates of efavirenz pharmacokinetics and pharmacogenetics following a single oral dose. *Br J Clin Pharmacol* **75**, 997-1006 (2013).
(163) Mollan, K.R. *et al.* Race/Ethnicity and the Pharmacogenetics of Reported Suicidality With Efavirenz Among Clinical Trials Participants. *J Infect Dis* **216**, 554-64 (2017).
(164) Haas, D.W., Severe, P., Jean Juste, M.A., Pape, J.W. & Fitzgerald, D.W. Functional CYP2B6 variants and virologic response to an efavirenz-containing regimen in Port-au-Prince, Haiti. *J Antimicrob Chemother* **69**, 2187-90 (2014).
(165) Bolton Moore, C. *et al.* CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. *AIDS* **31**, 1129-36 (2017).
(166) Hui, K.H., Lee, S.S. & Lam, T.N. Dose Optimization of Efavirenz Based on Individual CYP2B6 Polymorphisms in Chinese Patients Positive for HIV. *CPT Pharmacometrics Syst Pharmacol* **5**, 182-91 (2016).
(167) Damronglerd, P., Sukasem, C., Thipmontree, W., Puangpetch, A. & Kiertiburanakul, S. A pharmacogenomic prospective randomized controlled trial of CYP2B6 polymorphisms and efavirenz dose adjustment among HIV-infected Thai patients: a pilot study. *Pharmgenomics Pers Med* **8**, 155-62 (2015).
(168) Martin, A.S. *et al.* Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics. *Pharmacogenomics* **15**, 997-1006 (2014).

(169) Bushyakanist, A., Puangpetch, A., Sukasem, C. & Kiertiburanakul, S. The use of pharmacogenetics in clinical practice for the treatment of individuals with HIV infection in Thailand. *Pharmgenomics Pers Med* **8**, 163-70 (2015).
(170) Kitabi, E.N. *et al.* Long-term efavirenz pharmacokinetics is comparable between Tanzanian HIV and HIV/Tuberculosis patients with the same CYP2B6*6 genotype. *Sci Rep* **8**, 16316 (2018).