CYP2B6: efavirenz 4754, 4755 and 6928 to 6930

ART = antiretroviral therapy, AUC = area under the time-concentration curve, BMI = body mass index, cART = combination antiretroviral therapy, CI = confidence interval, CNS = central nervous system, CTCAE = Common Terminology Criteria for Adverse Events, HIV = human immunodeficiency virus, HR = hazard ratio, HR_{adj} = adjusted hazard ratio, IM = a fully active allele in combination with an allele with reduced activity (e.g. *1/*6 or *1/*18) (reduced CYP2B6 enzyme activity), NM = normal metaboliser (e.g. *1/*1, *1/*5) (normal CYP2B6 enzyme activity), NS = non-significant, OR = odds ratio, OR_{adj} = adjusted odds ratio, PM = two alleles with reduced activity (e.g. *6/*6, *6/*18, *18/*18) (very low or absent CYP2B6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, SNP = single nucleotide polymorphism.

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Efavirenz is mainly converted by CYP2B6 to 8-hydroxyefavirenz. Efavirenz is metabolised to a limited extent by CYP3A4/5 and CYP2A6 and efavirenz is metabolised by UGT2B7 by direct N-glucuronidation. Efavirenz induces CYP2B6 and CYP3A and thus its own metabolism.
The therapeutic range established for efavirenz is 1000-4000 ng/ml at 12 hours after dosing (AUC 35-180 µg.h/ml). Studies consistently show an increased efavirenz plasma concentration in patients with reduced or very low or absent CYP2B6 enzyme activity (intermediate metabolisers (IM) and poor metabolisers (PM)) (Ngayo 2022 (139 IM, 45 PM), Mugusi 2020 (115 IM, 32 PM), Torgersen 2019 (393 IM, 189 PM), Gross 2017 (396 IM, 192 PM), Cusato 2016 (73 IM, 12 PM), Swart 2016 (100 IM, 43 PM) Meng 2015 (84 IM, 19 PM), Bertrand 2014 (123 IM, 43 PM), Sarfo 2014 (235 IM, 133 PM), Ngaimisi 2013 (181 IM, 49 PM), Ribaudo 2010 (75 PM), Carr 2010 (86 IM, 31 PM), Gatanaga 2007 (28 IM, 16 PM), and Haas 2005 (148 IM, 32 PM)). This resulted in a decrease in patients with subtherapeutic efavirenz concentrations, but an increase in patients with supratherapeutic efavirenz concentrations (Cusato 2016 (73 IM, 12 PM), Swart 2016 (100 IM, 43 PM), Meng 2015 (84 IM, 19 PM), Bertrand 2014 (123 IM, 43 PM), Carr 2010 (86 IM, 31 PM), and Gatanaga 2007 (28 IM, 16 PM). For PM, most patients had supratherapeutic efavirenz concentrations on normal efavirenz doses (Ngayo 2022 (45 PM), Torgersen 2019 (189 PM), Bolton Moore 2017 (7 paediatric PM), Cusato 2016 (12 PM), Swart 2016 (43 PM), Meng 2015 (19 PM), Bertrand 2014 (43 PM), Carr 2010 (31 PM), and Gatanaga 2007 (16 PM)). Because of the increased risk for supratherapeutic efavirenz concentrations, the KNMP Pharmacogenetics Working Group decided that action is needed for these gene-drug interactions (yes/yes-interactions).
A justification for the type of action recommended is given below.
Interracial differences in efavirenz effect independent of CYP2B6 and plasma concentration have been observed. Despite the higher efavirenz plasma concentrations observed in black patients, they were less likely to discontinue therapy due to adverse events than White patients (Wyen 2011 (169 IM, 34 PM)).
PM: *Adverse events*

Studies have not shown whether or not the effect of CYP2B6 gene variants with low activity on adverse events and treatment continuation due to adverse events is ethnicity dependent.
A study found an increased risk of therapy discontinuation for all, White, and Black PM patients compared to NM patients, although the study confirmed that Black patients were less like to discontinue therapy than White patients (Wyen 2011 (34 PM, 169 IM)). Another study found an increased risk for therapy discontinuation due to central nervous system (CNS) symptoms in all patients and White patients, but the effect did not reach significance for Black patients (Leger 2016 (184-194 IM, 72 PM)). For each genotype group, the difference of the risk between White and Black patients was not significant, but there was a trend for a lower risk for Blacks. In this study, the risk for therapy discontinuation due to all causes was increased for Whites, there was a trend for all patients, while significance was not reached for Black patients. A third study with different ethnicities found an increase in treatment discontinuation for PMs after 96 weeks, but no significant effect after 48 weeks (Dickinson 2016 (59 PM)). A fourth study with mixed ethnicities did not find an effect of CYP2B6 phenotype on treatment discontinuation (Haas 2005 (148 IM, 32 PM)).
A meta-analysis of 8 studies found the *6 allele to increase the risk of central nervous system adverse events (Cheng 2020 (at least 581 IM and 159 PM)). A study found an increased risk for neuropsychiatric adverse events

in Whites, but not in Blacks or Hispanics (Ribaudo 2010 (75 PM)). Another study with different ethnicities did not find an increase in CNS adverse events for *6, but found a decrease for the *18-variant, which is mainly restricted to and though selects for Black patients (Dickinson 2016 (262 IM, 59 PM for *6 and 36 IM and 3 PM for *18)). A study in Botswanan patients found a decrease in the CNS adverse event score after 1 month, but not after 6 months of therapy (Gross 2017 (396 IM, 192 PM)). A study in Ghanaian patients found no association of *6 and *18 with neuropsychiatric toxicity, apart from a trend for *1/*6+*6/*6. However, median efavirenz plasma concentration in this study was subtherapeutic for NMs and only just within the therapeutic range for IMs (Sarfo 2014 (235 IM, 133 PM for *6 and 42 IM and 1 PM for *18)). A study in Tanzanians did not find an effect on neuropsychiatric adverse events (Mugusi 2018 (145 IM, 54 PM). A study in Ugandan patients did not find an effect of CYP2B6 phenotype on probable depression (Chang 2018 (110 IM, 30 PM)).
A study in Botswanan patients of 50 years or older did not find an effect of CYP2B6 phenotype on adverse event score after 1 month (Torgersen 2019 (49 IM, 25 PM)).
Two African studies found the *6 allele to increase efavirenz-induced liver injury (Yimer 2012 (114 IM, 20 PM).and Mugusi 2012 (148 IM, 54 PM)).
A study in Ethiopian patients found the *6 allele to increase the risk for diabetes mellitus, but not the risk for glucose metabolism disorders, impaired fasting glucose, and insulin resistance (Tadesse 2022 (108 IM, 21 PM)).
Efficacy
Most studies and a meta-analysis of 9 studies point to an absence of an effect of CYP2B6 gene variants with low activity on efavirenz efficacy. The meta-analysis did not find an effect of the *6 allele on virological response (Cheng 2020 (at least 452 IM and 99 PM)) Two studies with different ethnicities (and four with Black patients did not find an effect on efficacy (3 studies analysed viral suppression, one study change in $CD4^+$ cell count, one study failure of therapy (treatment discontinuation, virologic failure), $CD4^+$ cell count, and the emergence of resistant HIV mutants, and one study the composite endpoint death, loss to care, or virological failure, the separate components of this composite endpoint, and $CD4^+$ cell count) (Dickinson 2016 (262 IM, 59 PM), Haas 2005 (148 IM, 32 PM), Mugusi 2020 (115 IM, 32 PM), Chang 2018 (110 IM, 30 PM)), Gross 2017 (396 IM, 192 PM), and Haas 2014 (176 IM, 77 PM)). A study with Black patients found an increased risk for loss to care (including death) for PM, but only in patients of 50 years or older (Torgersen 2019 (189 PM, of whom 25 aged 50 years or older)). A study with Black patients found a decreased risk for late virologic failure (i.e. after initial viral suppression) (Vujkovic 2017 (276 cases and 1062 controls). Another study found a decrease in virologic failure in Blacks, but not in Whites or Hispanics (Ribaudo 2010 (75 PM)). A study in Ghana with a subtherapeutic median efavirenz plasma concentration for NM found that *6 decreased the risk of immunological failure (insufficient $CD4^+$ cells), but not the risk of clinical failure (development of AIDS, no follow-up or death) (Sarfo 2014 (235 IM, 133 PM)). A study with Ethiopian and Tanzanian patients found a trend for a stronger increase in $CD4^+$ cell count in Ethiopians with *6, but median efavirenz plasma concentration in this study were only just above the lower limit of the therapeutic range for NM (Ngaimisi 2013 (181 IM, 49 PM)).
Efavirenz exposure
In 7 large and 2 small studies, the median or mean plasma concentrations or AUCs in PM patients were above the therapeutic range (Ngayo 2022 (45 PM), Torgersen 2019 (189 PM), Bolton Moore 2017 (7 paediatric PM), Cusato 2016 (12 PM), Swart 2016 (43 PM), Meng 2015 (19 PM), Bertrand 2014 (43 PM), Carr 2010 (31 PM), and Gatanaga 2007 (16 PM)). Only in 2 of the 5 studies performed in Africa (both with low median plasma efavirenz concentrations in NM patients) and a study with different ethnicities in the USA and Italy, the median plasma concentration or AUC in PM was not supratherapeutic ((Sarfo 2014 (235 IM, 133 PM), (Ngaimisi 2013 (181 IM, 49 PM), and Haas 2005 (148 IM, 32 PM)). In the latter study, the lower limit of the therapeutic AUC range was 71% of the median AUC for NM. Because this lower limit corresponds with an efavirenz plasma concentration of 700 ng/ml, this might indicate a plasma concentration around the lower limit of the therapeutic range for NM. A study in the Netherlands including 255 patients confirmed the two African studies to be not representative of the situation in the Netherlands (Burger 2006). It showed that in the Netherlands 18.9% had efavirenz plasma concentrations above the therapeutic range and 3.1% plasma concentrations below the therapeutic range.
Dosing recommendations in adults and children with a body weight ≥ 40 kg
Given the effect found on therapy withdrawal due to neuropsychiatric adverse events, the recommendation is to reduce the dose for PM patients either immediately or guided by therapeutic drug monitoring. For *6/*6, the median plasma concentration or AUC increased by 94-306% versus NM (Ngayo 2022 (45 PM), Cusato 2016 (12 PM), Swart 2016 (43 PM), Sarfo 2014 (133 PM), Ngaimisi 2013 (49 PM), Carr 2010 (31 PM), and Haas 2005 (32 PM)). The mean efavirenz plasma concentration increased by 288-372% in two studies (Meng 2015 (19 PM) and Gatanaga 2007 (16 PM)). For *18/*18, the median plasma efavirenz concentration increased by 248-810% in 2 studies (Swart 2016 (5 PM) and Sarfo 2014 (1 PM)), suggesting a stronger effect of *18 than *6. For *6/*6+*6/*18+*18/*18, the mean plasma concentration increased by 329% (Torgersen 2019 (189 PM)). As efavirenz induces CYP2B6 and thereby its own metabolism, a reduction of the dose by a certain percentage will usually lead to plasma concentrations reduced by a higher percentage. Therefore, the required dose reduction cannot be reliably deduced from the observed increase in plasma concentration or AUC. For adults, two studies found therapeutic plasma concentrations for *6/*6 at doses of either 400 mg (approximately 1/3 of 24 patients) or 200 mg (approximately 2/3 of 24 patients) (Martin 2014 and Gatanaga 2007). In both studies, dose reduction did not affect efficacy (HIV remained undetectable) and decreased CNS adverse events. Based on this information, the recommended initial dose is a dose reduction to 400 mg/day and further dose adjustments down to 200 mg/day

or up to 600 mg/day should subsequently be guided by plasma concentrations. The 600 mg daily dose will be too high for the majority of PM patients. Only for patients treated with a combination preparation or with a body mass index > 25, an initial dose of 600 mg/day is recommended (see below for a justification). A note is added to the recommendation, that patients with the *18/*18-genotype might require larger dose reductions.
Children with a body weight ≥ 40 kg receive the same efavirenz dose as adults.
Dosing recommendations in children with a body weight < 40 kg
For children, the only study investigating dose adjustment found therapeutic plasma concentrations for *6/*6 at doses of approximately 10 mg/kg per day (dosed as opened capsules) for children aged 3 months to 3 years and with a body weight of 3-17 kg (Bolton Moore 2017). These results were based on 2 patients getting the lower dose and on pharmacokinetic modelling with data of these patients and 7 PM that only received a 3 to 4-fold higher dose. The exact reduced doses applied were 100 mg/day for 7-14 kg and 150 mg/day for 14-17 kg. 82% of the NM+IM in these weight categories achieved therapeutic plasma concentrations at doses of 500 mg/day, suggesting the recommended doses of respectively 200 and 250 mg/day for these patients as being too low. Because especially for young children, the recommended normal doses might be relatively low, because too low doses can result in development of efavirenz resistance, and because for most age group there is no information about suitable doses for PM, no reduction of the initial dose is recommended for children with a body weight of less than 40 kg. Instead, therapeutic drug monitoring guided dose adjustment is recommended. A note is added to the recommendation, that for adult PM therapeutic efavirenz concentrations were observed at either 2/3 or 1/3 of the normal dose and for PM below 3 years of age at doses of approximately 10 mg/kg per day (dosing as opened capsules, 100 mg/day for 7-14 kg and 150 mg/day for 14-17 kg).
Justification for initial doses of 400 mg for adult PMs and unchanged initial doses for adult PMs either receiving a combination preparation or with a body mass index > 25
Two of the three HIV physicians consulted recommended an initial dose of 600 mg/day in adult PM patients, as efavirenz resistance can readily develop. One of them gave as additional reason that the use of an efavirenz/tenofovir/emtricitabine combination preparation also improves compliance. This combination preparation contains 600 mg efavirenz. The third HIV physician recommended an initial dose of 400 mg efavirenz in PM patients, based on an article that showed similar virological responses to 400 mg and 600 mg efavirenz in combination with tenofovir and emtricitabine (ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet 2014;383:1474-82. PubMed PMID: 24522178). This article describes a study that treated 321 non-genotype-selected patients with 400 mg efavirenz and 309 with 600 mg efavirenz for 48 weeks. 30% of the study population were White patients. 400 mg efavirenz gave a similar virological response as 600 mg. There were no differences in virological response between different ethnicities (African, Asian and other (Whites and Australasian)). There were no significant differences between different BMI classes, but the virological response was non-significantly poorer for 400 mg in the group with BMI > 25, while this response was non-significantly superior in patients with lower BMI and the total population. There were no differences in adverse events and therapy withdrawal between the groups. The number of patients with efavirenz-related adverse events was lower for 400 mg than for 600 mg (37% versus 47%) (S), as well as the percentage of patients that switched to non-efavirenz-based therapy due to efavirenz-related adverse events (2% versus 6%) (S). The results of the study concern patients not treated with rifampicin: five patients who required treatment with rifampicin were switched to efavirenz 600 mg. As PM patients have low or absent metabolic capacity of CYP2B6, induction of CYP2B6 by rifampicin is of little to no relevance. In addition, independent of the CYP2B6 genotype, the net effect of enzyme induction by rifampicin and enzyme inhibition by isoniazide seems to be small.

IM: The evidence for a clinical effect for IM patients is mainly based on the NM, IM, PM trend. Only a meta-analysis of 8 studies and 6 studies provide some independent evidence for IM patients. The meta-analysis found an increased risk of central nervous system adverse events for IM (OR = 1.43) (Cheng 2020 (at least 581 IM)). A study in Tanzanians did not find an increased risk of neuropsychiatric adverse events for IM (Mugusi 2018 (145 IM))..An African study found a decreased risk for late HIV failure (i.e. after initial viral suppression) for IM compared to NM (OR = 0.69) (Vujkovic 2017 (276 cases and 1062 controls)). A study found an increase in the percentage of patients who discontinued treatment (HR_{adj} = 1.80) (Dickinson 2016 (262 IM). This increase was only observed if patients were followed for 96 weeks and was not significant after 48 weeks. Three studies did not find a change in efficacy for IM (Mugusi 2020 (115 IM, outcome $CD4^+$ cell count), Torgersen 2019 (393 IM of whom 49 aged 50 years or older, outcome loss to care (including death)), and Chang 2018 (110 IM, outcome viral suppression)).
Next to little evidence for a clinical effect, the median plasma concentrations or AUCs and mean plasma concentrations observed in IM patients are not above the therapeutic range (Ngayo 2022 (139 IM), Torgersen 2019 (393 IM), Cusato 2016 (73 IM), Swart 2016 (100 IM), Meng 2015 (48 IM), Bertrand 2014 (123 IM), Carr 2010 (68 IM), and Gatanaga 2007 (28 IM)). High plasma concentrations have incidentally been observed in IM patients. Dose reduction guided by plasma concentration is therefore only recommended in IM patients in case of adverse events.

You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping of patients with body mass index ≤ 25 and scheduled to receive efavirenz in a single drug preparation before starting efavirenz to be potentially beneficial for avoiding therapy discontinuation due to adverse events. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 7 out of the maximum of 10 points. Pre-emptive genotyping is considered to be essential for scores ranging from 6 to 10 points (see below and the clinical implication score tables at the end of this risk analysis). However, the KNMP Pharmacogenetics Working Group decided to downgrade this score to potentially beneficial, because discontinuation of therapy does not have a severe clinical impact in the Netherlands (so severity code ≤ C, corresponding to CTCAE grade ≤ 2). Discontinuation of therapy is not due to diminished efficacy, but to adverse events. In addition, although it concerns discontinuation of a life-saving therapy, in resource-rich settings the patient will generally be switched to another combined antiretroviral therapy and not left without therapy, strongly diminishing the clinical impact of discontinuation of efavirenz therapy. Even though efavirenz is not a first-choice drug in resource-rich setting, alternatives will generally still be available. In addition, the KNMP Pharmacogenetics Working Group restricts the genotyping recommendation to patients with body mass index ≤ 25 and scheduled to receive efavirenz in a single drug preparation. Because the therapeutic recommendation for patients with a body mass index > 25 and/or receiving efavirenz in a combination preparation is to give no a priori dose reduction, genotyping does not or only to a limited extent decrease the risk for therapy discontinuation in these patients.
The rationale for the (sub)scores of the clinical implication score is indicated below:
PM and IM have been shown to have an increased risk for discontinuation of the life-saving efavirenz combination therapy (severity code E, corresponding to CTCAE grade 4). This results in 1 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for CTCAE grade 3-4).
4 studies have severity code E (corresponding to CTCAE grade 4) due to an observed increased risk for therapy discontinuation in PM and/or IM (Leger 2016, Dickinson 2016, Torgersen 2013, and Wyen 2011), and Vujkovic 2017 has severity code E due to an observed increase in late HIV failure in IM+PM. This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).
The number needed to genotype was deduced from the largest study with a mainly White population having a severity code, corresponding to CTCAE grade ≥ 3 (Leger 2016). This study indicates that the positive predictive value for discontinuation of efavirenz therapy in PM is 16.1%. Considering the observed PM frequency of 12.8% in this study, this would correspond with 2% of the patients discontinuing efavirenz therapy due to the PM phenotype and so, a number needed to genotype to prevent this in one patient of 50. The calculated number to genotype of 50 results in 2 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (2 points for 10 ≤ NNG ≤ 100).
The Summary of Product Characteristics (SmPC) of efavirenz mentions the *6/*6 genotype to increase efavirenz plasma concentrations, but indicates that the clinical implication is unknown. So, the genotype is neither mentioned as a contra-indication, nor does the SmPC contain a recommendation to genotype. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).
In addition to the clinical implication score indicating pre-emptive genotyping to be essential, a cost-effectiveness analysis suggests that CYP2B6 genotype-guided dosing saves more than US$ 100,000 per quality-adjusted life year (QALY) gained compared with standard care (Schackman 2015). This saving is due to the lower efavirenz costs due to lower doses in PM and IM. However, Schackman 2015 also indicates that antiretroviral therapy with efavirenz 400 mg once daily for all patients was more cost-effective than genotype-guided therapy.

The table below follows KNMP nomenclature for CYP2B6 polymorphisms. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.
Unless stated otherwise, *6 is based on nucleotide substitution 516G>T and *18 on nucleotide substitution 983T>C.

Source	Code	Effect	Comments
ref. 1 Tadesse WT et al. CYP3A and CYP2B6 genotype predicts glucose metabolism disorder among HIV patients on long-term	3	In a case-control study, 240 Ethiopian patients on efavirenz-based therapy for at least one year with (n =75) and without (n = 165) glucose metabolism disorders were compared. The case and control groups were matched to each other in terms of age, duration since cART start, duration on current cART, weight, waist circumference, and BMI. Glucose metabolism disorders were defined as the presence of impaired fasting glucose (fasting glucose level between	Authors' conclusion: 'CYP3A haplotype and CYP2B6*6 genotype are independent significant predictors of glucose metabolism disorders and diabetes

<table>
<tr>
<td>efavirenz-based a case-control study. J Pers Med 2022;12:1087. PMID: 35887584.

ref. 1, continuation</td>
<td>IM+PM: C</td>
<td>110 and 125 mg/dL), insulin resistance (homeostasis model assessment insulin resistance (HOMA-IR) value of ≥ 3.8, fasting plasma insulin of ≥ 20 µU/mL, or fasting glucose/ insulin ratio of ≥4.5’), or diabetes mellitus (fasting glucose level ≥ 126 mg/dL).
Diabetes mellitus at treatment start was excluded, as were concomitant antipsychotics, anti-cancer agents, anti-tuberculosis agents, corticosteroids, hormonal agents, and anti-diabetic agents.
Casus were significantly more often male (53% of cases versus 22% of controls) and there was a trend for an higher age in cases (p = 0.06) (mean age 46.6 years in cases and 43.8 years in controls).
The association of glucose metabolism disorders with genetic variants was determined through logistic regression analysis (univariate followed by multivariate adjusting for factors such as age, sex, and BMI among the groups).

Genotyping:
- 111x *1/*1
- 108x *1/*6
- 21x *6/*6

Results:
<table>
<tr><td colspan="2">Results for *1/*6+*6/*6 compared to *1/*1:</td></tr>
<tr><td>glucose metabolism disorders</td><td>NS</td></tr>
<tr><td>impaired fasting glucose</td><td>NS</td></tr>
<tr><td>insulin resistance</td><td>NS</td></tr>
<tr><td>diabetes mellitus</td><td>OR_{adj} = 4.0 (95% CI: 1.1-14.5) (S)</td></tr>
</table>
NOTE: Genotyping was performed for *6. This is the most important gene variant in this population.</td>
<td>mellitus, respectively, among HIV patients on long-term efavirenz-based cART.’</td>
</tr>
<tr>
<td>ref. 2
Ngayo MO et al. Effects of cytochrome P450 2B6 and constitutive androstane receptor genetic variation on efavirenz plasma concentrations among HIV patients in Kenya. PLoS One 2022;17:e0260872. PMID: 35235559.</td>
<td>3</td>
<td>312 Kenyan patients were on efavirenz-based therapy for at least one year. Steady state plasma concentrations were determined between 12 and 16 hours after efavirenz administration.
63.8% of patients had therapeutic efavirenz plasma concentrations (1000-4000 ng/ml), 31.7% had supratherapeutic concentrations (> 4000 ng/ml) and 4.5% has subtherapeutic concentrations (< 1000 ng/ml).
Tuberculosis and though tuberculosis medication was excluded. However, it was not stated if all relevant comedication was excluded. Hepatitis B or C virus coinfection and resulting liver function impairment was not excluded. Living with a partner resulted in more supratherapeutic and less subtherapeutic concentrations, but was not included as a covariate in multiple regression analysis.
The association of efavirenz plasma concentrations with genetic variants was determined through quartile regression analysis.

Genotyping:
*6:
- 128x no *6
- 139x *6 heterozygotes
- 45x *6/*6
*18:
- 268x no *18
- 42x *18 heterozygotes
- 2x *18/*18

Results:
<table>
<tr><td colspan="4">Median efavirenz plasma concentration compared to no variant allele:</td></tr>
<tr><td>variant</td><td>homozygotes</td><td>heterozygotes</td><td>value for</td></tr>
</table></td>
<td>Authors’ conclusion: ‘The SNPs of CYP2B6 516G>T, CYP2B6 983T>C, 21563C>T, presence of higher numbers of SNPs per patient and haplotypes CTGCTTCC, CTGCTTCT, TTGCTTCT and CGACCCCT could efficiently serves as genetic markers for efavirenz plasma concentration and could guide personalization of efavirenz based ART treatment in Kenya.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>PM: A
IM: A</td>
<td>
<table>
<tr><td>allele</td><td>for the variant allele</td><td>for the variant allele</td><td>no variant allele (ng/ml)</td></tr>
<tr><td rowspan="2">*6</td><td>x 4.06</td><td>x 1.35</td><td rowspan="2">2037.5</td></tr>
<tr><td colspan="2">S in univariate and multivariate regression analysis.</td></tr>
<tr><td rowspan="2">*18</td><td>x 3.30</td><td>x 1.48</td><td rowspan="2">2580</td></tr>
<tr><td colspan="2">S in univariate and multivariate regression analysis.</td></tr>
</table>

NOTE: Genotyping was performed for 329G>T, 341T>C, 444 G>T/C, 15582C>T, 516G>T, 548T>G, 637T>C, 785A>G, 18492C>T, 835G>C, 1459C>T, and 21563C>T. This includes the most important gene variants in this population *6 (516G>T and 785A>G) and *18 (983T>C)).

NOTE: Due to low prevalence, analysis of data was not performed for 329G>T, 341T>C, 444 G>T/C, 637T>C, 835G>C, and 548T>G.

NOTE: In this summary, no data were reported for 1459C>T (*5), because it has no changed activity. No data were reported for 785A>G, 15582C>T, and 18492C>T, because there was either no effect in univariate analysis or it was not confirmed in multivariate analysis suggesting the effect to be due to linkage disequilibrium with a relevant polymorphism. No data were reported for 21563C>T because this polymorphism is not reported in PharmVar. An effect of this polymorphism was found in multivariate analysis despite a strong linkage disequilibrium with both polymorphisms in *6 (516 G>T and 785A>G), suggesting it to be part of the *6 allele.
</td>
<td>Median efavirenz plasma concentration versus NM:
IM: 135%
PM: 406%</td>
</tr>
<tr>
<td>ref. 3
Cheng L et al. Meta-analysis of the associations of CYP2B6-516G>T polymorphisms with efavirenz-induced central nervous system side effects and virological outcome in HIV-infected adults. Pharmacogenomics J 2020;20:246-59. PMID: 31636355.</td>
<td>3</td>
<td>Meta-analyses of 16 studies with a total of 3431 adult patients without tuberculosis coinfection. The meta-analysis studying the effect of *6 on central nervous system side effects contained 8 studies with a total of 1327 patients (including 541 without *6, 581 *6 heterozygotes, and 159 *6/*6). The meta-analysis studying the effect of *6 on virological response contained 9 studies with a total of 2710 patients (including 450 without *6, 452 *6 heterozygotes, and 99 *6/*6). Virological response was evaluated by OR (4 studies) and effect size (6 studies). Effect sizes were based on adjusted ORs. Quality of the included studies was assessed based on the presence or absence of 10 items in the publications (clear statement of objectives and hypotheses, clear eligibility criteria for study participants, clear definition of all variables, clear definition of the outcome, credible genetic testing method, replicability of statistical methods, assessment of Hardy-Weinberg equilibrium, sufficient descriptive demographic data, clear report of dropout and reasons, and statement of genotype frequencies and outcome data). For central nervous system side effects, 3 of the studies had all 10 items present, 5 did not describe an assessment of Hardy-Weinberg equilibrium and 1 did not have a clear definition of the outcome. For virological response, 4 of the studies had all 10 items present, 3 did not describe an assessment of Hardy-Weinberg equilibrium, 1 did not describe a credible testing method and 1 neither described a credible testing method nor assessment of Hardy-Weinberg equilibrium.
Of the 8 studies in the central nervous system side effect meta-analysis, 1 was included in this risk analysis separately (Dickinson 2016). Of the 9 studies in the virological response meta-analysis, 5 were included in this risk analysis separate-</td>
<td>Authors' conclusion: 'Our results demonstrated that compared with the normal efavirenz clearance genotype CYP2B6-516 GG, the slow and very slow efavirenz clearance genotypes GT and TT were significantly associated with an increased risk of efavirenz-induced central nervous system side effects but not an increased virological response. To promote the tolerance of efavirenz, it is better to adjust the dosage of efavirenz according to the polymorphisms of CYP2B6-516 in HIV-infected adults.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>IM+PM: C
IM: C</td>
<td>ly (Chang 2018, Gross 2017, Vujkovic 2017, Haas 2014, Dickinson 2016). The studies not included in this risk analysis investigated less than 200 patients.
Meta-analyses were performed with a random-effects model in case of heterogeneity between the studies and with a fixed-effects model otherwise. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
The quality of the included studies was judged, but not with a widely accepted quality assessment scale focussing on the risk of confounding.
Publication bias analysis was performed by Egger’s test and plot and by Begg’s test. However, for central nervous system side effects, publication bias was only performed for one comparison and it was not stated which (probably*6 heterozygote + *6/*6 compared to no *6).

Results:
<table>
<tr><td colspan="3">Results compared to no *6:</td></tr>
<tr><td></td><td>*6 heterozygote + *6/*6</td><td>*6 heterozygote</td></tr>
<tr><td>central nervous system side effects</td><td>OR = 1.47 (95% CI: 1.10-1.96) (S)</td><td>OR = 1.43 (95% CI: 1.06-1.96) (S)</td></tr>
<tr><td>virological response (OR)</td><td>NS</td><td></td></tr>
<tr><td>virological response (effect size (ES))</td><td>NS</td><td></td></tr>
<tr><td colspan="3">Heterogeneity between studies was not significant, neither for central nervous system side effects, nor for virological response.</td></tr>
<tr><td colspan="3">There were no indications for publication bias, neither for central nervous system side effects, nor for virological response.</td></tr>
<tr><td colspan="3">Sensitivity analyses by removing one study at a time did not change the results.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Mugusi S et al. Impact of population and pharmacogenetics variations on efavirenz pharmacokinetics and immunologic outcomes during anti-tuberculosis co-therapy: a parallel prospective cohort study in two sub-Sahara African populations. Front Pharmacol 2020;11:26. PMID: 32116703.</td>
<td>3

PM: A
IM: A</td>
<td>293 patients with tuberculosis coinfection (148 Ethiopians and 145 Tanzanians) were treated with efavirenz-based therapy for 48 weeks. Patients were started on rifampicin-based tuberculosis therapy 4 weeks prior to HIV therapy (rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months). The Tanzanian patient group overlaps with that in Mugusi 2012 and that in Mugusi 2018.
Co-medication with an effect on CYP2B6 was not excluded.

Genotyping:
Ethiopians:
- 74x NM
- 62x IM
- 12x PM

Tanzanians:
- 72x NM
- 53x IM
- 20x PM

Results:
<table>
<tr><td colspan="2">Percent change in CD4 T cell count from baseline to 48 weeks of efavirenz based therapy compared to NM:</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>PM</td><td>NS</td></tr>
<tr><td colspan="2">Note: CYP2B6 genotype was a significant predictor of efavirenz plasma concentrations at both 4 and 16 weeks, with *6 increasing the plasma concentration.
(This is not included in the table above, because no</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘In tuberculosis-HIV patients, baseline body mass index (BMI), viral load, and WHO clinical-stage but not genotype, population-variation, or efavirenz concentration were significant predictors of immunologic outcome at week-48.’</td>
</tr>
</table>

<table>
<tr><td>ref. 4, continuation</td><td></td><td>values per genotype were reported.)

NOTE: Genotyping was for *6. This is the most important gene variant in these populations.</td><td></td></tr>
<tr><td>ref. 5
Torgersen J et al. Impact of efavirenz metabolism on loss to care in older HIV+ Africans.
Eur J Drug Metab Pharmacokinet 2019;44:179-87.
PMID: 30168000.</td><td>3

PM: E</td><td>790 Botswanan patients (687 aged < 50 years and 103 aged ≥ 50 years) were treated with efavirenz-based therapy for 6 months.
Loss to care was defined as participant death or no identifiable clinical interaction following enrolment with the participant during the final assessment window period (between 1 and 6 months after start of efavirenz-based therapy).
The percentage of patients lost to care was 22% for < 50 years and 35% for ≥ 50 years. The percentage of death as the cause of loss to care was 16% for < 50 years and 25% for ≥ 50 years.
One and three months after treatment start, patients completed a 35-item Subject Experience Questionnaire (SEQ) to assess severity of adverse events, including 19 items regarding neurocognitive symptoms, and pharmacy refill data were obtained to calculate ART medication possession ratio.
Steady state efavirenz plasma concentrations were measured one month after treatment start.
Tuberculosis and so antituberculosis treatment was not excluded.
Odds ratios were adjusted for sex, body mass index, and baseline CD4 < 50 cells/ml.

Genotyping:
< 50 years: ≥ 50 years:
- 179x NM - 29x NM
- 344x IM - 49x IM
- 164x PM - 25x PM

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>age</td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="4">loss to care (including death)</td><td>< 50</td><td>NS</td><td>NS</td><td>27%</td></tr>
<tr><td>≥ 50</td><td>OR_{adj} = 5.97 (95% CI: 2.03-17.49) (S)</td><td>NS</td><td>21%</td></tr>
<tr><td></td><td colspan="2">Age significantly modified the effect of CYP2B6 phenotype.</td><td></td></tr>
<tr><td></td><td colspan="2">Note: The outcome death was not determined separately, so it was not clear from the study whether risk of death also increased.</td><td></td></tr>
<tr><td>adverse event score (SEQ score) after 1 month</td><td>≥ 50</td><td colspan="2">Trend for a decrease with increasing number of gene variants (p = 0.06) (NS)</td><td>4,5</td></tr>
<tr><td rowspan="2">patients who did not complete adverse event scoring (with SEQ)</td><td>≥ 50</td><td>x 9.3</td><td>x 5.3</td><td>3%</td></tr>
<tr><td></td><td colspan="2">S for PM versus IM versus NM</td><td></td></tr>
<tr><td>patients with</td><td>≥ 50</td><td colspan="2">Trend for an increase with</td><td>68%</td></tr>
</table>
</td><td>Authors’ conclusion: ‘Older age was associated with loss to care, especially among those with slow efavirenz metabolism. Understanding the relationship between older age and CYP2B6 genotype will be important to improving outcomes in an aging population initiating efavirenz-based ART in similar settings.’

Efavirenz plasma concentration versus NM:</td></tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>IM: A</td>
<td>
<table>
<tr><td>adherence ≥ 95%</td><td></td><td colspan="2">increasing number of gene variants (p = 0.06) (NS)</td><td></td></tr>
<tr><td>patients discontinuing efavirenz</td><td>≥ 50</td><td colspan="2">NS for PM versus IM versus NM</td><td>6.9%</td></tr>
<tr><td rowspan="5">efavirenz plasma concentration (in µg/ml)</td><td>all</td><td>x 4.29</td><td>x 1.43</td><td>1.7</td></tr>
<tr><td>< 50</td><td>x 4.47</td><td>x 1.47</td><td>1.7</td></tr>
<tr><td>≥ 50</td><td>x 3.26</td><td>x 1.21</td><td>1.9</td></tr>
<tr><td></td><td colspan="2">S for PM versus IM versus NM</td><td></td></tr>
<tr><td></td><td colspan="2">Age did not significantly affect efavirenz plasma concentration.</td><td></td></tr>
</table>

NOTE: Genotyping was for *6 and *18. These are the most important gene variants in this population.
</td>
<td>IM: 143%
PM: 429%</td>
</tr>
<tr>
<td>ref. 6
Mugusi S et al. Neuropsychiatric manifestations among HIV-1 infected African patients receiving efavirenz-based cART with or without tuberculosis treatment containing rifampicin.
Eur J Clin Pharmacol 2018;74:1405-15.
PMID: 30003275.</td>
<td>3

IM: AA
PM: AA</td>
<td>341 Tanzanian patients with or without tuberculosis coinfection were treated with efavirenz-based therapy for 16 weeks. Patients with tuberculosis coinfection were started on rifampicin-based tuberculosis therapy 4 weeks prior to HIV therapy. The patient group overlaps with that in Mugusi 2012.
A 29-item questionnaire formulated from different tools used by other research groups was used to collect data on patients' neuropsychiatric status before and 1, 2, 4, 8, 12, and 16 weeks after efavirenz initiation. During the same visit, the clinicians examined patients for clinical signs of neuropsychiatric and other adverse events.
57.6% of patients had some form of neuropsychiatric manifestations during the 16-week study period. Neuropsychiatric adverse events were transient. The incidence peaked in the first two weeks of treatment and dropped to 4-5% of patients after 16 weeks. The incidence was lower in patients receiving antituberculosis treatment. Rifampicin has been reported to lower efavirenz plasma concentration particularly during early initiation of efavirenz-based treatment, but to have no significant long-term effect.
Co-medication with an effect on CYP2B6 was not excluded. However, regression analysis also adjusted for treatment group (with or without tuberculosis, i.e. with or without rifampicin).
Association of neuropsychiatric adverse events with CYPB6 phenotype was assessed with multivariate Cox proportional hazards regression analysis. Adjustment was for treatment group (with or without tuberculosis), sex, body mass index, smoking, other comorbidities, other cART drugs, WHO stage, CD4 cells, and log efavirenz concentration at week 4.

Genotyping:
- 142x NM
- 145x IM
- 54x PM

Results:
<table>
<tr><td colspan="2">Neuropsychiatric adverse events compared to NM:</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>PM</td><td>NS</td></tr>
<tr><td colspan="2">Note: No correlation of efavirenz and 8-hydroxyefavirenz plasma concentrations at week 4 and 16 with neuropsychiatric adverse events was found either.</td></tr>
</table>

NOTE: Genotyping was for *6. This is the most important gene variant in this population.
</td>
<td>Authors' conclusion: 'No association of sex or genotype was seen in relation to neuropsychiatric manifestations.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7
Chang JL et al.
CYP2B6 genetic polymorphisms, depression, and viral suppression in adults living with HIV initiating efavirenz-containing antiretroviral therapy regimens in Uganda: pooled analysis of two prospective studies.
AIDS Res Hum Retroviruses 2018;34:982-92.
PMID: 29973058.</td>
<td>3

PM: AA
IM: AA</td>
<td>242 Ugandan patients were treated with efavirenz-based therapy. Patients were derived from two studies, with 2 years follow-up in one study (n = 153) and 1 year follow-up in the other (n = 89). The mean number of follow-up visits per patient was 4.2.
Probable depression was defined as a mean score on the items of an adapted version of the Hopkins Symptom Checklist Depression subscale (HSCL-D),of > 1.75. In the adapted version, a 16th item (‘‘feeling like I don’t care about my health’’) is added to the 15-item depression subscale. 7% of follow-up visits met criteria for probable depression during follow-up. 25.6% of patients screened positive for probable depression at enrolment.
Viral suppression was defined as an undetectable viral load, with limit of detection varying by type of assay (20-400 copies/ml). It was determined after 6 months (between 3 and 9 months) of therapy in 202 patients. 85% of patients achieved viral suppression.
Tuberculosis coinfection and so, co-medication with an effect on CYP2B6, was not excluded.
Association of results with CYPB6 gene variants was assessed with logistic regression analysis. Adjusting was for the following baseline variables: age, sex, marital status, education, asset index, year of enrolment, $CD4^+$ T lymphocyte count, log_{10} viral load, probable depression, health status, heavy drinking, and study data source.

Genotyping:
*6:
- 102x no *6
- 110x *6 heterozygotes
- 30x *6/*6
*18:
- 206x no *18
- 36x *18 heterozygotes
Note: There were 15 compound heterozygotes (*6/*18).

Results:
<table>
<tr><td colspan="4">Results compared to no variant allele:</td></tr>
<tr><td></td><td>variant allele</td><td>homozygotes for the variant allele</td><td>heterozygotes for the variant allele</td></tr>
<tr><td rowspan="2">probable depression</td><td>*6</td><td colspan="2">NS</td></tr>
<tr><td>*18</td><td>-</td><td>NS</td></tr>
<tr><td rowspan="2">viral suppression</td><td>*6</td><td>NS</td><td>NS</td></tr>
<tr><td>*18</td><td>-</td><td>NS</td></tr>
</table>

NOTE: Genotyping was for *6 and *18. This are the most important gene variants in this population.

Note: In addition, rs4803419 (15582C>T) was not directly genotyped, but imputed using the 1000 Genomes database. Data on this gene variant or on metaboliser definitions also based on this gene variant (i.e. homozygote variant included in IM) were not included in the abstract above, because this gene variant is not mentioned in PharmVar.</td>
<td>Authors’ conclusion: ‘CYP2B6 metabolizer strata did not have a statistically significant association with either depression or 6-month viral suppression.’</td>
</tr>
<tr>
<td>ref. 8
Gross R et al.
CYP2B6 genotypes and early efavirenz-based HIV treatment outcomes in Botswana.
AIDS 2017;31:2107-13.
PMID: 28692529.</td>
<td>3</td>
<td>801 Botswanan patients were treated with efavirenz-based therapy. Follow-up visits occurred 1 month and 6 months (3-9 months) after treatment start.
Death was determined by documentation in the medical record or by verbal report from the participant’s family. Loss to care was determined by inability to identify any records on the participant up to 9 months after initiation of therapy. The lower limit of quantification of plasma HIV RNA was 25 copies/ml. Participants lost to the study but found to be alive and in care but without available viral load data were classi-</td>
<td>Authors’ conclusion: ‘Slow metabolism alleles were associated with lower efavirenz clearance but not any of the treatment endpoints. Slow efavirenz metabolism did not exacerbate CNS</td>
</tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>PM: AA#
IM: AA#</td>
<td>fied as having met the composite endpoint death, loss to care, or viremia. Adverse events were assessed at months 1 and 6 using the 35-item Subject Experience Questionnaire. Each item on this scale is rated 0–3 with higher scores representing greater adverse events. Central nervous system adverse events were assessed by taking only the central nervous system items of this scale into account.
288 patients (36%) met the endpoint death, loss to care, or viremia with 34 (4%) who died, 151 (19%) lost to care, 11 (1%) lost to the study, but alive and in care, and 92 (11%) with detectable plasma viremia. In the patients with viremia, the level was low with a median of 85 copies/ml. Eleven (12%) of those with viremia had plasma HIV RNA>1000 copies/ml.
Relevant comedication was not excluded. However, excluding patients treated with isoniazide (n = 13) did not have a substantive effect on the endpoint death, loss to care, or viremia. Isoniazide, like rifampicin part of antituberculosis treatment has been reported to further decrease efavirenz clearance in PM.
Associations between results and phenotypes were assessed with logistic or linear regression analyses. Adjustment was for log_{10} baseline HIV RNA for the endpoint death, loss to care, or viremia and its components.
940 patients were enrolled to achieve 80% power to detect a relative risk of 2.0 for the association between PM and the endpoint death, loss to care, or viremia at 6 months. A prevalence of the variant allele with the more common gene variant (*6) of 40% and a rate of the endpoint death, loss to care, or viremia of 20% was assumed in the target sample size calculation. The target sample size was increased by 50% to account for the presence of potential effect modifiers of the relation between genotype and endpoint.

Genotyping:
- 213x NM
- 396x IM
- 192x PM

Results:
<table>
<tr><td colspan="4">Results for PM versus IM versus NM or compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>death, loss to care, or virologic failure</td><td colspan="2">NS for PM versus IM versus NM</td><td></td></tr>
<tr><td>virologic failure</td><td colspan="2">NS for PM versus IM versus NM</td><td></td></tr>
<tr><td>loss to follow-up</td><td colspan="2">NS for PM versus IM versus NM</td><td></td></tr>
<tr><td>death</td><td colspan="2">NS for PM versus IM versus NM</td><td></td></tr>
<tr><td>CD4 increase (in cells/ml)</td><td>NS</td><td>NS</td><td>95</td></tr>
<tr><td rowspan="2">total adverse event score after 1 month</td><td>x 0.54</td><td>x 0.88</td><td rowspan="2">5.2</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td>total adverse event score after 6 months</td><td colspan="2">NS for PM versus IM versus NM</td><td>2.3</td></tr>
<tr><td rowspan="2">CNS adverse event score after 1 month</td><td>x 0.53</td><td>x 0.93</td><td rowspan="2">3.0</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td>CNS adverse event</td><td colspan="2">NS for PM versus IM</td><td>1.3</td></tr>
</table>
</td>
<td>toxicity. These results should allay concern that slow efavirenz metabolism adversely impacts individuals in sub-Saharan African settings in which these alleles are common.’</td>
</tr>
</table>

ref. 8, continuation		score after 6 months | versus NM *6 and *18 were shown to decrease efavirenz clearance. However, because results were not indicated per phenotype, they are not included in this table. NOTE: Genotyping was for *6 and *18. This are the most important gene variants in this population.	
ref. 9 Vujkovic M et al. CYP2B6 516G>T minor allele protective of late virologic failure in efavirenz-treated HIV-infected patients in Botswana. J Acquir Immune Defic Syndr 2017;75:488-91. PubMed PMID: 28481785.	3 IM: E (IM+PM): E	Patients from Botswana were treated with efavirenz 600 mg per day in combination with two nucleoside reverse transcriptase inhibitors for at least 6 months. 276 cases with late HIV failure (plasma HIV RNA > 1000 copies/ml after maintaining viral suppression (< 400 copies/ml) for at least 6 months) were compared with 1062 controls with plasma HIV RNA < 400 copies/ml for at least 6 months. Genotyping results were available in 1100 patients. The frequency of the *6 variant in this population was approximately 38%. Relevant co-medication was not excluded. A total of 1660 patients was calculated to be needed to detect an OR of 2.0. Age and CD4 count at start of treatment differed between genotypes, but logistic regression was employed to correct for this. Results: Risk for late HIV failure compared to *1/*1: *6/*6: OR = 0.71 (95% CI: 0.41-1.18) (NS) *1/*6: OR = 0.69 (95% CI: 0.49-0.97) (S) The risk was decreased for (*6/*6+*1/*6) versus *1/*1 (OR = 0.70 (95% CI: 0.50-0.97) (S)), while there was a trend for *6/*6 versus *1/*6 versus *1/*1 (p = 0.06). NOTE: Genotyping was performed for *6. This is the most important gene variant in this population.	Authors' conclusion: 'The CYPB2B6 516 T-allele was protective against late virologic breakthrough in patients with initial (6 month) HIV RNA suppression on efavirenz-based antiretroviral therapy.'
ref. 10 Bolton Moore C et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. AIDS 2017;31:1129-1136. PubMed PMID: 28323755.	3	47 patients of 3-36 months old (median 19 months) without tuberculosis were treated with efavirenz in combination with two nucleoside reverse transcriptase inhibitors for 24 weeks. Efavirenz was given as capsules opened into porridge, formula or expressed breast milk. Doses were 200 mg/day for patients of 3-5 kg, 300 mg/day for 5-7 kg, 400 mg/day for 7-14 kg and 500 mg/day for 14-17 kg (approximately $1600*(\text{weight in kg}/70)^{0.7}$ mg = approximately 40 mg/kg). Reduced doses were 50 mg/day for 3-7 kg, 100 mg/day for 7-14 kg and 150 mg/day for 14-17 kg (approximately $400*(\text{weight in kg}/70)^{0.7}$ mg = approximately 10 mg/kg). Two weeks after start of treatment or after each dose adjustment, efavirenz AUC was determined and doses were adjusted with 50%. The target AUC was 35-180 µg.h/ml. This AUC corresponds to a trough concentration of approximately 0.7-4.0 µg/ml. The last 2 patients with genotype *6/*6 were started on the reduced dose instead of the normal dose. If target AUC was not achieved after one dose adjustment, efavirenz treatment and study participation was discontinued. Relevant co-medication was not excluded, except for previous use of efavirenz or nevirapine by the child or pregnant mother. Genotyping: - 21x *1/*1 - 17x *1/*6 - 9x *6/*6 Results:	Authors' conclusion: 'CYP2B6 G516T genotype strongly influences efavirenz exposures in this age group. Genotype-directed dosing yields therapeutic efavirenz concentrations and appears to outperform other dosing approaches.'

<table>
<tr>
<td>ref. 10, continuation</td>
<td>PM: AA</td>
<td>
<table>
<tr><td colspan="4">% of patients with therapeutic, supratherapeutic or subtherapeutic AUC with different doses of efavirenz (therapeutic AUC = 35-180 µg.h/ml):</td></tr>
<tr><td>geno-type</td><td>dose</td><td>AUC</td><td>% of patients</td></tr>
<tr><td rowspan="4">*1/*1 +*1/*6</td><td rowspan="4">normal</td><td>therapeutic</td><td>82%</td></tr>
<tr><td>supratherapeutic</td><td>8%</td></tr>
<tr><td>subtherapeutic</td><td>10%</td></tr>
<tr><td colspan="2">3 of 4 patients with subtherapeutic AUC met the target after a 50% dose increase, but only 1 of 3 patients with supratherapeutic AUC did so after a 50% dose reduction.
The authors conclude that doses of approximately 40 mg/kg are suitable for this patient group.</td></tr>
<tr><td rowspan="2">*6/*6 (n = 7)</td><td rowspan="2">normal</td><td>supratherapeutic</td><td>100%</td></tr>
<tr><td colspan="2">3 of 7 patients discontinued the study because a 50% dose reduction failed (n = 2) or was predicted to fail (n = 1) in bringing the AUC within target levels.</td></tr>
<tr><td rowspan="2">*6/*6 (n = 2)</td><td rowspan="2">reduced</td><td>therapeutic</td><td>100%</td></tr>
<tr><td colspan="2">Pharmacokinetic modelling predicted 90% of patients on this dose to achieve a therapeutic AUC and the remaining 10% a supratherapeutic AUC, indicating that doses of approximately 10 mg/kg are suitable for this patient group.</td></tr>
<tr><td colspan="4"><u>Toxicities</u>:
24% of *1/*1, 35% of *1/*6 and 44% of *6/*6 experienced non-life-threatening toxicities that were deemed at least ‘possibly related to antiretroviral treatment’ (significance not determined).
13% of patients, consisting of all three CYP2B6 genotypes, reported neurologic toxicities of lethargy, sleepiness or sleep disturbances (14% of *1/*1, 12% of *1/*6 and 11% of *6/*6).
4% of patients (1x *1/*1 and 1x *6/*6) discontinued treatment due to toxicities possibly related to efavirenz.
40% of patients with toxicity had a supratherapeutic AUC after 2 weeks.</td></tr>
<tr><td colspan="4"><u>Virologic success</u>:
All patients who completed 24 weeks of treatment had virologic success. None of the treatment discontinuations was due to virologic failure.</td></tr>
</table>

NOTE: Kinderformularium and Informatorium Medicamentorum only mention doses for children 3 years and older and 13 kg or heavier. For dosing by tablets, the mentioned doses correspond to those mentioned by the FDA for children younger than 3 years (200 mg/day for children of 13-15 kg and 250 mg/day for children of 15-17 kg). Modelling predicted the FDA doses to lead to 63% of *1/*1+*1/*6 and 44% of *6/*6 with therapeutic AUCs. For *1/*1+*1/*6, 32% of AUCs was predicted to be subtherapeutic and 5% supratherapeutic. For *6/*6, 56% of AUCs was predicted to be supratherapeutic. The authors conclude that the FDA doses are not suitable for these patient groups. Subtherapeutic efavirenz levels have been shown to lead to decreased effectiveness and resistance to efavirenz. Supratherapeutic levels increase the risk of (central nervous system) toxicity.
</td>
<td>Suitable dose compared to NM+IM:
PM: 25%

Suitable dose compared to recommended dose:
PM: 50%
NM+IM: 200%</td>
</tr>
</table>

<table>
<tr><td>ref. 10, continuation</td><td></td><td>NOTE: For dosing by the efavirenz solution of 30 mg/ml, the doses that Kinderformularium and Informatorium Medicamentorum mention are more increased for children than for adults (adults 720 mg/day, children 5-18 years and 15-20 kg 300 mg/day, children 5-18 years and 13-15 kg 270 mg/day, children 3-5 years and 15-20 kg 390 mg/day, and children 3-5 years and 13-15 kg 360 mg/day). In the adults, increase is needed because the tablets and solution are not bioequivalent.

NOTE: Genotyping was performed for *6. This is the most important gene variant in this population, consisting mainly of children of African or Asian origin (74% and 23% respectively, 1 patient (2%) was of unknown origin).</td><td></td></tr>
<tr><td>ref. 11
Leger P et al. Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. Pharmacogenet Genomics 2016;26:473-80. PubMed PMID: 27509478.</td><td>3

PM: E
IM: AA</td><td>563 patients from the United States) were started on efavirenz-containing antiretroviral therapy and followed up for 12 months. 335 patients were non-Hispanic White, 198 were Black, 25 were Hispanic and 5 were Asian.
99 patients discontinued efavirenz within 12 months. Central nervous system symptoms were the primary cause of discontinuation (n = 29: 20 non-Hispanic Whites, 9 Blacks). Adjusted hazard ratios were adjusted for ethnicity. Relevant co-medication was not excluded.

Genotyping:
- 260x NM (*1/*1)
- 231x IM+NM (184-194x IM (*1/*6 or *1/*18) and 37-47x NM (*1/*1))
- 72x PM (*6/*6, *6/*18 or *18/*18)

Results:
<table>
<tr><td colspan="4">Risk of discontinuation for CNS symptoms compared to NM:</td></tr>
<tr><td>ethnicity</td><td>PM</td><td>IM+NM</td><td>% of discontinued NM</td></tr>
<tr><td>all</td><td>HR_{adj} = 4.86 (S) (95% CI: 1.91-12.39)
positive predictive value for discontinuation = 16.1% (95% CI: 8.0-27.7%)</td><td>NS</td><td>ca. 4%</td></tr>
<tr><td>White</td><td>HR = 6.50 (S) (95% CI: 1.91-12.39)
positive predictive value for discontinuation = 27.2% (95% CI: 10.7-50.2%)</td><td>NS</td><td>ca. 5%</td></tr>
<tr><td>Black</td><td>NS</td><td>NS</td><td>ca. 4%</td></tr>
<tr><td>Hispanic</td><td colspan="3">None of the patients discontinued treatment for CNS symptoms.</td></tr>
<tr><td colspan="4">There was no significant difference in risk of continuation between Whites and Blacks for each of the genotype groups, however there was a trend for a smaller risk in Blacks (p = 0.081).</td></tr>
</table>
<table>
<tr><td colspan="3">Risk of discontinuation for all causes compared to NM:</td></tr>
<tr><td>ethnicity</td><td>PM</td><td>IM+NM</td></tr>
<tr><td>all</td><td>trend for a higher risk (NS) (p = 0.069)</td><td>NS</td></tr>
<tr><td>White</td><td>HR = 2.96 (S) (95% CI: 1.32-6.61)</td><td>NS</td></tr>
</table></td><td>Authors’ conclusion: ‘Slow metabolizer genotypes were associated significantly with efavirenz discontinuation for reported CNS symptoms. This association was considerably stronger in Whites than in Blacks.’</td></tr>
</table>

<table>
<tr>
<td>ref. 11, continuation</td>
<td></td>
<td>
<table>
<tr><td>Black</td><td>NS</td><td>NS</td></tr>
<tr><td>Hispanic</td><td colspan="2">20% of the patients discontinued treatment because of skin rash, 4% because of treatment failure and 4% because of unspecified reasons.</td></tr>
</table>

NOTE: Genotyping was performed for *6, *18 and 15582 C>T.
In this summary, 15582C>T is ignored, because it has only a modest effect on efavirenz plasma concentrations. Two large studies did not find a significant effect of 15582C>T on efavirenz pharmacokinetics after taking into account or correcting for *6 and *18 (Dickinson L et al. Pharmacokinetic and pharmacodynamic comparison of once-daily efavirenz (400 mg vs. 600 mg) in treatment-naïve HIV-infected patients: results of the ENCORE1 study. Clin Pharmacol Ther 2015;98:406-16. PubMed PMID: 26044067 and Evans J et al. 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 2015;19:332-8. PubMed PMID: 26415139). According to the CYP allele nomenclature website (http://www.cypalleles.ki.se/cyp2b6.htm), 15582T appears in two alleles with reduced activity, but other polymorphisms in these alleles are responsible for the reduced enzyme activity (both polymorphisms in *6 in the case of *13B and 1172T>A in the case of *15). In addition, 15582T is present in *1C, which is not known to lead to a reduced enzyme activity.
</td>
<td></td>
</tr>
<tr>
<td>ref. 12
Cusato J et al. Efavirenz pharmacogenetics in a cohort of Italian patients.
Int J Antimicrob Agents 2016;47:117-23. PubMed PMID: 26774523.</td>
<td>4

PM: A

IM: A</td>
<td>201 Italian patients were treated with antiretroviral therapy with efavirenz 600 mg once daily for more than 7 days (median 24 months). Efavirenz plasma concentrations were determined approximately 12 hours after dosing. Interacting drugs were excluded.

Genotyping:
- 116x *1/*1
- 73x *1/*6
- 12x *6/*6

Results:
<table>
<tr><td colspan="2">Median plasma concentration of efavirenz 12 hours after dosing compared to *1/*1 (2315 ng/ml):</td></tr>
<tr><td rowspan="3">*6/*6</td><td>x 2.80 (S)</td></tr>
<tr><td>The median plasma concentration was supratherapeutic (higher than 4000 ng/ml).</td></tr>
<tr><td>Multivariate logistic regression analysis showed *6/*6 to be an independent predictor of supratherapeutic plasma concentrations (OR = 31.39 (95% CI: 5.92-166.37) (S).</td></tr>
<tr><td>*1/*6</td><td>x 1.36 (S for *6/*6 versus *1/*6 versus *1/*1)</td></tr>
</table>

NOTE: Genotyping was performed for *6 and *18. *18 was not found in this Italian population.</td>
<td>Authors’ conclusion: ‘This study confirmed the role of CYP2B6 and ABCB1 polymorphisms, showed a relationship with HNF4α, and the lack of association of CYP2A6, UGT2B7, NR1I2and NR1I3 SNPs on efavirenz plasma exposure.’

Median efavirenz plasma concentration versus NM:
IM: 136%
PM: 280%</td>
</tr>
<tr>
<td>ref. 13
Dickinson L et al. Comprehensive pharmacokinetic, pharmacodynamic and pharmacogenetic evaluation of once-daily efavirenz</td>
<td>3</td>
<td>574 patients of 16 years or older were treated with efavirenz 600 mg (49% of patients) or 400 mg (51% of patients) once daily in combination with tenofovir/emtricitabine 300/200 mg once daily for 96 weeks. 37% of patients was African (n = 213), 33% Asian (n = 195), 17% Hispanic, 13% White and 0.2% Aboriginal/Torres Strait Islander. Non-Hispanic Whites, Hispanics and Aboriginal/Torres Strait Islanders were grouped together as Whites (n = 166).</td>
<td>Authors’ conclusion: ‘Achieving plasma HIV-RNA <200 copies/mL at 96 weeks was not associated with the selection of single nucleotide polymorphisms (SNP;</td>
</tr>
</table>

<table>
<tr>
<td>400 and 600 mg in treatment-naïve HIV-infected patients at 96 weeks: results of the ENCORE1 study. Clin Pharmacokinet 2016;55:861-73. PubMed PMID: 26715213.

ref. 13, continuation</td>
<td>PM: E
IM: E

PM: AA#</td>
<td>Discontinuation was defined as interruption in efavirenz treatment for more than 30 days.
Adverse events were categorised as efavirenz-related based on either the SPC or on clinician decision. CNS adverse events were defined as in the SPC (including abnormal dreams, anxiety, dizziness, headache, impaired concentration, insomnia and somnolence).
98% of patients had plasma HIV-RNA ≤ 200 copies/ml after 96 weeks. 12% of patients discontinued efavirenz treatment.
Adjusted hazard ratios were adjusted for dose, age and sex, and results were stratified by country.
Relevant co-medication was not excluded.

Genotyping:
*6:
- 253x *1/*1
- 262x *1/*6
- 59x *6/*6

*18:
- 535x *1/*1
- 36x *1/*18
- 3x *18/*18

Results:
<table>
<tr><td colspan="4">Results compared to *1/*1:</td></tr>
<tr><td></td><td>*6/*6</td><td>*1/*6</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with viral load < 200 copies/ml</td><td colspan="2">NS for *6/*6 versus *1/*6 versus *1/*1</td><td>98%</td></tr>
<tr><td rowspan="2">% of patients who discontinued treatment</td><td>HR_{adj} = 2.66 (S) (95% CI: 1.26-5.60)</td><td>HR_{adj} = 1.80 (S) (95% CI: 1.01-3.21)</td><td rowspan="2">8.7%</td></tr>
<tr><td colspan="2">The association was not significant after 48 weeks of treatment (7% of patients who discontinued treatment versus 12% after 96 weeks).</td></tr>
<tr><td>efavirenz related adverse events (based on the SmPC)</td><td colspan="2">NS for *6/*6 versus *1/*6 versus *1/*1</td><td></td></tr>
<tr><td>efavirenz related adverse events (clinician decision)</td><td colspan="2">NS for *6/*6 versus *1/*6 versus *1/*1</td><td></td></tr>
<tr><td>CNS adverse events (based on the SmPC)</td><td colspan="2">NS for *6/*6 versus *1/*6 versus *1/*1</td><td></td></tr>
</table>
<table>
<tr><td colspan="3">Results compared to *1/*1:</td></tr>
<tr><td></td><td>*18/*18+*1/*18</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with viral load < 200 copies/ml</td><td>NS</td><td>98%</td></tr>
<tr><td>% of patients who discontinued treatment</td><td>trend for a higher risk (NS) (p = 0.082)</td><td>11%</td></tr>
<tr><td>efavirenz-related adverse events (based on the SmPC)</td><td>NS</td><td></td></tr>
<tr><td>efavirenz-related adverse events (clinician decision)</td><td>NS</td><td></td></tr>
<tr><td>CNS adverse events (based on the SmPC)</td><td>OR = 0.30 (S) (95% CI: 0.12-0.75)</td><td></td></tr>
</table>
</td>
<td>CYP2B6, CYP2A6, CYP3A4, NR1I3, NR1I2, ABCB1) assessed. … CYP-2B6 15582CT/TT and ABCB1 3435TT carriers were at higher risk (46 and 131%, respectively) of CNS related adverse events compared with 35% lower risk in CYP2B6 983TC/CC patients. Possession of the CYP2B6 516 GT and TT variants and CYP2A6*9B CA/AA carriers was associated with a higher risk of overall efavirenz discontinuation (80, 166 and 100%, respectively).’</td>
</tr>
</table>

<table>
<tr><td>ref. 13, continuation</td><td></td><td>NOTE: The authors indicate that the lower threshold of the therapeutic concentration of evafirenz (1000 ng/ml) might not be applicable for this more potent antiretroviral therapy (combination with tenofovir and emtricitabine instead of lamivudine, zidovudine, nelfinavir and/or amprenavir).

NOTE: Genotyping was performed for *6, *18 and 15582 C>T.
In this summary, 15582C>T is ignored. See the summary of Leger 2016 for a justification.</td><td></td></tr>
<tr><td>ref. 14
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 2016;6:356.
PubMed PMID: 26779253.</td><td>3

PM: A
IM: A</td><td>222 South African patients were treated with efavirenz-based antiretroviral therapy for at least 6 months.
Efavirenz plasma concentrations were determined 14-18 hours after dosing.
3% of patients had an efavirenz plasma concentration below and 31% above the therapeutic range (1-4 µg/ml).
Relevant co-medication was not excluded. In the whole group, concurrent treatment of tuberculosis did not significantly increase the median efavirenz concentration.
p-values were corrected for multiple testing (significance for p < 0.001 after correction for the total number of SNPs for different genes tested and for p < 0.006 after correction for 8 covariates in multivariate analysis).

Genotyping:
*6 (516G>T): - 79x *1/*1 - 100x *1/*6 - 43x *6/*6
*6 (785A>G): - 81x *1/*1 - 100x *1/*6 - 40x *6/*6
*18: - 192x *1/*1 - 21x *1/*18 - 5x *18/*18
There was a strong linkage disequilibrium (91%) between the two single nucleotide polymorphisms in *6.

Results:
<table>
<tr><td colspan="4">Median plasma concentration of efavirenz 14-18 hours after dosing compared to *1/*1:</td></tr>
<tr><td>variant</td><td>variant/variant</td><td>*1/variant</td><td>value for *1/*1</td></tr>
<tr><td>*6 (516 G>T)</td><td>x 3.80
S for *6/*6 versus *1/*6 versus *1/*1</td><td>x 1.27</td><td>1.97 µg/ml</td></tr>
<tr><td>*6 (785 A>G)</td><td>x 3.97
S for *6/*6 versus *1/*6 versus *1/*1</td><td>x 1.29</td><td>1.94 µg/ml</td></tr>
<tr><td>*18</td><td>x 9.10
S for *18/*18 versus *1/*18 versus *1/*1</td><td>x 1.51</td><td>2.40 µg/ml</td></tr>
<tr><td colspan="4">The median plasma concentrations for *6/*6 (both definitions) and *18/*18 were supratherapeutic (higher than 4 µg/ml), with the median plasma concentration being 5-fold the upper limit for *18/*18.</td></tr>
</table>
<table>
<tr><td colspan="4">% of patients with supratherapeutic efavirenz plasma concentrations (> 4 µg/ml) for different genotypes:</td></tr>
<tr><td>variant</td><td>variant/variant</td><td>*1/variant</td><td>*1/*1</td></tr>
<tr><td>*6 (516 G>T)</td><td>77%</td><td>27%</td><td>11%</td></tr>
<tr><td>*18</td><td>100%</td><td>48%</td><td>28%</td></tr>
<tr><td>*6 and/or *18</td><td>82%</td><td colspan="2">13%</td></tr>
<tr><td colspan="4">Multivariate logistic regression analysis showed *6 (516 G>T) and *18 to be the most significant predictors of supratherapeutic plasma concentrations (S).</td></tr>
</table></td><td>Authors' conclusion: 'We have shown that CYP2B6c.516 G>T and c.983T>C SNPs are the most important predictors of efavirenz plasma concentration after taking into account all other SNPs, including genetic variation in the 3′-UTR, and variables affecting efavirenz metabolism.'

Median efavirenz plasma concentration versus NM (based on *6):
IM: 127%
PM: 380%

Median efavirenz plasma concentration versus NM (based on *18):
IM: 151%
PM: 910%</td></tr>
</table>

<table>
<tr>
<td>ref.14, continuation</td>
<td></td>
<td>
The positive predictive value of *6/*6 (516 G>T) for a supratherapeutic efavirenz plasma concentration was 76.7% with a sensitivity of 47.8% and a negative predictive value of 79.9%.
The positive predictive value of *18/*18 for a supratherapeutic efavirenz plasma concentration was 100% with a sensitivity of 7.2% and a negative predictive value of 70.0%.
The positive predictive value of PM (*6/*6, *6/*18 and *18/*18) for a supratherapeutic efavirenz plasma concentration was 82.5% with a sensitivity of 68.1%, specificity of 93.4% and a negative predictive value of 86.5%.

NOTE: Genotyping was performed for *6 (both 516G>T and 785A>G), *18, 136A>G, 485-18C>T, 1355A>G and 1421T>C.
In this summary, 136A>G, 485-18C>T, 1355A>G and 1421 T>C are ignored. None of these gene variants had a significant effect on the median efavirenz plasma concentration.
</td>
<td></td>
</tr>
<tr>
<td>ref. 15
Meng X et al.
Effect of CYP2B6 gene polymorphisms on efavirenz plasma concentrations in Chinese patients with HIV infection.
PLoS One 2015;10:e0130583.
PubMed PMID: 26107645.</td>
<td>3

PM: A
IM: A</td>
<td>
322 Chinese patients were treated with antiretroviral therapy with efavirenz 600 mg once daily for at least 2 weeks (mean 17 months).
Efavirenz plasma concentrations were determined 12-16 hours after dosing.
13% of patients had an efavirenz plasma concentration below and 9% above the therapeutic range (1-4 µg/ml).
Patients were advised not to take co-medication that could reduce or induce CYP-enzymes (such as rifampicin).

Genotyping:
*6 (516G>T):
- 219x *1/*1
- 84x *1/*6
- 19x *6/*6
*6 (785A>G):
- 183x *1/*1
- 108x *1/*6
- 31x *6/*6
1355A>G:
- 49x *1/*1
- 153x *1/*18
- 120x *18/*18
There was a strong linkage disequilibrium between the two single nucleotide polymorphisms in *6.

Results:
Plasma concentration of efavirenz 12-16 hours after dosing compared to *1/*1:
<table>
<tr><th>variant</th><th>variant/variant</th><th>*1/variant</th><th>value for *1/*1</th></tr>
<tr><td>*6 (516 G>T)</td><td>x 4.72 (S)</td><td>x 1.56 (S)</td><td>1.72 µg/ml</td></tr>
<tr><td>*6 (785 A>G)</td><td>x 3.32 (S)</td><td>x 1.26 (S)</td><td>1.79 µg/ml</td></tr>
<tr><td>1355A>G</td><td>x 2.01 (S)</td><td>x 1.14 (S)</td><td>1.63 µg/ml</td></tr>
</table>
The mean plasma concentration for *6/*6 (both definitions) was supratherapeutic (higher than 4 µg/ml), but the mean plasma concentration for 1355G/1355G was not.

% of patients with supratherapeutic efavirenz plasma concentrations (> 4 µg/ml) for different genotypes:
<table>
<tr><th>variant</th><th>variant/variant</th><th>*1/variant</th><th>*1/*1</th></tr>
<tr><td>*6 (516 G>T)</td><td>89%</td><td>12%</td><td>1%</td></tr>
<tr><td>*6 (785 A>G)</td><td>58%</td><td>48%</td><td>2%</td></tr>
<tr><td>1355A>G</td><td>19%</td><td>4%</td><td>0%</td></tr>
</table>
NOTE: Because of the relatively small effect of 1355A>G on the efavirenz plasma concentration and the risk for supratherapeutic plasma concentrations and because of the lin-
</td>
<td>Authors' conclusion: 'We observed significant association of 171+967C>A, 171+4335T>C, 516G>T, 785A>G and *1355 A>G with high plasma efavirenz levels. We observed strong linkage disequilibrium for 171+967 C>A, 171+4335T>C, 516G>T and 785 A>G.'

Efavirenz plasma concentration versus NM (based on *6 (516 G>T)):
IM: 156%
PM: 472%</td>
</tr>
</table>

<table>
<tr><td>ref. 15, continuation</td><td></td><td>kage disequilibrium analysis between this gene variant and *6 being not informative, 1355A>G was not included as variant with reduced activity in the background information text of the CYP2B6 gene.

NOTE: Genotyping was performed for *6 (both 516G>T and 785A>G), 171+967C>A, 171+3212C>T, 171+4335T>C, 1295-913G>A, and 1355A>G.
In this summary, 171+3212C>T, 1295-913G>A, 171+967 C>A and 171+4335T>C are ignored. 171+3212C>T and 1295-913G>A did not have a significant effect on the efavirenz plasma concentration. 171+967 C>A and 171+4335 T>C were in linkage disequilibrium with *6 (516G>T).</td><td></td></tr>
<tr><td>ref. 16
Haas DW et al.
Functional CYP2B6 variants and virologic response to an efavirenz-containing regimen in Port-au-Prince, Haiti.
J Antimicrob Chemother 2014;69:2187-90.
PubMed PMID: 24695352.</td><td>3

PM: AA
IM: AA</td><td>359 Haitian patients were treated with efavirenz 600 mg once daily in combination with zidovudine/lamivudine 300/ 150 mg twice daily for 48 weeks. Therapy was started CD4 cells/mm^3 (standard timing, 16% of patients) or at 350 CD4 cells/mm^3 (early timing, 84% of patients).
Relevant co-medication was not excluded. The efavirenz dose was increased to 800 mg once daily in case of co-medication with rifampicin.
Multivariate logistic regression analyses controlled for baseline log_{10} HIV-1 RNA, sex, age and baseline CD4 count.

Genotyping:
- 102x *1/*1
- 180x IM+NM (176x IM (146x *1/*6 and 30x *1/*18), 4x NM (*1/*1))
- 77x PM (58x *6/*6, 18x *6/*18, 1x *18/*18)

Results:<table><tr><td colspan="4">Viral load after 48 weeks of treatment compared to NM:</td></tr><tr><td></td><td>PM</td><td>IM+NM</td><td>value for NM</td></tr><tr><td>% of patients with viral load < 50 copies/ml</td><td>NS</td><td>NS</td><td>79%</td></tr><tr><td>% of patients with viral load < 200 copies/ml</td><td>NS</td><td>NS</td><td>84%</td></tr><tr><td colspan="4">Multivariate logistic regression analyses did not find a significant effect of CYP2B6 phenotype on both efficacy outcome measures (NS).
In addition, there was no effect of either *6 or *18 in univariate analyses (NS).</td></tr></table>
NOTE: Genotyping was performed for 49 CYP2B6 gene variants, including *6, *18 and 15582C>T.
In this summary, 15582C>T is ignored. See the summary of Leger 2016 for a justification.
In addition, 46 gene variants are ignored, because it is not known whether they influence the efavirenz plasma concentration.</td><td>Authors’ conclusion: ‘Virologic failures in efavirenz-containing regimens in protocol HT 001 were not explained by genetic polymorphisms known to define the lowest plasma efavirenz concentration stratum.’</td></tr>
<tr><td>ref. 17
Martín AS et al.
Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics.
Pharmacogenomics 2014;15:997-1006.</td><td>4</td><td>In 31 of 190 Spanish patients treated with antiretroviral therapy containing efavirenz 600 mg once daily, efavirenz dose was reduced based on the presence of adverse events and/or on plasma levels. Before dose adjustments, most patients showed a good clinical evolution but 77.4% had efavirenz concentrations above the therapeutic range and 83.9% had adverse central nervous system (CNS) effects. The most common CNS adverse effects were abnormal dreams (54.8%), hyperhidrosis (51.6%), somnolence (45.2%), sadness (45.2%), nervousness (45.2%), irritability (45.2%) and mood changes (41.9%). For 74.2% of patients,</td><td>Authors’ conclusion: ‘The individualization of efavirenz dosage guided by genotyping 516G>T CYP2B6 and therapeutic drug monitoring could increase the efficiency of efavirenz use in</td></tr>
</table>

<table>
<tr>
<td>PubMed PMID: 24956253.

ref. 17, continuation</td>
<td>PM: C
IM: C</td>
<td>dose decrease to 400 mg/day sufficed to reach a therapeutic plasma concentration (1-4 µg/ml). For the remaining 25.8% (all PM and 62% of the total number of PM), dose had to be reduced to 200 mg/day to reach a therapeutic plasma concentration. The mean duration of efavirenz dose adjustment was 2.3 years.
Co-medication with known inducers or inhibitors of efavirenz was excluded.

Genotyping:
- 3x *1/*1
- 14x *1/*6
- 13x *6/*6

Results:
<table>
<tr><td colspan="3">Results after dose reduction compared to before dose reduction:</td></tr>
<tr><td></td><td>after dose reduction</td><td>value before dose reduction</td></tr>
<tr><td>adverse events</td><td>x 0.12 (S)</td><td>84% of patients</td></tr>
<tr><td>abnormal dreams</td><td>x 0.12 (S)</td><td>55% of patients</td></tr>
<tr><td>hyperhidrosis</td><td>x 0.00 (S)</td><td>52% of patients</td></tr>
<tr><td>somnolescence</td><td>x 0.00 (S)</td><td>45% of patients</td></tr>
<tr><td>sadness</td><td>x 0.21 (S)</td><td>45% of patients</td></tr>
<tr><td>nervousness</td><td>x 0.00 (S)</td><td>45% of patients</td></tr>
<tr><td>irritability</td><td>x 0.07 (S)</td><td>45% of patients</td></tr>
<tr><td>mood change</td><td>x 0.16 (S)</td><td>42% of patients</td></tr>
<tr><td>muscle stick</td><td>x 0.00 (S)</td><td>39% of patients</td></tr>
<tr><td>difficulty in sleeping</td><td>x 0.01 (S)</td><td>32% of patients</td></tr>
<tr><td>fatigue</td><td>x 0.00 (S)</td><td>26% of patients</td></tr>
<tr><td>dizziness</td><td>x 0.00 (S)</td><td>23% of patients</td></tr>
<tr><td>memory loss</td><td>x 0.00 (S)</td><td>23% of patients</td></tr>
<tr><td>impaired concentration</td><td>x 0.00 (S)</td><td>19% of patients</td></tr>
<tr><td>euphoria</td><td>NS</td><td>10% of patients</td></tr>
<tr><td>$CD4^+$ lymphocyte count</td><td>x 1.2 (S)</td><td>$484x10^6$ cells/µl</td></tr>
<tr><td>undetectable plasma HIV load</td><td>NS</td><td>94% of patients</td></tr>
<tr><td>efavirenz through concentration</td><td>x 0.42 (S)</td><td>5.7 µg/ml</td></tr>
</table>

NOTE: In this preselected study population, an association was found of *6 with an increase in the risk for somnolescence (S) and with an increase in the efavirenz trough concentration before dose adjustment (S).

NOTE: Genotyping was performed for *6. This is the most important gene variant in this Spanish population.</td>
<td>antiretroviral treatment.’</td>
</tr>
<tr>
<td>ref. 18
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 2014;209:399-408.</td>
<td>3</td>
<td>287 Cambodian patients with HIV-infection and tuberculosis were treated with efavirenz 600 mg once daily and stavudine 30 mg and lamivudine 150 mg twice daily. Antiretroviral therapy was started 2 or 8 weeks after the start of standard antituberculosis treatment (early versus standard timing of antiretroviral therapy start). Antituberculosis treatment consisted of isoniazid 4-5 mg/kg, rifampicin 10 mg/kg, ethambutol 15-20 mg/kg and pyrazinamide 20-30 mg/kg per day for 2 months, followed by isoniazid 4-5 mg/kg and rifampicin 10 mg/kg for 4 months.
Efavirenz plasma concentrations were determined at week 22 (with antituberculosis treatment) and week 50 (without antituberculosis treatment). Samples were taken 8.4-18.0 hours (mean 14 hours) after dosing.</td>
<td>Authors’ conclusion: ‘Patients carrying the CYP2B6 516 TT genotype and slow-acetylation NAT2 phenotype had the lowest efavirenz apparent clearance. These data suggest that the inducing effect of rifampicin is counterbalanced by a concentration-dependant inhibitory</td>
</tr>
</table>

<table>
<tr>
<td>PubMed PMID: 23990572.

ref. 18, continuation</td>
<td>PM: A
IM: A</td>
<td>Less than 5% of patients had an efavirenz plasma concentration below and 30% above the therapeutic range (1-4 µg/ml).
Relevant co-medication was not excluded.
12 patients per CYP2B6 genotype were calculated to provide a power of 90% to detect a 50% decrease in efavirenz clearance between *1/*1 and *6/*6.

Genotyping:
- 133x *1/*1
- 123x *1/*6
- 31x *6/*6

Results:
<table>
<tr><td colspan="4">% of patients with supratherapeutic efavirenz plasma concentrations (> 4 µg/ml) for the different genotypes:</td></tr>
<tr><td>antituberculosis treatment</td><td>*6/*6</td><td>*1/*6</td><td>*1/*1</td></tr>
<tr><td>no</td><td>100%</td><td>18%</td><td>6%</td></tr>
<tr><td>yes</td><td>95%</td><td>38%</td><td>11%</td></tr>
<tr><td colspan="4">Significance of the difference in supratherapeutic plasma concentrations between the genotype groups was not determined. However, in a pharmacokinetic model, *6 was the most important determinant of efavirenz clearance (S).</td></tr>
</table>
<table>
<tr><td colspan="4">% of patients with subtherapeutic efavirenz plasma concentrations (< 1 µg/ml) for the different genotypes:</td></tr>
<tr><td>antituberculosis treatment</td><td>*6/*6</td><td>*1/*6</td><td>*1/*1</td></tr>
<tr><td>no</td><td>0%</td><td>2%</td><td>5%</td></tr>
<tr><td>yes</td><td>0%</td><td>4%</td><td>7%</td></tr>
</table>
NOTE: The effect of co-administration of antituberculosis drugs was small compared to the effect of *6. On average, co-administration of antituberculosis drugs had no influence on efavirenz disposition. However, efavirenz clearance was increased in *1/*1 and decreased in *1/*6 and *6/*6 (S).

NOTE: Genotyping was performed for *6, *18, 1459C>T and 485-18C>T. *18 was not found in this Cambodian population.
In this summary, 1459C>T and 485-18C>T are ignored. 1459C>T did not have a significant effect on the efavirenz clearance. 485-18C>T did have a significant effect in this study, but not in Swart 2016. In addition, the effect in this study was smaller than and might not be independent from that of *6.</td>
<td>effect of isoniazid on efavirenz clearance.’</td>
</tr>
<tr>
<td>ref. 19
Sarfo FS et al. Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients.
J Antimicrob Chemother 2014;69:491-9.
PubMed PMID: 24080498.</td>
<td>3</td>
<td>496 Ghanaian patients were treated with efavirenz in combination with lamivudine and with zidovudine or stavudine. The clinical outcomes were investigated in 299 patients.
Efavirenz plasma concentrations were determined approximately 12 hours after administration. Both HIV regimens led to equal median efavirenz plasma concentrations. Relevant co-medication was not excluded.

Genotyping performed for *6:
- 128x *1/*1
- 235x *1/*6
- 133x *6/*6

Genotyping performed for *18 (n=494):
- 451x *1/*1
- 42x *1/*18
- 1x *18/*18</td>
<td>Authors’ conclusion: “CYP2B6 and CYP2A6 SNPs were associated with higher plasma efavirenz concentrations due to reduction in major and minor phase I routes of elimination, respectively. Further prospective studies are needed to validate the pharmacodynamic correlates of these polymor-</td>
</tr>
</table>

ref. 19, continuation	PM: AA[#] IM: A	*6/*6 versus *1/*6 versus *1/*1 and *18/*18 versus *1/*18 versus *1/*1: - The risk of immunological failure (insufficient CD4 T cells or increase not maintained) was decreased for *6/*6 compared to *1/*1 (HR = 0.59; 95% CI: 0.36-0.96) - No significant association of *6 and *18 with neuropsychiatric toxicity, but there was a trend towards a higher risk for (*1/*6 + *6/*6) (NS) - No association of *6 and *18 with clinical failure (development of AIDS during follow-up, no follow-up and/or death) (NS) - The median efavirenz plasma concentration increased with the number of *6 alleles (1800 versus 1073 versus 929 ng/ml) (S) - The median efavirenz plasma concentration increased with the number of *18 alleles (3235 versus 1053 versus 929 ng/ml) (S) - Multivariate analysis showed that both *6 and *18 independently correlated with plasma concentration (S)	phisms in this population." Median efavirenz plasma concentration versus NM (based on *6): IM: 116% PM: 194% Median efavirenz plasma concentration versus NM (based on *18): IM: 113% PM: 348%
ref. 20 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 2013;8:e67946. PubMed PMID: 23861838.	3 IM: A PM: A	207 Ethiopian and 180 Tanzanian patients were treated with efavirenz in combination with lamivudine and with zidovudine, stavudine or tenofovir. Efavirenz plasma concentrations were determined 16 hours after administration. Relevant co-medication was not excluded. Tuberculosis patients were excluded due to possible interactions with co-medication (rifampicin). Genotyping: - *1/*1: 94x Ethiopian and 63x Tanzanian - *1/*6: 97x Ethiopian and 84x Tanzanian - *6/*6: 16x Ethiopian and 33x Tanzanian *6/*6 versus *1/*6 versus *1/*1: - No difference in increase in CD4 T cell count, but a trend towards a greater increase for Ethiopians (NS) - The median efavirenz plasma concentration had increased 4 weeks after initiation of treatment (2670 versus 1338 versus 1018 ng/ml in Ethiopians and 4594 versus 1814 versus 1472 ng/ml in Tanzanians) (S). *6 explains 9.8% of the variation in plasma concentration at 4 weeks (8.3% in Ethiopians and 11% in Tanzanians). - The median efavirenz plasma concentration had increased 16 weeks after initiation of treatment (3307 versus 1425 versus 1024 ng/ml in Ethiopians and 3381 versus 1588 versus 1216 ng/ml in Tanzanians) (S). *6 explains 17.9% of the variation in plasma concentration at 16 weeks (13.3% in Ethiopians and 20.6% in Tanzanians). - *6 is a predictor for intracellular efavirenz concentration, but is not an independent predictor. Efavirenz plasma concentration is an independent predictor.	Authors' conclusion: "We report substantial differences in efavirenz pharmacokinetics, extent of auto-induction and immunologic recovery between Ethiopian and Tanzanian HIV patients, partly but not solely, due to pharmacogenetic variations. The observed inter-ethnic variations in efavirenz plasma exposure may possibly result in varying clinical treatment outcome or adverse event profiles between populations." Median efavirenz plasma concentration versus NM: Ethiopians: IM: 139% PM: 323% Tanzanians: IM: 131% PM: 278%
ref. 21 Yimer G et al. High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naïve HIV patients from Ethiopia: a prospective cohort	4	245 Ethiopian patients were treated with efavirenz in combination with lamivudine and with zidovudine, stavudine or tenofovir. Comorbidities that necessitated co-medication were excluded. 37 of the 245 patients developed efavirenz-induced liver injury. 22% of these patients developed severe liver injury and 5% of these patients required adjustment of antiretroviral therapy due to peripheral neuropathy. Liver injury always occurred in the first 12 weeks of therapy. Genotyping: - 111x *1/*1 - 114x *1/*6	Authors' conclusion: "Elevated baseline alanine amino-transferase, aspartate amino-transferase, alkaline phosphatase, plasma efavirenz level and CYP2B6 *6 were good predictors for the development of drug-induced liver injury.

study. Pharmacogenomics J 2012;12:499-506. PubMed PMID: 21862974. **ref. 21, continuation**	PM: C IM: C	- 20x *6/*6 *6/*6 versus *1/*6 versus *1/*1: - The percentage of patients who developed efavirenz-induced liver injury increased (25% versus 18% versus 11%) (S for the trend and for *6/*6 versus *1/*1). The risk was higher for *6/*6 versus *1/*1; RR = 2.7 (95% CI: 1.067-6.91) and OR = 3.31 (95% CI: 1.01-10.94).	CYP2B6 genotyping and/or regular monitoring of efavirenz and liver enzymes level during early therapy is advised for early diagnosis and management of drug-induced liver injury.”
ref. 22 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 2012;7:e40180. PubMed PMID: 22808112.	3 PM: C IM: C	349 Tanzanian patients, of whom 40% also had tuberculosis, were treated with efavirenz in combination with lamivudine and with zidovudine or stavudine. Tuberculosis patients were started on rifampicin-based tuberculosis therapy 4 weeks prior to HIV therapy. Co-medication with hepatotoxic medicinal products was excluded apart from co-trimoxazole 960 mg/day. Co-medication with an effect on CYP2B6 was not excluded. 5.9% of the patients with HIV and 10.0% of the patients with HIV and tuberculosis developed drug-induced liver injury. Severe liver injury developed in 20% and 36.4% of these patients, respectively. Withdrawal of therapy (temporary or permanent) was not needed. Liver injury was temporary and always occurred in the first 12 weeks of therapy. Genotyping: - 147x *1/*1 - 148x *1/*6 - 54x *6/*6 *6/*6 versus *1/*6 versus *1/*1: - The percentage of patients who developed drug-induced liver injury increased (11.1% versus 10.8% versus 4.1%) (NS for the trend, S for PM versus NM). *6/*6 was a significant predictor of development of drug-induced liver injury (HR = 2.82; 95% CI: 1.04-7.65). - The frequency of the *6 allele was higher in patients with drug-induced liver injury (S)	Authors’ conclusion: “Genetic make-up mainly CYP2B6 genotype influences the development of efavirenz based HAART liver injury in Tanzanians.”
ref. 23 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 2011;66:2092-8. PubMed PMID: 21715435.	4 *6: E PM: E	242 German patients on stable efavirenz therapy for at least 3 months were compared to 131 patients who discontinued efavirenz therapy within 3 months. The most important reason for withdrawal of efavirenz was the occurrence of neuropsychiatric adverse events. Anti-retroviral medication was similar in both groups. Relevant co-medication was excluded. Genotyping *6: - 170x *1/*1 - 169x *1/*6 - 34x *6/*6 Genotyping *18 (most likely distribution based on allele frequency): - 365x *1/*1 - 8x *1/*18 *6/*6 versus *1/*6 versus *1/*1: - The percentage of patients who discontinued therapy increased (44.1% versus 32.5% versus 33.5%) (S). - *6/*6 had an elevated risk of therapy withdrawal both in the total population (56% versus 33%), the Whites (58% versus 37%; n = 278) and the black patients (50% versus 20%; n = 95) (S).	Authors’ conclusion: “These data indicate that genetic variability in CYP 2B6 and CAR contributes to early treatment discontinuation for efavirenz-based antiretroviral regimens.”

ref. 23, continuation		*6/*6 was an independent predictor of therapy withdrawal (OR = 2.81; 95% CI: 1.34-5.9).	
	*18: AA	*18 allele: - No significant association with therapy withdrawal (NS) Alongside CYP2B6 and CAR polymorphisms, ethnicity remained an independent predictor of therapy withdrawal. Despite the higher efavirenz plasma concentrations observed in black patients, they were less likely to discontinue therapy than White patients. NOTE: Detection of the pseudogene CYP2B6*7 was excluded from the CYP2B6*6 analysis by preamplification of DNA with primers specific for the *6 allele. CYP2B6*7 also contains the nucleotide substitution 516G>T.	
ref. 24 Ribaudo HJ et al. Effect of CYP2B6, ABCB1, and CYP-3A5 polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. J Infect Dis 2010;202:717-22. PubMed PMID: 20662624.	3 PM: C PM: AA[#] *4: AA *5: AA	821 patients received efavirenz in combination with lamivudine and zidovudine or with stavudine and didanosine. Some patients received nelfinavir or abacavir as a fourth anti-HIV agent. Pharmacokinetics were determined in 317 patients and clinical effects in 643. Neuropsychiatric adverse events (≥ grade 2) were recorded during the first 24 weeks of therapy, virological failure during the entire period of participation in the study (up to 192 weeks). Relevant co-medication was not excluded. PM versus (NM + IM) (determined on the basis of *6 and *18): - The percentage of patients with neuropsychiatric adverse events was higher in the group of White patients (n = 276, including 16 PM) (S), but not in the group of Black patients (n = 217, including 43 PM) or in the group of Hispanic patients (n = 128, including 16 PM) (NS) - The percentage of patients with virological failure was lower in the group of black patients (S), but not in the group of White patients or in the group of Hispanic patients (NS). In the group of black patients, there was no interaction between the CYP2B6 genotype and self-reported poor compliance. - PM was an independent factor for high efavirenz plasma concentration. A model including BMI and the CYP2D6 genotype had a specificity of > 90% and a sensitivity of approximately 50%. This suggests that PM was a good predictor of concentration in the upper 75th percentile, but that absence of PM was not a reliable predictor of efavirenz concentrations under this percentile. Including *18 in the model improved the predictive power of efavirenz plasma concentration. Other polymorphisms: - The polymorphisms 785A>G and 1459C>T, the first of which occurs in *4 and in *6 and *7 and the second of which in *5 and *7, did not show independent associations with plasma concentration (NS) - The allele frequency of the other 12 polymorphisms did not exceed 5% in any of the ethnic groups. A possible association with efavirenz plasma concentration could therefore not be established. There was no association with ABCB1 and CYP3A5 polymorphisms. NOTE: genotyping was performed for 16 CYP2B6 polymorphisms. Two of these did not occur in any of the ethnic groups.	Authors' conclusion: "Models that included CYP2B6 516/983 genotype best predicted pharmacokinetics. Slow-metabolizer genotypes were associated with increased central nervous system events among white participants and decreased virologic failure among black participants."

ref. 25 Carr DF et al. Haplotype structure of CYP2B6 and association with plasma efavirenz concentrations in a Chilean HIV cohort. J Antimicrob Chemother 2010;65:1889-93. PubMed PMID: 20639527.	3 IM: A PM: A rs8192719: A rs10403955: A	206 Chilean patients were treated with efavirenz for a median 3.6 years. Efavirenz plasma concentrations were determined a median 11.7 hours after administration. Co-medication with rifampicin was excluded. Genotyping *6: - 89x *1/*1 - 86x *1/*6 - 31x *6/*6 *6/*6 versus *1/*6 versus *1/*1: - The median efavirenz plasma concentration increased (4.95 versus 2.92 versus 2.24 µg/ml) (S) - *6/*6 predicts plasma concentrations above the minimum toxic concentration (4 µg/ml) with a positive predictive power of 71.1% and a negative predictive power of 90.2%. Other polymorphisms: - An association with efavirenz plasma concentration was found for 10 polymorphisms in intron 1, intron 5 and intron 8 (S) - 3 polymorphisms (rs10403955 in intron 1, rs2279345 in intron 5 and rs8192719 in intron 8) were representative of the 10 polymorphisms above and *6 in exon 4. The least common allele was associated with higher efavirenz plasma concentrations for all three polymorphisms. Presence of 4-6 of the least common alleles of these polymorphisms had a higher predictive power for plasma concentrations above the minimum toxic concentration than *6/*6 alone. The positive predictive power was 80.9% and the negative predictive power 91.9%.	Authors' conclusion: "These data indicate that a composite genetic model that includes multiple CYP2B6 SNPs is more strongly associated with efavirenz plasma concentrations than the c.516G>T polymorphism alone." Median efavirenz plasma concentration versus NM (based on *6): IM: 130% PM: 221%
ref. 26 Gatanaga H et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007;45:1230-7. PubMed PMID: 17918089.	3 IM: A PM: A	111 patients were treated with efavirenz for a median 3.6 years. The group included 101 non-selected patients and 10 patients with the *6/*6 genotype. Efavirenz plasma concentrations were determined 9-16 hours after administration in patients who had used a fixed dose of efavirenz for more than 2 weeks. Relevant co-medication was not excluded. Genotyping 516G>T: - 67x NM (*1/*1) - 28x IM (25x *1/*6, 3x *1/*26) - 16x PM (14x *6/*6, 2x *6/*26) PM versus IM versus NM: - The average efavirenz plasma concentration increased (9500 versus 3550 versus 2450 ng/ml) (S) - The percentage of patients with plasma concentrations exceeding 6000 ng/ml increased (100% versus 7% versus 0%) Effect of dose reduction: The dose was reduced in 12 patients (9x *6/*6, 2x *6/*26, 1x *1/*26) with plasma concentrations ranging from 6170 to 14690 ng/ml in whom HIV was undetectable in plasma for more than 1 month. The dose was decreased to 400 mg/day in 11 patients and subsequently to 200 mg/day in 7 patients. The dose was immediately decreased to 200 mg/day in 1 patient. - The decrease in plasma concentration in 10 patients correlated with the dose reduction [approximately 1/3 (36-46%) on reduction from 600 to 400 mg/day and approximately 1/2 (51-59%) on reduction from 400 to 200 mg/day] - The plasma concentration decreased more significantly than the dose in the 2 patients with plasma concentrations	Authors' conclusion: "Genotype-based efavirenz dose reduction is feasible in CYP2B6 *6/*6 and *6/*26 carriers, which can reduce efavirenz-associated CNS symptoms." Mean efavirenz plasma concentrations versus NM: IM: 145% PM: 388%

<table>
<tr><td>ref. 26, continuation</td><td></td><td>over 14,000 ng/ml (by 69% on reduction from 600 to 400 mg/day, by 82% on reduction from 400 to 200 mg/day, and by 83% on reduction from 600 to 200 mg/day). The first patient subsequently required a dose increase to 400 mg/day, because the plasma concentration on 200 mg/day was lower than the therapeutic range.
- After dose reduction, HIV remained undetectable in plasma for more than 6 months (longest follow-up 26 months).
- The initial efavirenz dose caused neuropsychiatric adverse events in 71% of the patients, comprising mainly dizziness and strange dreams. All neuropsychiatric adverse events improved after dose reduction. Dizziness and concentration deficits disappeared in half of the patients, strange dreams and sleeping problems did not fully resolve.

NOTE: Genotyping was performed for 9 SNPs. For 3 of these SNPs, including 983T>C (*18), this Japanese group only had the wild-type allele. There were 6 allele variants for the other SNPs (*2, *4, *5, *6, *23 and *26). *26 has the same two SNPs as *6 and also a third SNP (499 C>G) and also leads to reduced CYP2B6 activity.</td><td></td></tr>
<tr><td>ref. 27
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 2006;61:148-54.
PubMed PMID: 16433869.</td><td>3

*5: AA</td><td>228 Dutch patients were treated with antiretroviral therapy with efavirenz 600 mg once daily. 63.5% of patients was White, 32.5% Black and 3.9% Asian. 14% of the White patients and 47% of the non-White patients was female. Non-adherent patients (based on the opinion of the physician and/or the absence of a detectable efavirenz plasma concentration) were excluded.
Efavirenz plasma concentrations were determined median 13 hours (interquartile range 12-16 hours) after dosing as part of routine therapeutic drug monitoring. Therapeutic drug monitoring is recommended in the Netherlands for all patients at week 4 and 24 after starting treatment, and when there is a suspicion of toxicity, suboptimal therapy, drug-drug interaction, or non-adherence. 3.1% of patients had a subtherapeutic plasma concentration efavirenz (< 1000 ng/ml) and 18.9% a toxic plasma concentration (> 4000 ng/ml). Relevant co-medication was not excluded.

Genotyping:
- 189x *1/*1
- 33x *1/*5
- 6x *5/*5

Results:
<table>
<tr><td colspan="2">Difference in plasma concentration of efavirenz compared to *1/*1 (3200 ng/ml):</td></tr>
<tr><td>*5/*5</td><td>NS</td></tr>
<tr><td>*1/*5</td><td>trend for a lower plasma concentration (p = 0.058) (NS)</td></tr>
<tr><td></td><td>The trend for a lower plasma concentration is most probably caused by the higher prevalence of *1/*5 in Whites (22% *1/*5+*5/*5) compared to Blacks (9% *1/*5+*5/*5) and Asians (0% *1/*5+*5/*5). Whites were observed to have lower efavirenz plasma concentrations than Blacks and Asians. In addition, the percentage of males in the White group (86%) was higher than in the non-White group (53%). Males were observed to have lower efavirenz plasma concentrations than females.</td></tr>
<tr><td>*5</td><td>There was a significant effect of the *5 allele in univariate analysis, but not in multivariate analysis (i.e. after adjustment for gender, ethnicity</td></tr>
</table></td><td>Authors' conclusion: 'Gender and race are important factors in determining interpatient variability in plasma efavirenz concentrations which were unaffected by the presence of the CYP2B6 C1459T polymorphism (present in CYP2B6*5 and CYP2B6*7).'</td></tr>
</table>

ref. 27, continuation		and time after intake of medication) (NS). NOTE: Genotyping was performed for the nucleotide substitution 1459C>T (present in *5 and *7). Because *7 has a low frequency, patients with the 1459T variant were reported to have the *5-allele in this summary.	
ref. 28 Haas DW 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 2005;192:1931-42. PubMed PMID: 16267764.	3 IM: A PM: A *5: AA	367 patients received efavirenz with or without nelvinavir in combination with didanosine and stavudine or with lamivudine and zidovudine. Clinical outcome measures were determined in 340 patients including 156 who did not receive nelvinavir. Patients were followed for 168 weeks. Relevant co-medication was not excluded. Genotyping *6: - 187x *1/*1 - 148x *1/*6 - 32x *6/*6 Genotyping *5: - 309x *1/*1 - 52x *1/*5 - 6x *5/*5 *6/*6 versus *1/*6 versus *1/*1: - No association with failure of therapy (need for switch to another regimen due to toxicity and/or virological failure) (NS) - No association with changes in CD4 T cell counts (NS) - No association with emergence of efavirenz-resistant HIV mutants (NS) - The median efavirenz $AUC_{0\text{-}24h}$ was elevated in both the total population (101.4 versus 57.9 versus 49.4 µg.h/ml), the White patients (n=177), the Black patients (n=123) and the Hispanic patients (n=61) (S). The median $AUC_{0\text{-}24h}$ in each group was approximately twofold higher in patients with *6/*6 than in those with *1/*1. The median $AUC_{0\text{-}24h}$ per genotype group was 3-12% higher in Black patients than in White patients. *5/*5 versus *1/*5 versus *1/*1: - No association with failure of therapy (need for switch to another regimen due to toxicity and/or virological failure) (NS) - No association with changes in CD4 T cell counts (NS) - No association with emergence of efavirenz-resistant HIV mutants (NS) - No significant association with median efavirenz $AUC_{0\text{-}24h}$ (NS) NOTE: Genotyping was performed for *5 and *6.	Authors' conclusion: "The present study confirms our initial discovery that a CYP2B6 polymorphism is associated with greater plasma efavirenz exposure, and it establishes this association not only in white and black subjects but also in Hispanic subjects. Importantly, in univariate analyses, this genotype was not associated with the time to failure of regimens containing efavirenz, the emergence of efavirenz-resistant virus at the time of virologic failure, or increases in the CD4 T cell count." Median efavirenz AUC versus NM: IM: 117% PM: 205%
ref. 29 SmPC Sustiva (efavirenz) 17-10-22.	PM: A	<u>Pharmacodynamics</u> The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with	

ref. 29, continuation		CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days. Pharmacokinetic properties Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown, however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.	
ref. 30 SmPC Sustiva (efavirenz), USA, 29-10-19.	PM: A	Warnings Nervous System Symptoms Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms which are associated with increased efavirenz levels despite standard dosing of Sustiva. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of Sustiva is warranted. Pharmacodynamics: The effect of Sustiva on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days.	

AA[#]: The phenotype has a significant effect, but this effect is favourable instead of unfavourable.

Risk group	IM with CYP2B6 inhibitors, such as clopidogrel, ticlopidine and thiotepa; PM with CYP2A6 inhibitors, such as isoniazide

Comments:

- From September 2017, studies investigating alleles not reported to result in a diminished CYP2B6 activity, like *5, were not included. The same was true for studies investigating polymorphisms not reported in alleles in PharmVar or investigating phenotypes defined differently due to inclusion of such polymorphisms (like defining homozygotes for the variant allele of 15528C>T in the absence of other polymorphism as IM).
  As there were a large number of articles that investigated the clinical effects as one of the outcome measures, studies on *6 and/or *18 were only included if the sample size exceeded 200. A study performed in 2011 investigating the risk of drug-induced liver injury in Ethiopians with HIV and tuberculosis was not included because it did not add to two more recent articles that investigated patients with HIV therapy alone. Studies investigating kinetic effects of *6 and/or *18 only were included if the sample size exceeded 200 and only if plasma concentrations or AUCs were determined and reported per phenotype (NM, IM and PM). Studies investigating the effect of (genotype guided) dose reduction were included if more than 1 patient received a reduced dose. Only the first of two published Chilean studies that determined plasma concentrations in the same patient group was included.
  The article of Röhrich 2016 (Röhrich CR 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 2016;32: 529-38. PubMed PMID: 26655325) was not included in the risk analysis, because it did not provide information on the effect of *5 on efavirenz exposure. In this study, *5 was only detected in patients of Cape Mixed Ancestry and did not significantly affect the efavirenz exposure measured in hair samples in this population (n

= 53). However, *6 and *18 also did not significantly affect the efavirenz exposure measured in hair samples in this population, whereas they increased the exposure measured in hair samples in a group of 81 South African Black patients and in both groups combined. So, from this study it can only be concluded that the population of 53 patients of Cape Mixed Ancestry is either too small and/or too diverse to determine a possible effect of *5 on efavirenz exposure.

- Other guidelines:
  - Desta Z et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2B6 and efavirenz-containing antiretroviral therapy. Clin Pharmacol Ther 2019;106:726-33. PMID: 31006110.
    Despite evidence for an association of the CYP2B6 *4 and *22 alleles with modestly reduced plasma efavirenz exposure being based on few patients, CPIC categorises *4 and *22 as increased function alleles and created the phenotypes rapid metaboliser (one normal function allele and one increased function allele) and ultrarapid metaboliser (two increased function alleles).
    CPIC indicates that substantial evidence links CYP2B6 genotype with variability in plasma efavirenz concentrations and with adverse effects. Because most studies have examined the impact of CYP2B6 516G>T (present in *6) and 983T>C (present in *18); these variants provide the basis for CPICs clinical recommendations. CPIC indicates that the evidence associating these two variants with increased plasma efavirenz concentrations was high, indicating that evidence includes consistent results from well-designed, well-conducted studies. In addition, CPIC indicates that multiple studies have shown that CYP2B6 PM is associated with decreased efavirenz clearance and increased risk for efavirenz toxicity (particularly CNS toxicity, hepatic injury (Yimer 2012), and QTc prolongation (Abdelhady AM 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 2016;27:1206-13. PubMed: 27333947) and/or treatment discontinueation, although some studies have not shown such an association. CPIC indicates that such associations appear to vary with race/ethnicity.
    CPIC indicates that associations have not been demonstrated with reduced efficacy, increased toxicity, or treatment discontinuation for other CYP2B6 alleles that are associated with interindividual variability in plasma efavirenz concentrations (e.g., CYP2B6*4, *22, and 15582C>T), perhaps because these alleles are either infrequent or have modest effects on plasma efavirenz exposure. For 15582C>T, CPIC indicates that patients who were homozygous for the minor allele (15582TT) had plasma efavirenz concentrations comparable to CYP2B6 IM, and that this SNP is not defining for any particular star allele but is part of the CYP2B6 *13 (no function) and *15 (unknown function) haplotypes, and the CYP2B6*1C (normal function) suballele as defined in PharmVar.
    CPIC indicates that CYP2B6-guided efavirenz dosing, particularly in the presence of 516G>T, has been shown in clinical studies to be associated with therapeutic plasma efavirenz concentrations and decreased CNS toxicity, while maintaining virologic efficacy. CPIC indicates that therapeutic recommendations for adults also apply to children weighing more than 40 kg, as adult dosing applies to this group. CPIC indicates that, based on current evidence, IM may experience higher dose-adjusted trough concentrations compared with NM, which may put these patients up to a 1.3-fold increased risk of adverse effects (Dooley KE et al. Pharmacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis coinfection. J Infect Dis 2015;211:197-205. PubMed: 25081933; McIlleron HM et al. Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. AIDS 2013;27:1933-40. PubMed: 24180002; Dooley KE 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 2012;59,455-62. PubMed: 22126739; Robarge JD et al. Population pharmacokinetic modeling to estimate the contributions of genetic and nongenetic factors to efavirenz disposition. Antimicrob Agents Chemother 2017;61:e01813-16. PMID: 27799204; Mollan KR et al. Race/ethnicity and the pharmacogenetics of reported suicidality with efavirenz among clinical trials participants. J Infect Dis 2017;216:554-64. PubMed: 28931220; 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 2005;15:1-5. PubMed: 15864119). For these patients, there is a “moderate” recommendation to consider initiating efavirenz with a decreased dose of 400 mg/day. CPIC indicates that PM are at greatest risk for higher dose-adjusted trough concentrations compared with NM and IM, and greater overall plasma efavirenz exposure, which puts these patients up to a 4.8-fold increased risk for adverse effects and treatment discontinuation (Dooley 2015; McIlleron 2013; Dooley 2012; Robarge 2017; Mollan 2017; Rotger 2005; Ribaudo 2010; Rotger M et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther 2007;81:557-66. PubMed: 17235330; Gross 2017; Cummins NW et al. Investigation of efavirenz discontinuation in multiethnic populations of HIV-positive individuals by genetic analysis. EBioMedicine 2015;2:706-12. PubMed: 26288843; Leger 2016; Johnson DH et al. Neuropsychometric correlates of efavirenz pharmacokinetics and pharmacogenetics following a single oral dose. Br J Clin Pharmacol 2013;75:997-1006. PubMed: 22957905). For these patients, there is a “moderate” recommendation to consider initiating efavirenz with a decreased dose of either 400 or 200 mg/day. This “moderate” rather than “strong” recommendation reflects the fact that most PM do not discontinue efavirenz 600 mg/day for adverse effects. Dose reduction to 400 mg/day may be feasible without increasing pill burden because in 2018 the U.S. Food and Drug Administra-

tion (FDA) approved a generic co-formulated product consisting of efavirenz (400 mg), lamivudine and tenofovir disoproxil fumarate. There is currently no co-formulated tablet with 200 mg efavirenz, so decreasing the dose to 200 mg/day may be complicated by increased pill burden. If therapeutic drug monitoring is available and a decreased efavirenz dose is prescribed, steady-state plasma efavirenz concentrations may be obtained to ensure therapeutic concentrations (~1 to 4 µg/mL). Among IM and PM, prescribing efavirenz at 400 mg/day will almost certainly not reduce virologic efficacy, based on results of the ENCORE study in which treatment-naïve patients were randomized to initiate efavirenz-based regimens (combined with tenofovir and emtricitabine) at either 600 mg/day or 400 mg/day regardless of CYP2B6 genotype, and which showed that 400 mg/day was non-inferior.
CPIC indicates that RM and UM may experience slightly lower dose-adjusted trough concentrations of efavirenz compared with NM, which may be clinically important for efavirenz. However, based on current evidence, the effect of the increased function alleles CYP2B6*4 and *22 appears to be modest (Rotger 2007; Ariyoshi N et al. Q172H replacement overcomes effects on the metabolism of cyclophosphamide and efavirenz caused by CYP2B6 variant with Arg262. Drug Metab Dispos 2011;39:2045-8. PubMed: 21821736; Desta Z et al. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. Pharmacogenomics 2007;8:547-58. PubMed: 17559344; Zukunft J et al. A natural CYP2B6 TATA box polymorphism (-82T-> C) leading to enhanced transcription and relocation of the transcriptional start site. Mol Pharmacol 2005; 67:1772-82. PubMed: 15722458). CPIC indicates that, as such, current data are not sufficient to recommend a change from normal prescribing at this time, and patients with the RM or UM phenotype should receive standard efavirenz dosing. CPIC notes that defining *4 requires documenting the absence of 516G>T.
CPIC indicates, that while the effect of CYP2B6 genotype on efavirenz exposure has been demonstrated in children older than three years of age who weigh less than 40 kg, specific clinical data supporting CYP2B6 genotype-guided dosing are limited. Thus, although CPIC cannot make a firm recommendation for dose adjustment based on CYP2B6 genotype in this age and weight group, CYP2B6 genotype almost certainly affects efavirenz exposure in these children such that efavirenz dose reduction in PM would also be reasonnable. Therapeutic drug monitoring, where available and accessible, could help guide dosing adjustments in this age/weight group, especially in a setting of potential drug-related toxicity, virologic rebound, or lack of response in an adherent patient.
CPIC indicates that, similar to U.S. Department of Health and Human Services (DHHS) guidelines, CPIC does not recommend use of efavirenz in infants and children aged 3 months to < 3 years, except under special circumstances such as tuberculosis co-infection. If a clinical situation requires use of efavirenz in this age group, C|PIC indicates that CYP2B6 testing may be informative and dosing could be guided by the current DHHS guidelines, which were informed by IMPAACT study P1070 (Guidelines for the use of antiretroviral agents in paediatric HIV infection <https://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf>. Accessed Dec 14 2018). The guidelines recommended an efavirenz dose reduction based on weight groups for PM (516TT): 5 kg to < 7 kg: 50 mg; 7 kg to < 14 kg: 100 mg; 14 kg to < 17 kg: 150 mg; and ≥ 17 kg: 150 mg. Dosing for NM (516GG) and IM (516GT) metabolizers is as follows: 5 kg to < 7 kg: 300 mg; 7 kg to < 14 kg: 400 mg; 14 kg to < 17 kg: 500 mg; and ≥ 17 kg: 600 mg. CPIC indicates that, although current DHHS guidelines for efavirenz dosing in paediatrics do not consider 983T>C, CPIC recommends that dosing recommendations for 516TT also be applied to 516GT/983TC and to 983CC.
CPIC also recommends measuring plasma efavirenz concentrations two weeks after initiation. CPIC indicates that the mid-dose plasma efavirenz concentration target of 1 to 4 mg/L derived from adult clinical monitoring data is typically also applied to trough concentrations in paediatric patients.

CPIC-recommendations:
Adults and children ≥ 40 kg:

CYP2B6 phenotype	**Therapeutic recommendation**	**Classification of recommendation[c]**
ultrarapid metaboliser (UM)	Initiate efavirenz with standard dosing (600 mg/day)	Strong
rapid metaboliser (RM)	Initiate efavirenz with standard dosing (600 mg/day)	Strong
intermediate metaboliser (IM)	Consider initiating efavirenz with decreased dose of 400 mg/day[a,b]	Moderate
poor metaboliser (PM)	Consider initiating efavirenz with decreased dose of 400 or 200 mg/day[a,b]	Moderate

[a] If therapeutic drug monitoring is available and a decreased efavirenz dose is prescribed, consider obtaining steady-state plasma efavirenz concentrations to ensure concentrations are in the suggested therapeutic range (~1 to 4 µg/mL).

[b] To prescribe efavirenz at a decreased dose of 400 mg/day or 200 mg/day in a multidrug regimen may require prescribing more than one pill once daily. If so, the provider should weigh the potential benefit of reduced dose against the potential detrimental impact of increased pill number.

[c] Strong = the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
Moderate = there is a close or uncertain balance as to whether the evidence is high quality and the desirable effects

clearly outweigh the undesirable effects.

Children age ≥ 3 years and weighing < 40 kg:

CYP2B6 phenotype	Therapeutic recommendation
ultrarapid metaboliser (UM)	No recommendation.
rapid metaboliser (RM)	No recommendation.
intermediate metaboliser (IM)	No recommendation.
poor metaboliser (PM)	Although CPIC cannot make a firm recommendation for dose adjustment based on CYP2B6 genotype in this age and weight group, CYP2B6 genotype almost certainly affects efavirenz exposure in these children such that efavirenz dose reduction would also be reasonable. Therapeutic drug monitoring, where available and accessible, could help guide dosing adjustments in this age/weight group, especially in a setting of potential drug-related toxicity, virologic rebound, or lack of response in an adherent patient.

Children age < 3 years (Note: Dutch guidelines (the Kinderformularium) indicate that efavirenz should not be used in children aged < 3 years):

CYP2B6 phenotype	Therapeutic recommendation
ultrarapid metaboliser (UM)	No recommendation.
rapid metaboliser (RM)	No recommendation.
intermediate metaboliser (IM)	No recommendation. CPIC does not recommend use of efavirenz in infants and children aged 3 months to < 3 years, except under special circumstances such as tuberculosis co-infection. If a clinical situation requires use of efavirenz in this age group, CPIC recommends to treat these patients as NM.
poor metaboliser (PM)	CPIC does not recommend use of efavirenz in infants and children aged 3 months to < 3 years, except under special circumstances such as tuberculosis co-infection. If a clinical situation requires use of efavirenz in this age group, C|PIC indicates that CYP2B6 testing may be informative and dosing could be guided by the current DHHS guidelines: 5 kg to < 7 kg: 50 mg 7 kg to < 14 kg: 100 mg 14 kg to < 17 kg: 150 mg ≥ 17 kg: 150 mg. CPIC also recommends measuring plasma efavirenz concentrations two weeks after initiation.

On 6-1-2023, there was not a more recent version of the recommendations present on the CPIC-site.

- Cost-effectiveness:
  - Schackman BR et al. Cost-effectiveness of CYP2B6 genotyping to optimize efavirenz dosing in HIV clinical practice. Pharmacogenomics 2015;16:2007-18. PubMed PMID: 26607811.
    CYP2B6 genotype-guided dosing saved more than US$ 100,000 per quality-adjusted life year (QALY) gained compared with standard care, even if lower dosing would reduce antiretroviral efficacy from 91% to 75% of patients. When generic efavirenz availability was assumed, conclusions were similar unless lower dosing reduced efficacy by 6% or more. The efavirenz dose was 600 mg once daily for standard care. For genotype-guided dosing, the efavirenz dose was 600 mg for NM, 400 mg for IM plus NM with homozygosity for the 15582T-variant (IM+NM) and 200 mg for PM.
    Antiretroviral therapy with efavirenz 400 mg once daily for all patients was more cost-effective than genotype-guided therapy, even if lower dosing would reduce efficacy from 91% to 77%.
    Costs were evaluated from a health system perspective. Lifelong medical costs were calculated. For 600 mg efavirenz for all patients, the calculated costs per patient were US$ 404,500 and the calculated QALYs 13.4686. For genotype guided therapy, the calculated costs per patient were US$ 386,000 and the calculated QALYs 13.4688. For all strategies, simulated patients who prematurely discontinued efavirenz due to side effects were assumed to require two extra outpatient visits and were switched to a different recommended or alternative first-line antiretroviral therapy regimen (medically supervised drug substitution, assumed to occur within the first month of antiretroviral therapy initiation). Opportunistic infection prophylaxis and antiretroviral therapy were initiated according to current US guidelines. Patients who experienced virologic rebound were switched to the next available antiretroviral regimen, up to a maximum of five additional regimens. Tablets assumed to be used were efavirenz/tenofovir disoproxil/emtricitabine 600/300/200 mg, efavirenz 200 mg and tenofovir disoproxil/emtricitabine 300/200 mg (and generic efavirenz 600 mg). The calcula-

tion was based on a price of antiretroviral therapy with efavirenz 600 mg of US$ 1,850/month, a price of antiretroviral therapy with efavirenz 400 mg of US$ 1,630/month, a price of antiretroviral therapy with efavirenz 200 mg of US$ 1,410/month, a weighted mean price of substitute first-line antiretroviral regimen of US$ 2,190/month, a price of subsequent antiretroviral therapy of US$ 2520 -3570/month, and genotyping costs of US$ 349. The cost of a generic version of efavirenz was assumed to be 25% lower, resulting in monthly costs of US$ 1,400, US$ 1,330 and US$ 1,260 for antiretroviral therapy with 600 mg, 400 mg and 200 mg of generic efavirenz respectively.

Genotype prevalence and efavirenz concentration associations were derived from a published genetic association study (Holzinger ER et al. Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several CYP2B6 variants. Pharmacogenet Genomics 2012;22:858-67). This includes a 39.7% prevalence for NM, 47.1% for IM+NM and 13.2% for PM. Baseline antiretroviral adherence, first-line antiretroviral efficacy, costs for clinical visits and lab test due to and duration of efavirenz treatment-limiting adverse event and non-antiretroviral medical costs were derived from literature. The overall HIV RNA suppression rate of 91% for the 600 mg efavirenz-based regimen was assumed the same when simulated patients were switched to a substitute regimen and when PM and NM+IM received lower efavirenz doses. From the reported 5% average baseline probability of discontinuing the 600 mg efavirenz-based regimen due to treatment-limiting toxicity, a 3% probability of discontinuing efavirenz was estimated for those with genotypes showing eligibility for the 600 mg dose, 6% for those eligible for 400 mg but who receive 600 mg, and 9% for those eligible for 200 mg but who receive 600 mg.

Genotype-guided dosing remained cost-effective if lowering the dose for IM+NM and PM would reduce the efficacy from 91% to 75%. However, only if lowering the dose had no effect on efficacy, genotype-guided therapy was both more efficient and less costly (more QALY and a lower price) than standard therapy.

With the reduced price for generic efavirenz, genotype-guided dosing was only more cost-effective than standard dosing if lowering the dose for IM+NM and PM would not reduce the efficacy of antiretroviral therapy. If efficacy was reduced by lowering the dose, standard dosing would be more cost-effective (costs less than US$ 100,000 per QALY gained). With generic efavirenz, antiretroviral therapy with efavirenz 400 mg once daily for all patients remained only more cost-effective than genotype-guided therapy if lowering the dose would not lower efficacy.

Results were not sensitive to variations in genotype test cost, the likelihood of early treatment discontinuation due to efavirenz toxicity, the quality of life effect and cost of efavirenz toxicity leading to treatment discontinuation, the proportion of the population eligible for lower dose efavirenz, mean age, or mean CD4 count.

The cost-effectiveness of a strategy with HIV drug monitoring was not calculated, because HIV drug monitoring is not routinely conducted or reimbursed by health insurance in the USA.

Date of literature search: 12 December 2022.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working group decision	IM	4 E	yes	yes	7 February 2023
	PM	4 E	yes	yes	

Mechanism:

Efavirenz is mainly converted by CYP2B6 to 8-hydroxyefavirenz. Efavirenz is metabolised to a limited extent by CYP3A4/5 and CYP2A6 and efavirenz is metabolised by UGT2B7 by direct N-glucuronidation. Efavirenz induces CYP2B6 and CYP3A and thus its own metabolism.

The therapeutic range established for efavirenz is 1000-4000 ng/ml at 12 hours after dosing (AUC 35-180 µg.h/ml).

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	++
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	7+
Corresponding Clinical Implication Score:		Essential
Score after taking additional considerations into account:		Potentially beneficial