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STEPPING UP THE PACE
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The drug interaction between rifampicin and efavirenz is time-dependent: systematic review of 12 pharmacokinetic studies.

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Introduction

Treatment guidelines do not include consistent advice on dose modifications when efavirenz is co-administered with rifampicin-based treatment.

Efavirenz is primarily metabolised by the hepatic cytochrome iso-enzymes CYP2B6 and CYP2A6. Efavirenz exhibits inter-individual pharmacokinetic variability primarily caused by genetic differences in cytochrome P450 (CYP) expression.

Efavirenz induces its own metabolism, and 4-16 weeks of treatment are required for efavirenz to reach steady-state plasma concentrations. Most tuberculosis (TB) drugs interact with the CYP metabolizing enzymes. Rifampicin is known to lower the plasma concentrations of several antiretrovirals. There have been discordant results from different drug interaction studies of efavirenz and rifampicin.

Methods

A systematic search of MEDLINE and EMBASE identified sequential or cross-over studies evaluating efavirenz and rifampicin. We searched Medline from 2000 to present (December 2013) for all studies of efavirenz pharmacokinetics in the presence of rifampicin (either Cmin or mid-dose concentration).

The following search terms were used: (("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("rifampin"[MeSH Terms] OR "rifampin"[All Fields] OR "rifampicin"[All Fields])) AND (pharmacokinetic[All Fields] OR ("pharmacokinetics"[Subheading] OR "pharmacokinetics"[All Fields] OR "pharmacokinetics"[MeSH Terms])). The Embase biomedical database was also searched. An advanced search was completed with the following search term: (exp *rifampicin/ and exp *efavirenz/) .

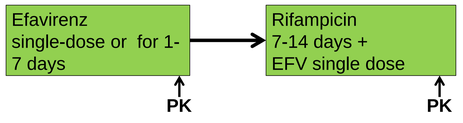
The studies were analysed by duration of efavirenz-rifampicin treatment before pharmacokinetic evaluation. Results from two longitudinal studies of efavirenz-treated patients with or without TB were used as supportive evidence.

Results

12 pharmacokinetic studies were identified with a sequential or cross-over design.

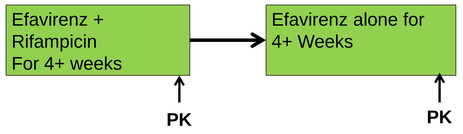
Six studies evaluated <8 days of combined efavirenz-rifampicin treatment, with reductions in efavirenz concentrations of -19% to -54% (Table 1), compared with efavirenz alone. One study of 2-6 weeks of efavirenz-rifampicin treatment showed mean Cmin reductions of -34%.

Summary design of short-term PK trials



Five longer-term studies evaluated 4-24 weeks of combined efavirenz-rifampicin treatment, with increases in efavirenz concentrations of +6% to +26%.

Summary design of longer-term PK trials



Results:

Effects of rifampicin-based treatment on EFV Cmin are shown in the table below:

Trial	n	Population	Country	Duration of EFV	Effects of rifampicin on efavirenz PK	PK parameter
Short-term studies						
Lee 2013	n=33	HIV-	UK	single-dose	-45%	C24h
Cho 2011	n=10	HIV-	USA	single-dose	-54%	AUC
Yenny 2011	n=8	HIV-	Indonesia	single-dose	-39%	AUC
Lopez 2002	n=8	HIV+	Spain	7 days	-22%	Cmin
BMS 1998	n=12	HIV-	USA	7 days	-32%	Cmin
Kwara 2011	n=11	HIV-	USA	8 days	-19%	C24h
Bienvenu 2014	n=21	HIV+	Rwanda	2-6 weeks	-34%	mid-dose conc.
Long-term studies						
Orrell 2011	n=34	HIV+	South Africa	4 weeks	+9%	mid-dose conc.
Semvua 2013	n=21	HIV+	Tanzania	8 weeks	+11%	Cmin
Luetkemeyer 2013	n=91	HIV+	International	24 weeks	+6%	Cmin
Friedland 2006	n=20	HIV+	South Africa	24 weeks	+26%	Cmin
Cohen 2009	n=17	HIV+	South Africa	24 weeks	+22%	mid-dose conc.

In two additional longitudinal studies, differences in efavirenz Cmin between rifampicin treated and untreated patients were only observed in the first 1-4 weeks of combined treatment, with no statistically significant effects during longer-term treatment (Mukonzo 2013). In a similar Tanzanian study, rifampicin co-treatment only reduced plasma efavirenz concentrations significantly during the first week, but not afterwards (Ngiamisi 2011).

Conclusions

- **In this systematic review, rifampicin only lowered efavirenz concentrations in the first 1-4 weeks of treatment – there were no reductions in efavirenz levels after 4-24 weeks of combined treatment.**
- **The short-term studies included mainly healthy volunteers, normally treated with efavirenz first, and then rifampicin with efavirenz. The longer-term studies involved only HIV-infected people, given rifampicin in combination with other TB drugs (in particular isoniazid) which may also affect the pharmacokinetics of efavirenz. In addition the longer-term studies normally evaluated the sequence of efavirenz + rifampicin followed by efavirenz alone.**
- **The reasons for the lack of long-term effect of rifampicin on efavirenz in several large studies, despite clear reductions in short-term studies, is unclear. The populations of patients enrolled may differ between the studies. Alternatively, rifampicin may only lower efavirenz concentrations in the short time before auto-induction of efavirenz metabolism has occurred.**
- **Based on these results, dose modification of efavirenz does not appear to be justified, when co-administered with rifampicin-based treatment**

References

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