

In Vivo Analysis of Efavirenz Metabolism in Genetically Characterized Individuals

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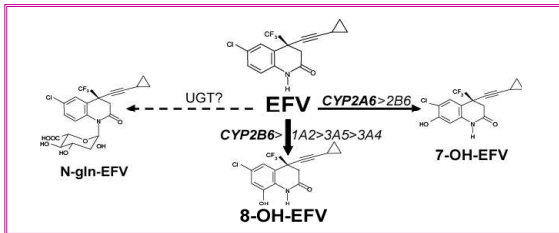
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Introduction

- Efavirenz (EFV) presents a wide inter-individual variability in exposure. It is extensively metabolized into three primary metabolites : 8-hydroxy-EFV (8-OH-EFV), 7-hydroxy-EFV (7-OH-EFV) and N-glucuronide-EFV (N-gln-EFV) (Figure 1).
- 8-hydroxylation is the main metabolic pathway (92%) and is essentially the result of cytochrome P450 (CYP) 2B6 activity, which can explain to a great extent EFV variability in exposure, and to a lesser extent to CYP3A4 activity.
- 7-hydroxylation is the second most important pathway (<8%) and is mainly due to CYP2A6 activity.
- The N-glucuronidation pathways have not been characterized.

Fig 1: Efavirenz metabolism pathways



Work Hypothesis:

In individuals with impaired CYP2B6 function, EFV metabolism might be redirected to accessory pathways, thus making functional polymorphisms in CYP2A6 and CYP3A4 of clinical importance

Methods

- **Study population:** 48 individuals representative of the various genetic profiles of CYP2B6, CYP2A6 and CYP3A4 (Table 1).

Table 1: Genetic profile of the study population

	CYP2B6 extensive metabolizers		CYP2B6 slow metabolizers		Total
	CYP3A4 extensive	CYP3A4 LOF	CYP3A4 extensive	CYP3A4 LOF	
CYP2A6 extensive	9	2	7	5	23
CYP2A6 LOF	8	8	4	5	25
Total	17	10	11	10	48

Methods

- **CYP2B6:** Individuals were fully characterized for CYP2B6 genetic variants in a previous study:
 - ◊ 27 individuals without impaired CYP2B6 function
 - ◊ 21 individuals homozygous (hom) for a decrease/loss-of-function (LOF) allele of CYP2B6 (*6, *11, *18, *27 or *28)
- **CYP2A6:**
 - ◊ Fully re-sequencing in the subgroup of 21 individuals
 - ◊ Genotyping of LOF alleles (*1H, *1J, *2, *5, *7, *9, *10, *12, *13, *15, *17, *19 & *34) in the remaining individuals
 - ◊ Gene copy number determination in all individuals
- **CYP3A4:**
 - ◊ Genotyping of LOF alleles/variants (*1B and rs 4646437) in the 48 individuals
- **Metabolites (8-OH, 7-OH and N-gln-EFV) :**
 - ◊ Concentration analysis by liquid chromatography coupled with triple quadrupole tandem mass spectrometry

Results

Fig 2: Chromatographic profile of ind. with different genetic background

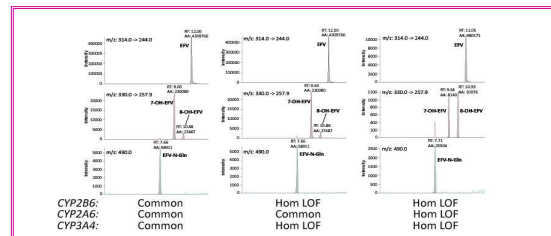
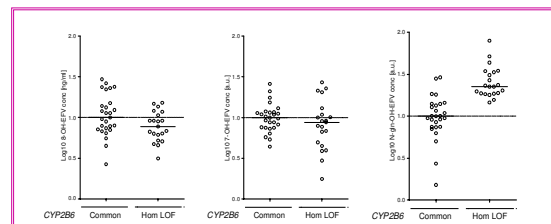


Fig 3: CYP2B6 genotype influence on EFV metabolites



Results

Fig 4: CYP2A6 genotype influence on EFV metabolites

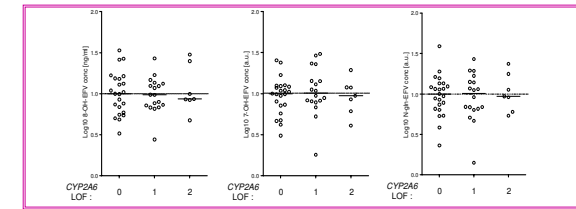


Fig 5: CYP3A4 genotype influence on EFV metabolites

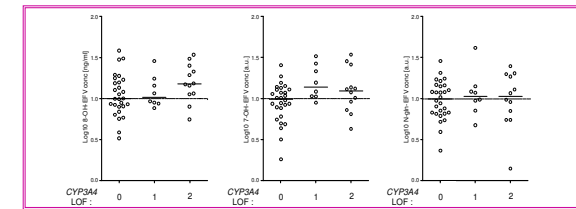
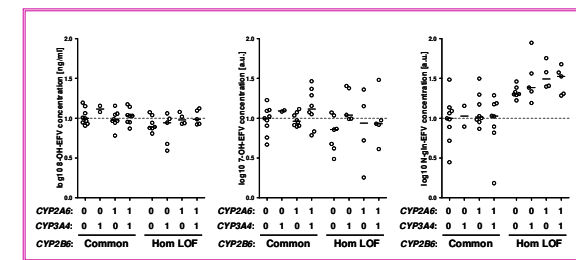


Fig 6: CYP2B6, 2A6 & 3A4 genotype influence on EFV metabolites



0, individuals with common alleles; 1, individuals carriers of LOF alleles

Conclusions

- CYP2A6 & CYP3A4 become increasingly relevant in the presence of impaired CYP2B6 function
- When both hydroxylating pathways are impaired, EFV metabolism is redirected through N-glucuronidation
- However, the N-glucuronidation pathway can not fully compensate for the loss of the others isoenzymes