

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, <i>et al.</i> 2003 (20) Ogburn, <i>et al.</i> 2010 (21)	High
In vitro	No association found between <i>CYP2B6</i> *4 (c.785 A>G) and catalytic activity of CYP2B6 or metabolism of efavirenz.	Supports statement: Zhang, <i>et al.</i> 2011 (22) Does not support statement: Ariyoshi, <i>et al.</i> 2011 (23)	Weak
In vitro	<i>CYP2B6</i> *5 (c.1459 C>T) is associated with increased catalytic activity of CYP2B6 and increased efavirenz metabolism.	Supports statement: Zhang, <i>et al.</i> 2011 (22) Does not support statement: Desta, <i>et al.</i> 2007 (24)	Weak
In vitro	<i>CYP2B6</i> *6 (c.516 G>T and c.785 A>G) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Zhang, <i>et al.</i> 2011 (22) Ariyoshi, <i>et al.</i> 2011 (23) Xu, <i>et al.</i> 2012 (25) Desta, <i>et al.</i> 2007 (24)	High
In vitro	<i>CYP2B6</i> *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, <i>et al.</i> 2011 (22)	Weak
In vitro	<i>CYP2B6</i> *8 (c.415 A>G) is associated with abolished catalytic activity of CYP2B6 and no efavirenz metabolism.	Zhang, <i>et al.</i> 2011 (22)	Weak
In vitro	<i>CYP2B6</i> *9 (c.516 G>T) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Zhang, <i>et al.</i> 2011 (22)	Weak
In vitro	<i>CYP2B6</i> *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, <i>et al.</i> 2007 (24)	Weak
In vitro	<i>CYP2B6</i> *14 (c.419 G>A) is associated with decreased catalytic activity of CYP2B6 and decreased efavirenz metabolism.	Desta, <i>et al.</i> 2007 (24)	Weak

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

		<p> Sinxadi, <i>et al.</i> 2015 (59) Winston, <i>et al.</i> 2015 (60) Mukonzo, <i>et al.</i> 2014 (61) Olagunju, <i>et al.</i> 2014 (62) Lee, <i>et al.</i> 2014 (63) Ramachandran, <i>et al.</i> 2013 (64) Mukonzo, <i>et al.</i> 2014 (65) Bienvenu, <i>et al.</i> 2014 (66) Naftalin, <i>et al.</i> 2014 (67) Salem, <i>et al.</i> 2014 (68) Sarfo, <i>et al.</i> 2014 (69) Bertrand, <i>et al.</i> 2014 (70) Lee, <i>et al.</i> 2014 (71) Ngaimisi, <i>et al.</i> 2013 (72) Swart, <i>et al.</i> 2013 (30) Mukonzo, <i>et al.</i> 2013 (73) Sukasem, <i>et al.</i> 2013 (31) Manosuthi, <i>et al.</i> 2013 (74) Cortes, <i>et al.</i> 2013 (75) Holzinger, <i>et al.</i> 2012 (76) Gandhi, <i>et al.</i> 2012 (77) Mutwa, <i>et al.</i> 2012 (78) Sukasem, <i>et al.</i> 2012 (79) Heil, <i>et al.</i> 2012 (33) Viljoen, <i>et al.</i> 2012 (80) Maimbo, <i>et al.</i> 2012 (81) Sanchez, <i>et al.</i> 2011 (82) Habtewold, <i>et al.</i> 2011 (83) Ngaimisi, <i>et al.</i> 2011 (84) Strehlau, <i>et al.</i> 2011 (85) Kwara, <i>et al.</i> 2011 (86) Elens, <i>et al.</i> 2010 (87) Lindfelt, <i>et al.</i> 2010 (88) Gounden, <i>et al.</i> 2010 (89) Cabrera Figueroa, <i>et al.</i> 2010 (90) </p>	
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		Chen, <i>et al.</i> 2010 (91) Cabrera Figueroa, <i>et al.</i> 2010 (92) Uttayamakul, <i>et al.</i> 2010 (93) Kwara, <i>et al.</i> 2009 (94) Cohen, <i>et al.</i> 2009 (95) Leger, <i>et al.</i> 2009 (96) To, <i>et al.</i> 2009 (97) Mahungu, <i>et al.</i> 2009 (98) Cabrera, <i>et al.</i> 2009 (99) Kwara, <i>et al.</i> 2009 (100) Ramachandran, <i>et al.</i> 2009 (101) Ramachandran, <i>et al.</i> 2009 (102) Gupta, <i>et al.</i> 2008 (103) Kwara, <i>et al.</i> 2008 (36) Wyen, <i>et al.</i> 2008 (104) Nyakutira, <i>et al.</i> 2008 (105) Lowenhaupt, <i>et al.</i> 2007 (106) Saitoh, <i>et al.</i> 2007 (107) Motsinger, <i>et al.</i> 2006 (108) Wang, <i>et al.</i> 2006 (109) Ribaud, <i>et al.</i> 2006 (110) Haas, <i>et al.</i> 2005 (111) Rodriguez-Novoa, <i>et al.</i> 2005 (112) Hasse, <i>et al.</i> 2005 (113) Liu, <i>et al.</i> 2017 (114) Haas, <i>et al.</i> 2004 (115) Rotger, <i>et al.</i> 2005 (116) Mathiesen, <i>et al.</i> 2006 (117) ter Heine, <i>et al.</i> 2008 (118) Puthanakit, <i>et al.</i> 2009 (119) Habtewold, <i>et al.</i> 2017 (120) Nemauro, <i>et al.</i> 2012 (121) Gengiah, <i>et al.</i> 2015 (122) Duarte, <i>et al.</i> 2017 (123) Aurpibul, <i>et al.</i> 2012 (124)	
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		Nijhawan, <i>et al.</i> 2008 (125) Luo, <i>et al.</i> 2016 (126) Reay, <i>et al.</i> 2017 (127)	
Clinical	<i>CYP2B6</i> c.516 G>T is associated with increased efficacy (decreased viral load, increased T-cell count) of efavirenz therapy.	Supports statement: Vujkovic, <i>et al.</i> 2017 (128) Ramachandran, <i>et al.</i> 2013 (64) Sarfo, <i>et al.</i> 2014 (69) Frasco, <i>et al.</i> 2012 (129) Habtewold, <i>et al.</i> 2011 (83) Does not support statement: Muller, <i>et al.</i> 2017 (130) Queiroz, <i>et al.</i> 2017 (131) Orrell, <i>et al.</i> 2016 (44) Dickinson, <i>et al.</i> 2016 (132) Dickinson, <i>et al.</i> 2015 (52) Bienvenu, <i>et al.</i> 2014 (66) Naftalin, <i>et al.</i> 2014 (67) Ngaimisi, <i>et al.</i> 2013 (72) Glass, <i>et al.</i> 2012 (133) Gounden, <i>et al.</i> 2010 (89) Uttayamakul, <i>et al.</i> 2010 (93) Saitoh, <i>et al.</i> 2007 (107) Haas, <i>et al.</i> 2005 (111) Haas, <i>et al.</i> 2004 (115) Puthanakit, <i>et al.</i> 2009 (119) Rohrich, <i>et al.</i> 2016 (27)	Weak
Clinical	<i>CYP2B6</i> c.516 G>T is associated with increased toxicity (CNS side effects) of efavirenz therapy.	Supports statement: Gallien, <i>et al.</i> 2017 (41) Pinillos, <i>et al.</i> 2016 (48) Lee, <i>et al.</i> 2014 (71) Mukonzo, <i>et al.</i> 2013 (73) Strehlau, <i>et al.</i> 2011 (85) Cabrera Figueroa, <i>et al.</i> 2010 (90) Lowenhaupt, <i>et al.</i> 2007 (106)	Moderate

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

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

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

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

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

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

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

^aRating scheme described in the **Supplemental Material**

^bThe *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.

^cDecreased efavirenz concentrations in hair samples were associated with *CYP2B6**17 in the South African Black cohort only.

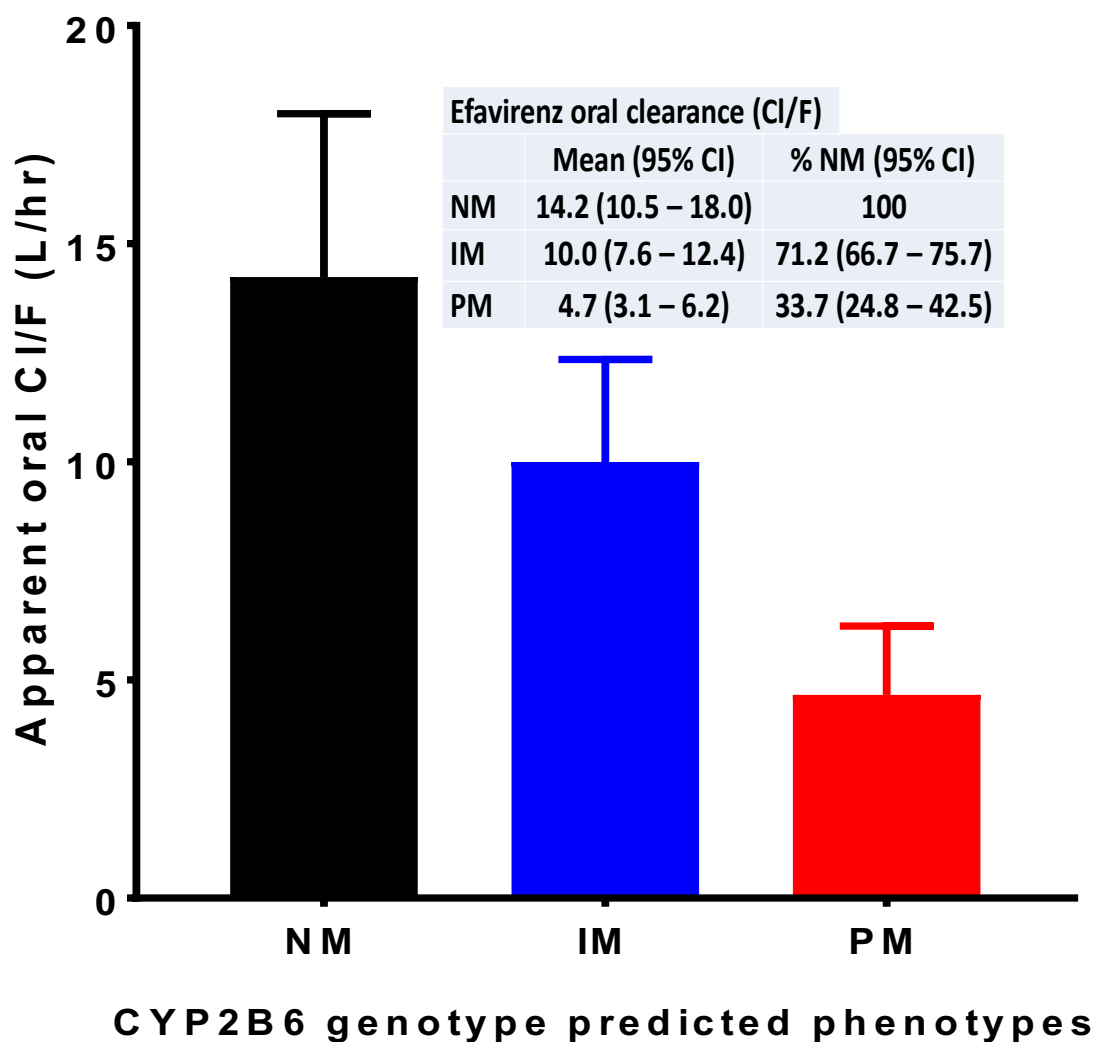


FIGURE S1. APPARENT ORAL CLEARANCE (CL/F) OF EFAVIRENZ (600 MG/DAY) IN HIV-POSITIVE INDIVIDUALS GENOTYPED FOR *CYP2B6* VARIANTS. Genotype predicted phenotypes were based on *CYP2B6**6 and *18 alleles as described in Table 1 (main manuscript). The data were derived from 10 independent clinical studies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

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