



*10th Residential Course on
Clinical Pharmacology
of Antiretrovirals*

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- Male, 56 ys

PAST HISTORY

- IVDU (1975-1999)
- 1983 endocarditis
- 2001: therapy for arterial hypertension (enalapril)
- Nov 2005 admitted for
 - PJP
 - HIV/HCV +
 - Mild tricuspid valve insufficiency

HIV-RNA 98.000 cp/ml
No resistance
HLA B5701 positive
T CD4+ 29/ μ l, 4%, ratio 0.1

HCV-RNA negative

TDF/FTC/EFV
TMP/SMX 1 tab/day

2005-2008

- Rapid virological response
- Good immunological response (increase to 491 CD4+) (*Stop TMP/SMX on sep 2006*)
- Good tolerability

but...

Dec 2008

T CD4+ 491/ μ l, 34%, ratio 0.6
HIV-RNA 2.500 cp/ml
➤ Res-test: 103N, 181C

RAL + FTC/TDF

RAL + FTC/TDF →

After 3 weeks: CK 1650 UI/l (confirmed)
with mild myalgias

DRV 800mg/RTV
+ FTC/TDF →

- Rapid viral suppression
- Good tolerability (but moderate hypercholesterolaemia)

Apr 2010:

Severe tricuspid valve insufficiency

- Surgery for replacement with prosthetic valve
- Warfarin (target: INR 2.5- 4.5)
 - Range of 1,5-2 tabs (5 mg) per day to ensure target INR range

DRV 800mg/RTV + FTC/TDF
Warfarin sec. INR

Jul 2014:

- HIV-RNA undetectable
- Moderate hypercholesterolaemia
 - On BP treatment (enalapril)
 - Smoker (20 cig/day)
- Asking simplification

EVG/COBI/FTC/TDF

But... ↑↑↑ INR!!! ⇒ Warfarin decreased to $\frac{3}{4}$ -1 tab/day to ensure target INR

Different impact on warfarin metabolism by RTV and COBI?

Warfarin is a mixture of enantiomers which are metabolized by different cytochromes:

- R-warfarin ⇒ by CYP1A2 and 3A4
- S-warfarin (more potent) ⇒ by CYP2C9

DRV/RTV + warfarin

- Coadministration *may decrease warfarin concentrations* (RTV strong inducer of CYP2C9)
- Data from 12 HIV- subjects showed that darunavir/ritonavir (600/100 mg twice daily)

decre

In our patient, switch from RTV to COBI led to a decrease of warfarin dosing, suggesting lower or no effect on its metabolism as compared to DRV/RTV.

EVG/COBI

- COBI

R-warfarin

- Elvitegravir is a modest inducer of CYP2C9: could (moderately) decrease S-warfarin
- *The net effect is unknown and unpredictable*

Conclusion

In comparison with RTV, the selective activity of COBI on 3A4 (without significant action on others CYP 450 isoforms), reduces the clinical impact of drug-drug interactions.

CYP Enzyme	Examples of substrates
1A2	Amitriptyline, Haloperidol, Verapamil, Warfarin
2B6	Cyclophosphamide, Efavirenz, Methadone, Erythromycin, Testosterone
2C-family	Diclofenac, Citalopram, Fluvastatin, Phenytoin, Testosterone, Warfarin , Zidovudine
2E1	Caffeine, Theophylline
2D6	Codeine, Fluoxetine, Haloperidol, Tramadol
3A4	Atorvastatin, Carbamazepine, Codeine, Erythromycin, Cyclophosphamide, Warfarin, Phenytoin, Testosterone, Zidovudine



Thank you.