# Pharmacology Update

***David Back***

***University of Liverpool***

***September 2013***

UNIVERSITY OF LIVERPOOL

LHPG


THE BEATLES
A HARD DAY'S NIGHT


THE BEATLES
A HARD DAY'S NIGHT


THE BEATLES
A HARD DAY'S NIGHT

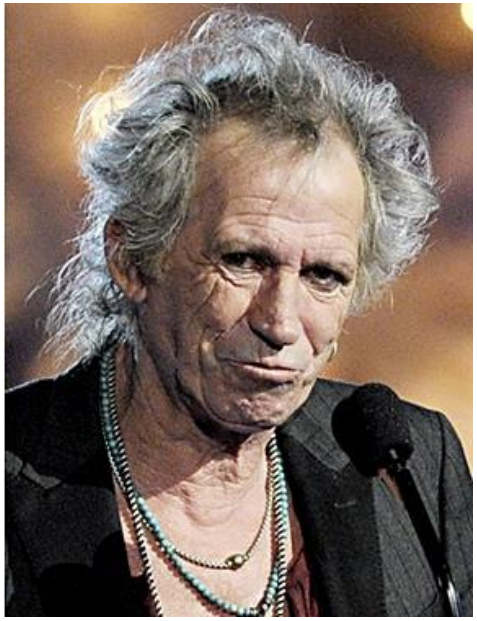

IT'S BEEN A HARD
DAY'S NIGHT
I HAVE BEEN WORKING
LIKE A DOG

# Overview

- Impact of aging on PK
- New & Emerging drug interactions
- Clinical Pharmacology – beyond 2013

# Aging

- Regulatory bodies usually consider older people to be those over **65** years of age - a definition including an extremely diverse group of people.



**69**

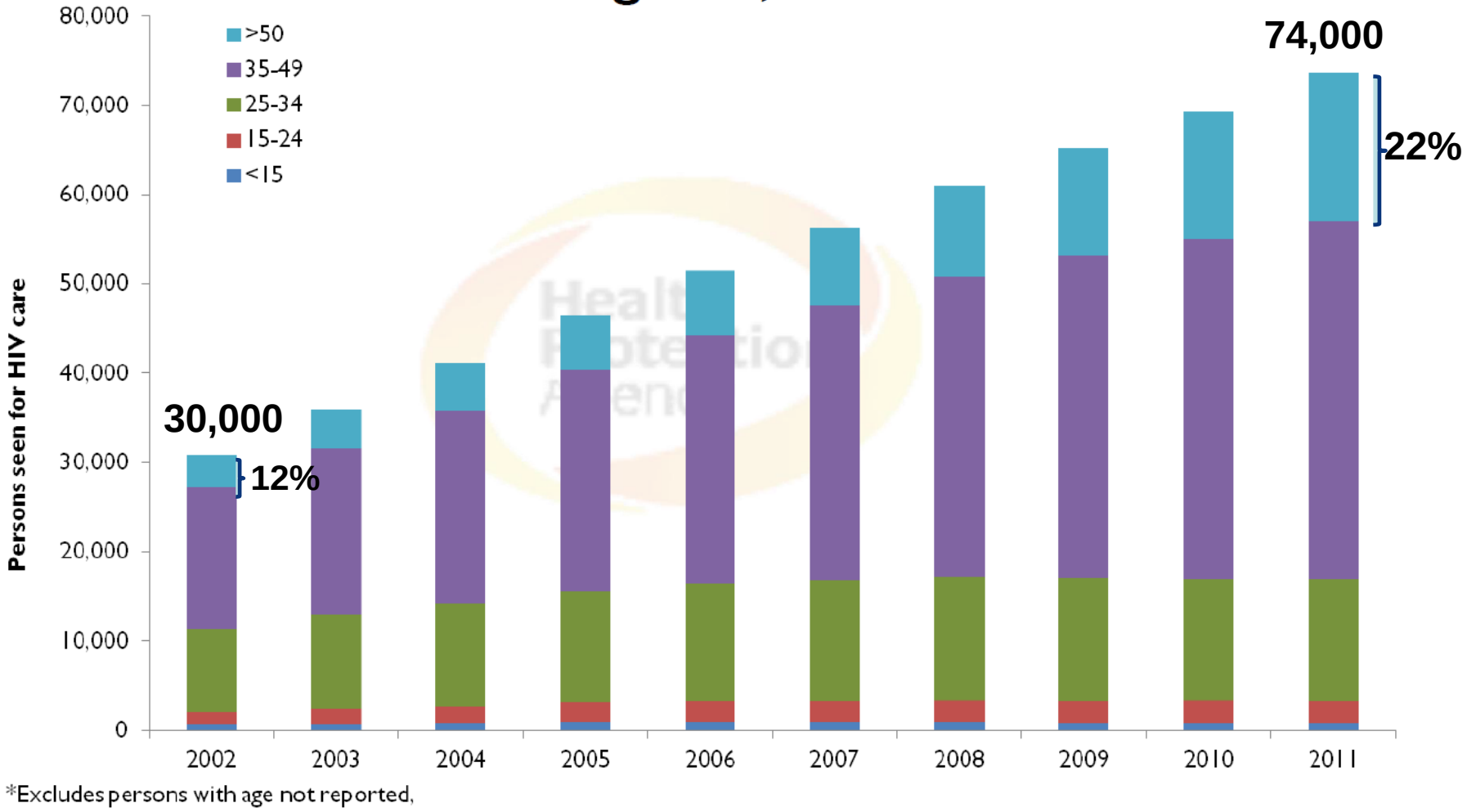

**70+**


## Stories from an Aging Epidemic

**By 2015 more than half of all people living with HIV in the US will be over 50.**

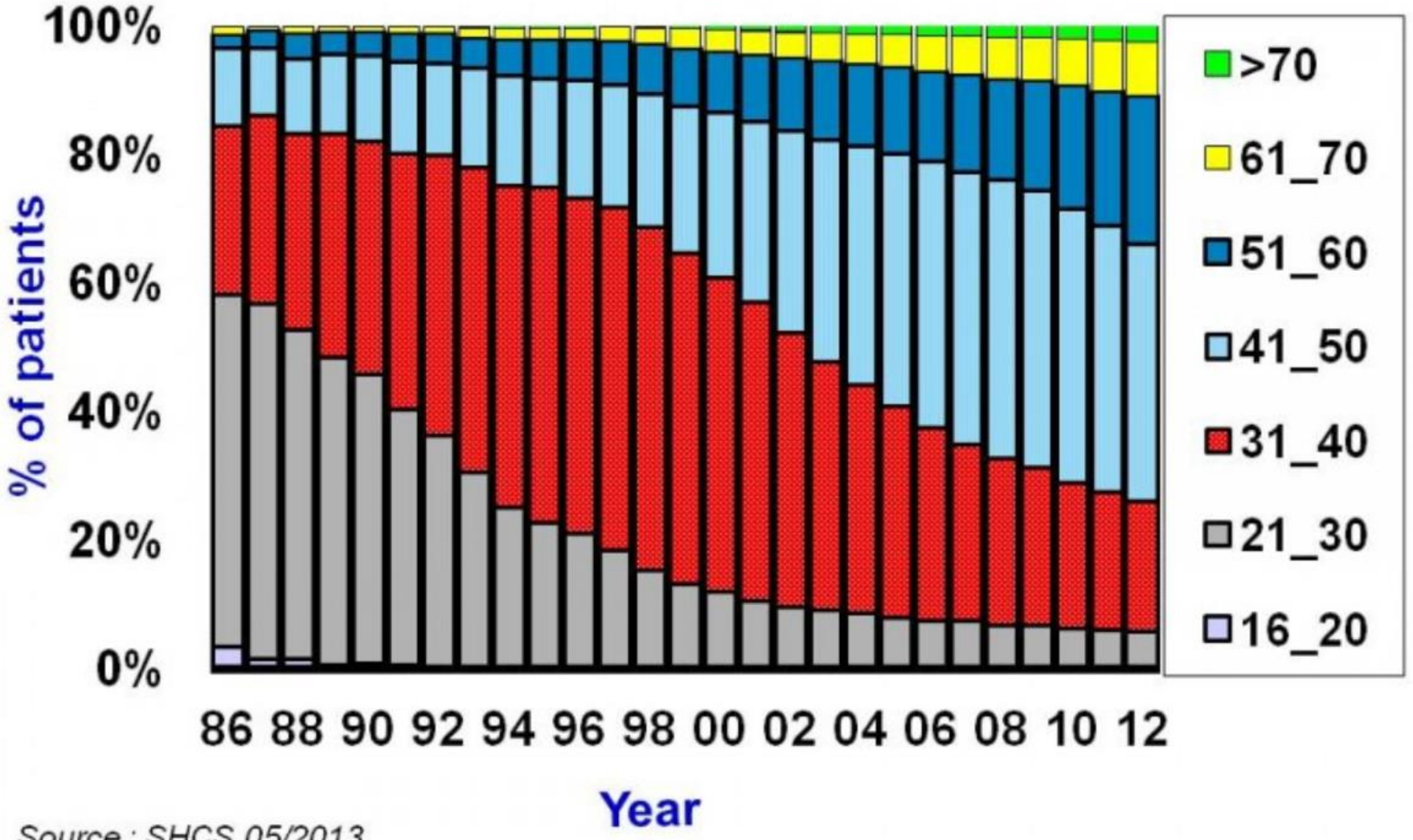
It doesn't matter how old you are: anyone can become infected with HIV. Thanks to advances in medical treatment, people are living longer with the virus—in some cases more than 20 years (and counting). At the same time, older adults are rarely targeted in HIV prevention campaigns and may not realize that their behaviors can put them at risk for HIV infection. As the population of older Americans at risk for—or living with—HIV/AIDS grows, the daily realities and challenges of their lives remain largely invisible in our youth-oriented culture.

# People diagnosed with HIV infection seen for HIV care by age group: United Kingdom, 2002-2011*




*Excludes persons with age not reported.

## Figure 19: Age distribution of active patients by year in the SHCS, 1986-2012

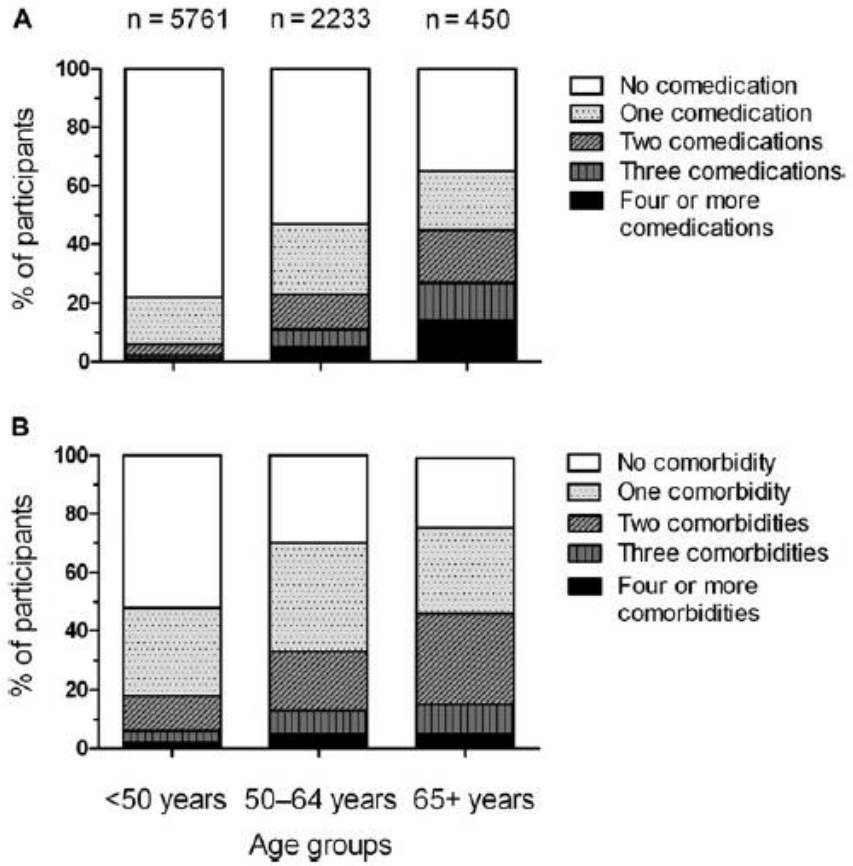



*Source : SHCS 05/2013*

# Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study

**Barbara Hasse,[1] Bruno Ledergerber,[1] Hansjakob Furrer,[2] Manuel Battegay,[3] Bernhard Hirschel,[4] Matthias Cavassini,[5] Barbara Bertisch,[6] Enos Bernasconi,[7] Rainer Weber,[1] and the Swiss HIV Cohort Study[a]**

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich and University of Zurich; [2]Division of Infectious Diseases, Bern University Hospital and University of Bern; [3]Division of Infectious Diseases, University Hospital Basel; [4]Division of Infectious Diseases, University Hospital Geneva; [5]Division of Infectious Diseases, Centre Hospitalier Universitaire Vaudois and University of Lausanne; [6]Division of Infectious Diseases, Cantonal Hospital of St. Gallen; and [7]Division of Infectious Diseases, Regional Hospital, Lugano, Switzerland



# Polypharmacy and Risk of Antiretroviral Drug Interactions Among the Aging HIV-Infected Population

*Carol Holtzman, PharmD[1], Carl Armon, PhD[2], Ellen Tedaldi, MD[3], Joan S. Chmiel, PhD[4], Kate Buchacz, PhD[5], Kathleen Wood, BSN[2], John T. Brooks, MD[5], and the HOPS Investigators*

[1]Temple University School of Pharmacy, Philadelphia, PA, USA; [2]Cerner Corporation, Vienna, VA, USA; [3]Temple University School of Medicine, Philadelphia, PA, USA; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [5]Centers for Disease Control and Prevention, Atlanta, GA, USA.

- N = 3674

- ARV – Non-ARV Interactions identified with the University of Liverpool web site www.hiv-druginteractions.org

- 261 (7%) prescribed at least 1 contraindicated ARV – drug combination
  - *Proton pump inhibitors with atazanavir*
  - *Simvastatin or lovastatin with boosted PI*
  - *Benzodiazepines and boosted PI*
- 1239 (34%) prescribed at least one ARV-drug combination with moderate or high evidence of interaction.

J Gen Intern Med
DOI: 10.1007/s11606-013-2449-6

# Polypharmacy and Risk of Antiretroviral Drug Interactions Among the Aging HIV-Infected Population

*Carol Holtzman, PharmD[1], Carl Armon, PhD[2], Ellen Tedaldi, MD[3], Joan S. Chmiel, PhD[4], Kate Buchacz, PhD[5], Kathleen Wood, BSN[2], John T. Brooks, MD[5], and the HOPS Investigators*

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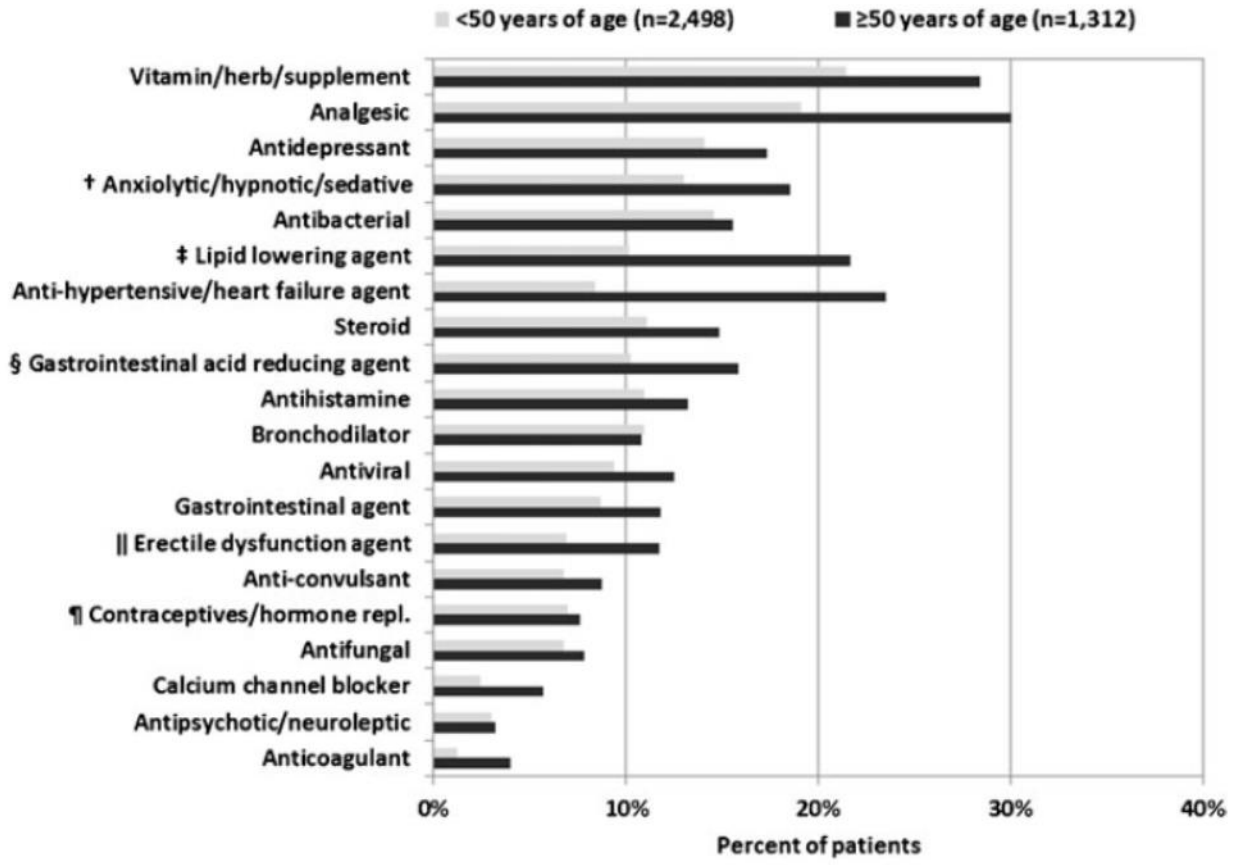

# Risk for 'clinically significant' interactions



| Study | Year | Setting | N | CSDI | Screening Tool | VL Effect |
|---|---|---|---|---|---|---|
| *de Maat* | 2004 | Netherlands (hospital) | 115 | 26% | Liverpool website | N/A |
| *Shah et al* | 2007 | USA (Medicaid) | 571 | 30% | Liverpool website; Micromedex | No VL impact |
| *Miller et al* | 2007 | USA (hospital) | 153 | 41% | DHHS; PI; Micromedex | N/A |
| *Kigen et al* | 2009 | Kenya (hospital) | 996 | 34% | Liverpool website | N/A |
| *Marzolini et al* | 2009 | Switzerland (SHCS) | 1497 | 40% | Liverpool website | No VL impact |
| *Evans-Jones et al* | 2009 | UK (hospital) | 159 | 27% | Liverpool website | N/A |
| *Patel et al* | 2011 | USA | 190 | 34% | Lex-interact | N/A |
| *Cordova et al* | 2013 | Argentina | 217 | 32% | Liverpool website | No VL impact |
| *Seden K et al* | 2013 | Uganda | 2000 | 19% | Liverpool website | N/A |

Miller et al Pharmacother 2007;27:1379
De Maat et al. *Clin Pharmacokinet* 2003;42:223
Shah et al. CROI 2007, Abstr 573. 2007
Cordova E et al IAS 2013; MOPE031
Seden K et al; IAS 2013; MOPE035

Marzolini et al. AVT 2010;15:413
Evans-Jones et al. CID 2010;50:1419
Kigen et al. Plos One 2010
Patel Ann Pharmacother 2011;45

# Considerations in Management of the Older HIV Patient

- **Co-morbid conditions**
  - *eg., cardiovascular, hepatic, metabolic*
  - *may be exacerbated by effects of HIV or its treatment*
- **Greater medication use**
  - *overlapping side effects or potential interactions with ARVs and concomitant medications*

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- **Co-morbid conditions**
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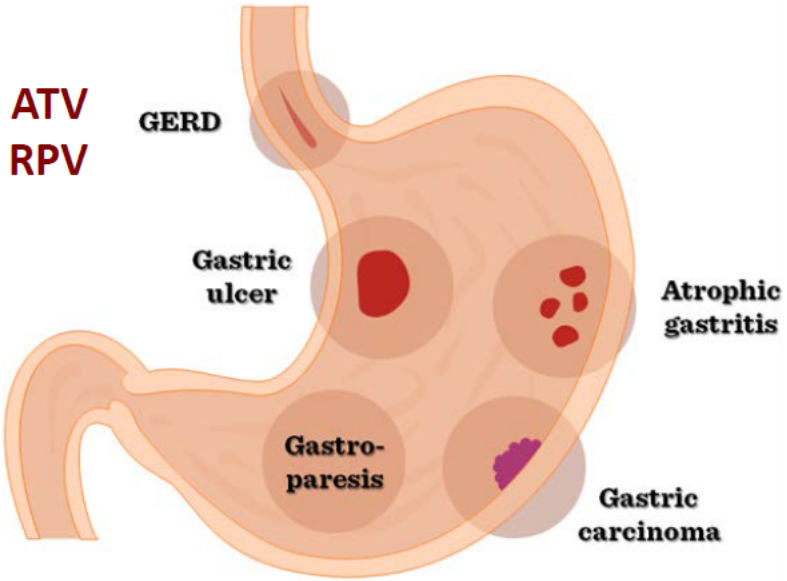
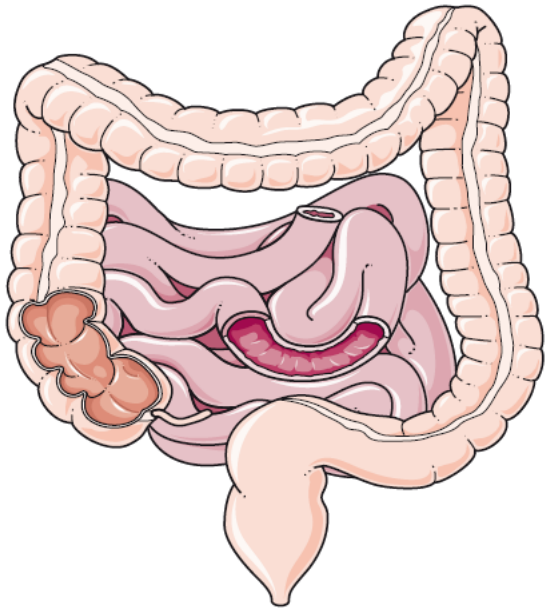
- **Greater medication use**
  - *overlapping side effects or potential interactions with ARVs and concomitant medications*
- **Age-related changes in drug handling (PK) and response (PD)**
  - *toxicity*

# Gastrointestinal Changes Associated with Aging

Increased pH
Delayed emptying
Decreased splachnic flow
Decreased motility
Decreased absorption surface

→ ATV, RPV



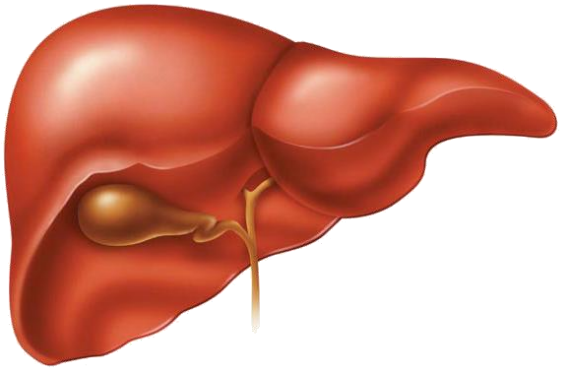



Reduced intestinal enzymes:

- CYP3A4
- ABCB1 (Pgp)

→ ↑ PIs, MVC, NNRTIs

# Hepatic Changes Associated with Aging

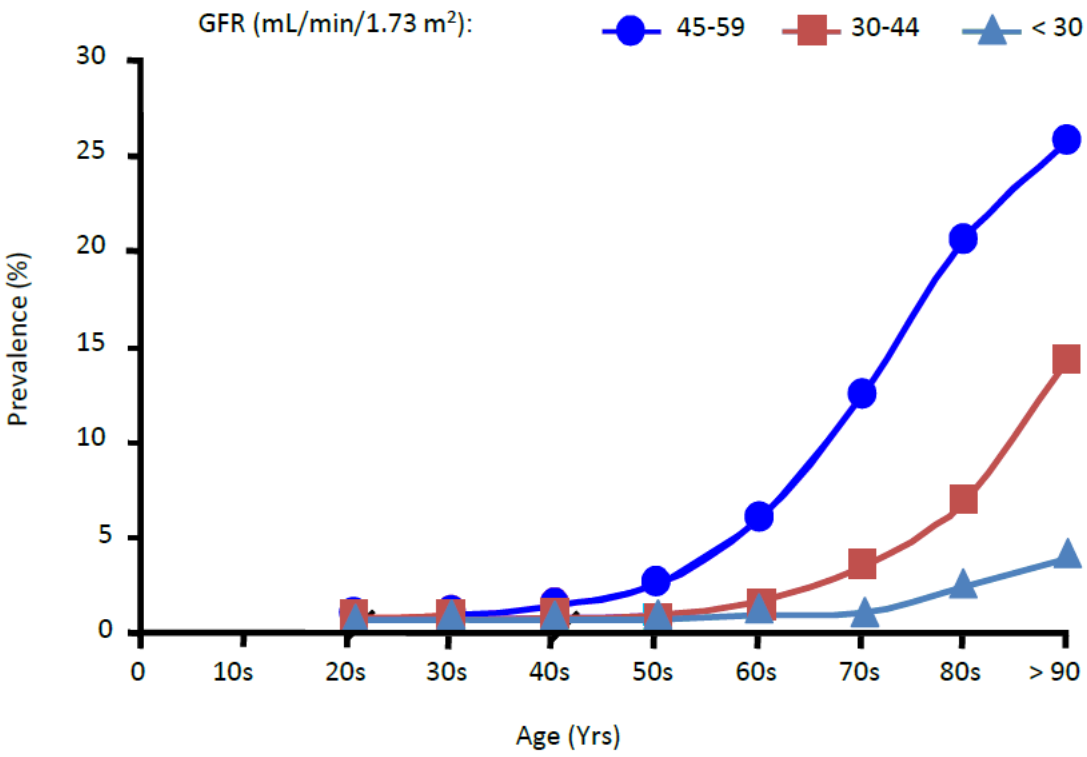


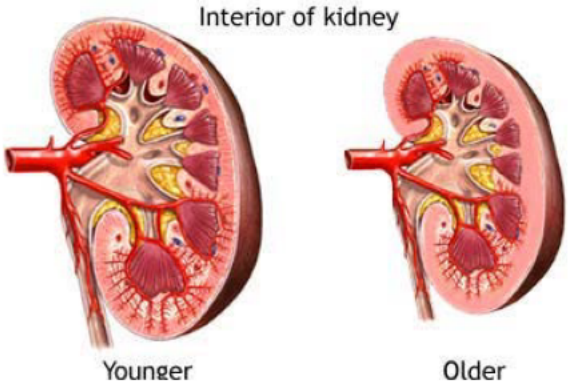
- Decrease in liver volume (~25-35%)
- Impaired hepatic blood flow (~ 40%)
- Decrease in some drug metabolising enzymes (although others seem to be preserved)
- Increased amount of fat, which impairs metabolism

Schmucker DL. Exp Gerontol. 2005; Maclean AJ et al. J Pathol 2003; Housset et al. Res Virol 1990; Banerjee et al. AIDS 1992; Blackard JT et al. J viral hepat. 2008; Hong F et al. Hepatology 2010.

# Renal Changes Associated with Aging

Age is a critical variable in the Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) which are used for estimating GFR for drug dosing




Decreased GFR

- " kidney mass
- " nephron size
- " nephron number
- " glomerular surface area
- " tubular function
- " renal blood flow

*Hallan SI, et al. Br Med J. 2006; 333:1047.*

# Some considerations for ARVs in older people

- There is an increase in exposure (20-30%) of some **boosted PIs**: This could increase the impact of a drug-drug interaction.

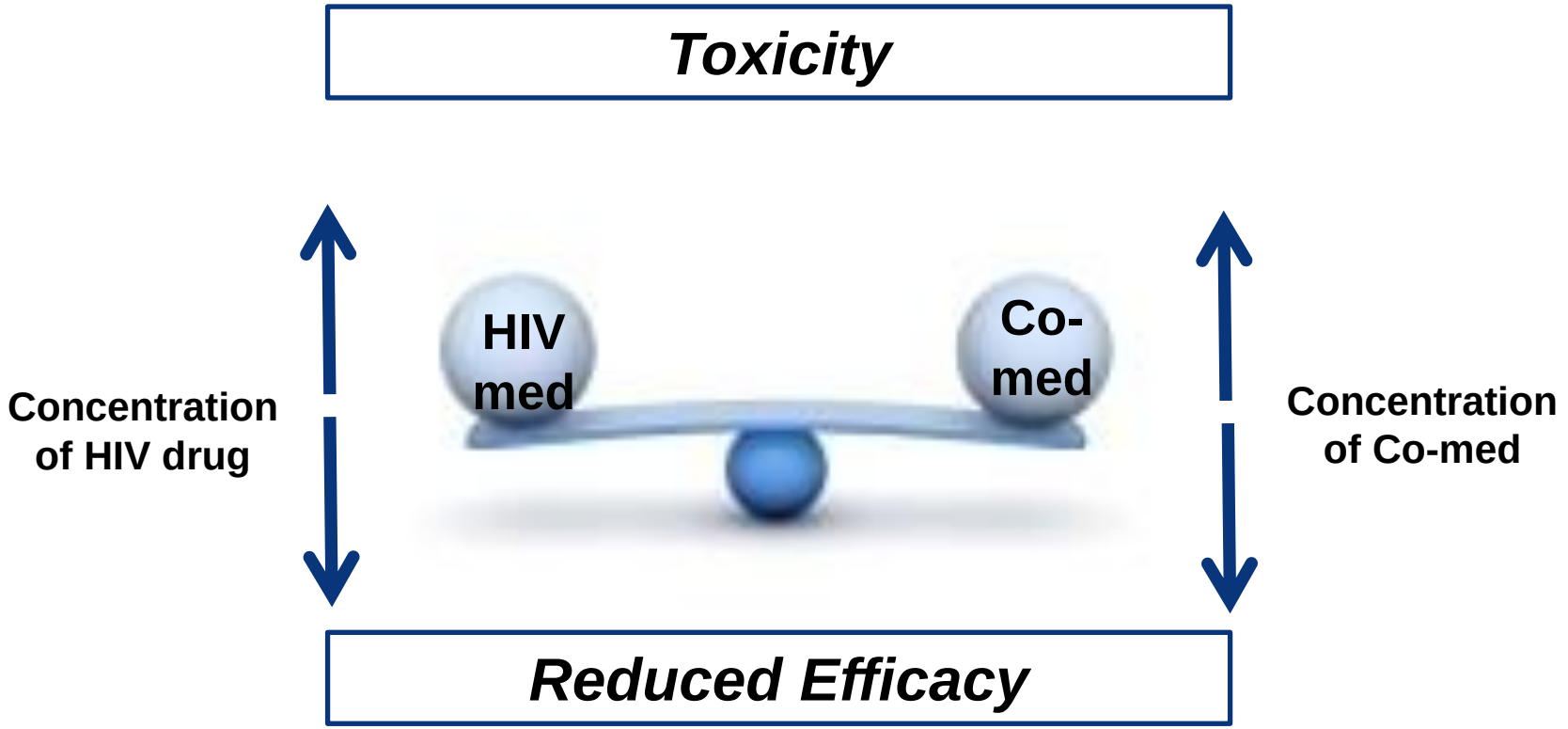
- No clear evidence of an age effect on exposure of **NNRTIs** *but* changes in protein binding could increase unbound concentration (EFV & CNS).

- There is an increase in **tenofovir** exposure (10-15%) in older patients which could be further increased by an interaction at the renal level.

*Crawford K et al AIDS Res Hum Retrovirus 2010; 26; Ahmed A et al EACS Belgrade 2011; Cevik M et al EACS Belgrade 2011; di Perri G et al IWCPHT Amsterdam 2013; Schoen JC et al, Expert Opin Drug Metab Toxico 2013; 9: 573-588*

# DDIs: Basics & key areas.

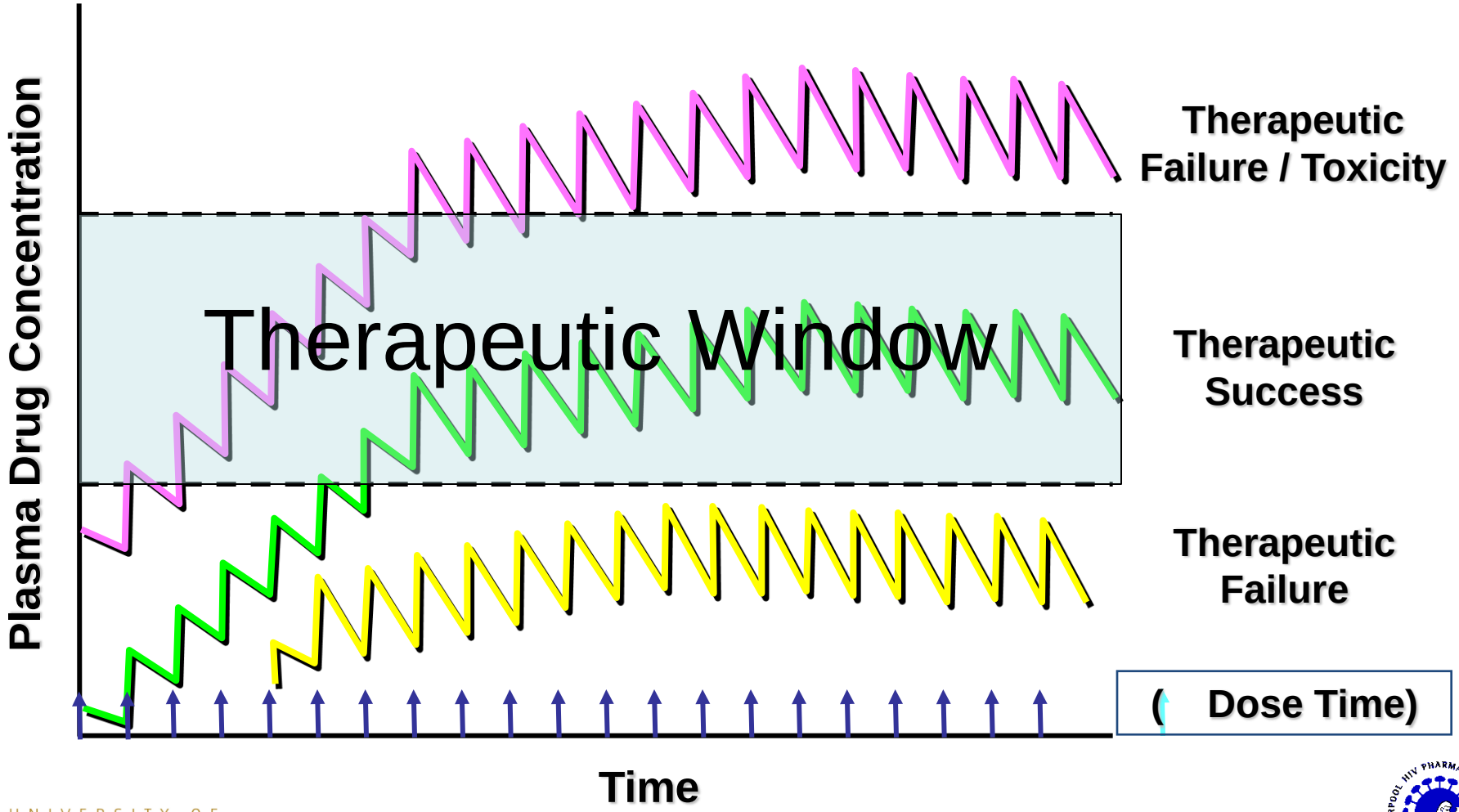
- Cobicistat v ritonavir
- non-oral drugs
- HIV-HCV Co-infection



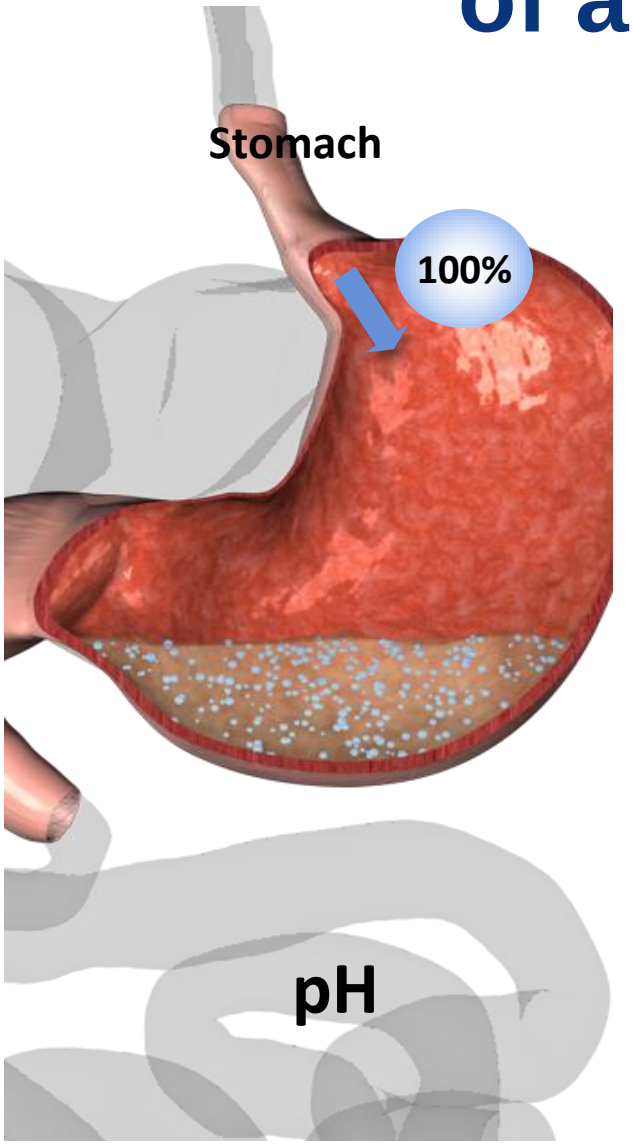

But what triggers concern?
20%, 30%, 50% decrease; 50%, 2-fold, 5-fold increase in exposure?

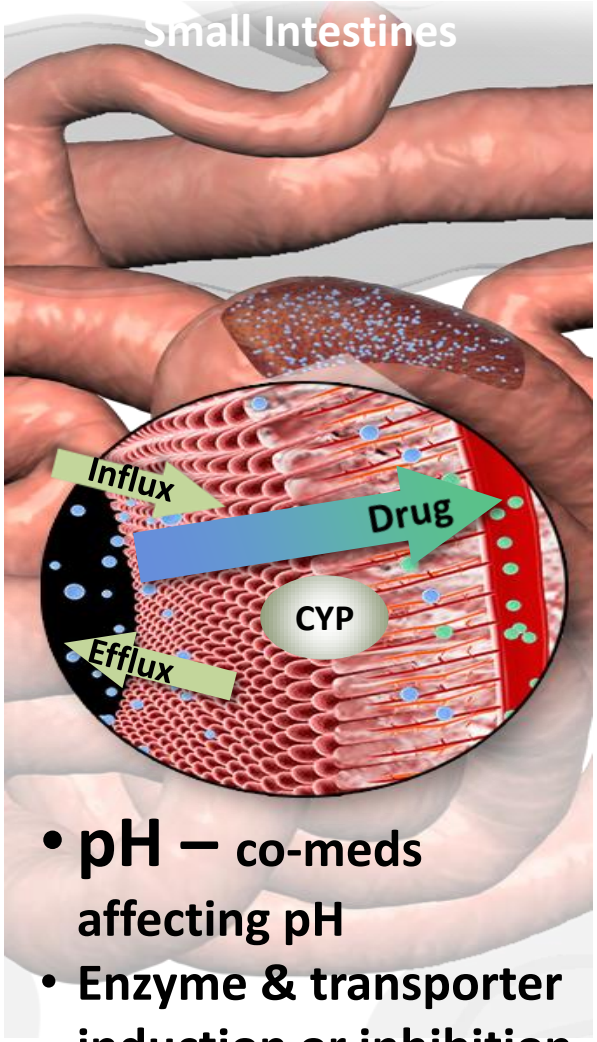
***Exposure – Response and Exposure – Adverse Response relationship***

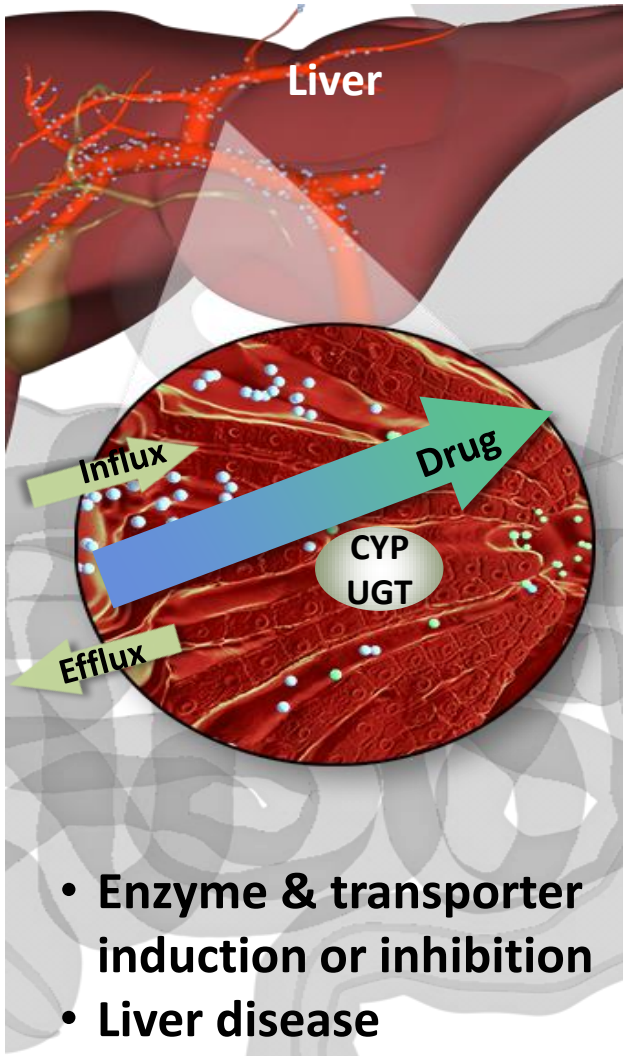
# Important for successful outcome: Maintain the drug in the Therapeutic Window



# Multiple factors can affect the exposure of a drug in the body



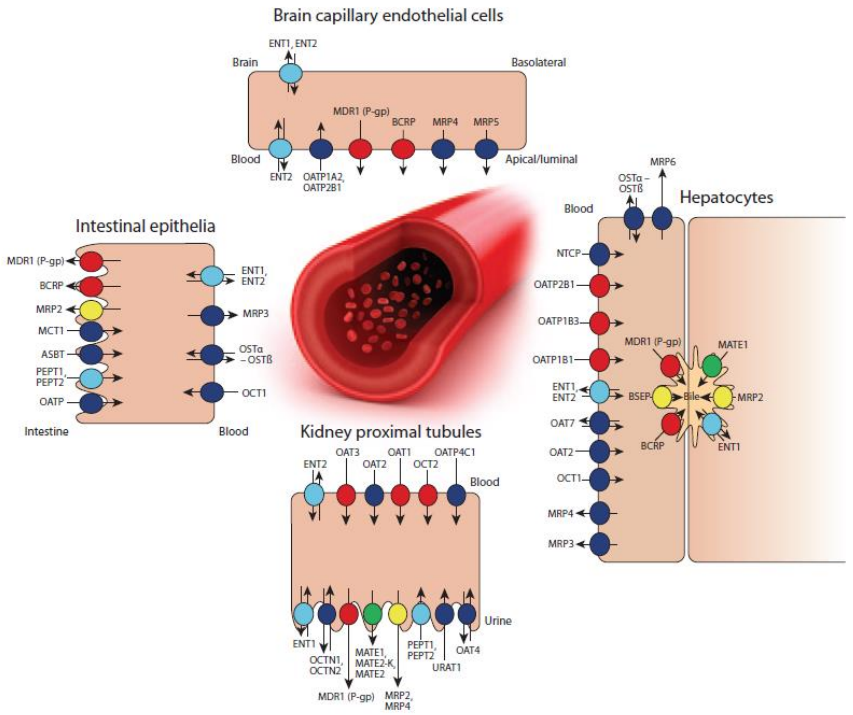




CYP=cytochrome P450; PGP=P-glycoprotein

Images supplied by Vertex Pharmaceuticals Inc, February 2011.

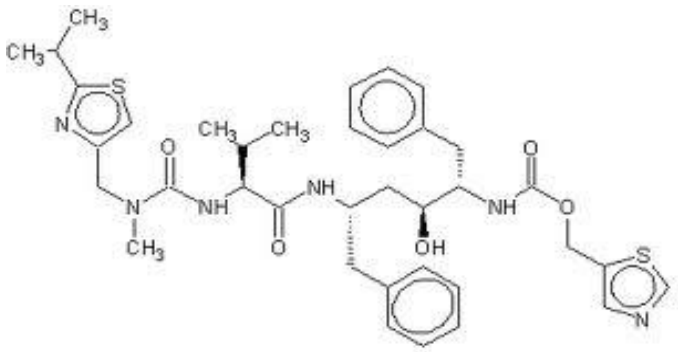
# Transporters

| Transporter | Pseudonym(s) | ITC recommendation (Apr 2013) |
|---|---|---|
| **ABCB1** | P-gp/MDR1 | ✓ |
| **ABCC2** | MRP2 | ✓ |
| **ABCG2** | BCRP | ✓ |
| **ABCB11** | BSEP | ✓ |
| **SLCO1B1** | OATP1B1 | ✓ |
| **SLCO1B3** | OATP1B3 | ✓ |
| **SLC22A1** | OCT1 | ✓ |
| **SLC22A2** | OCT2 | ✓ |
| **SLC22A6** | OAT1 | ✓ |
| **SLC22A8** | OAT3 | ✓ |
| **SLC47A1** | MATE1 | ✓ |
| **SLC47A2** | MATE2 | ✓ |



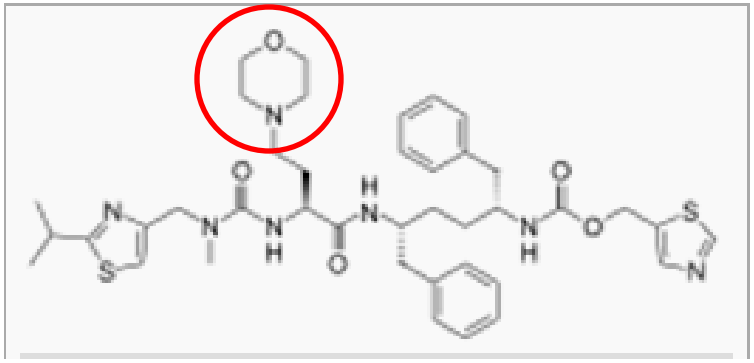

*Giacomini & Huang. Clin Pharm Ther 2013; 94: 3-9*

# Cobicistat (GS-9350): is it different?



***Ritonavir***

- Strong CYP3A4 inhibitor but not selective
- Also induces some enzymes

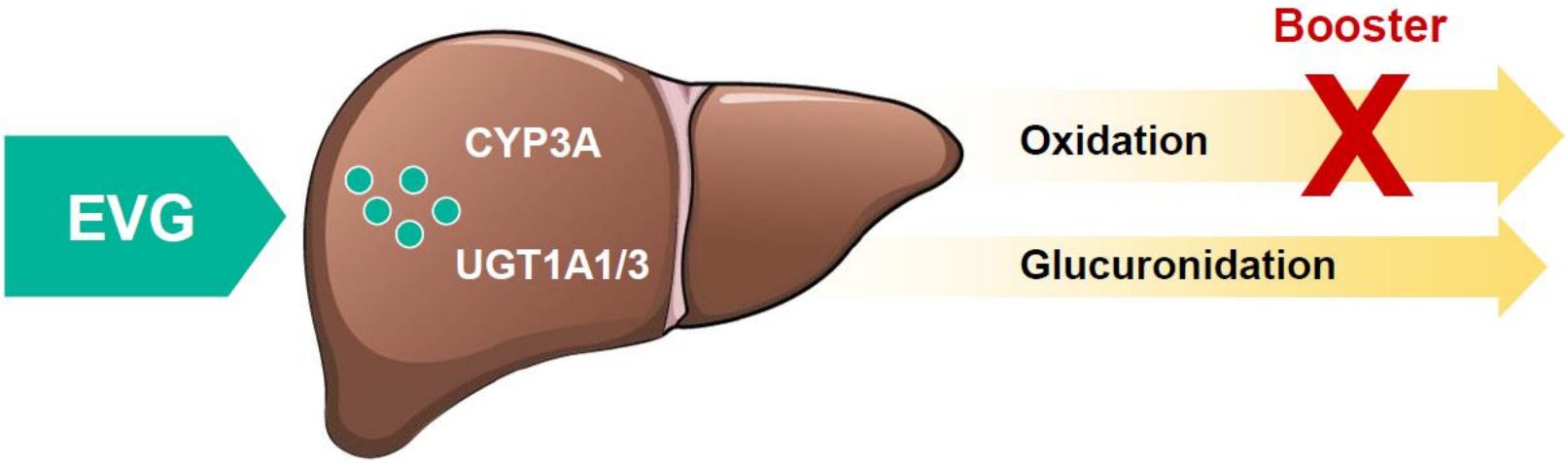


***Cobicistat***

- Designed as a CYP3A4 inhibitor without HIV activity
- Developed to boost **Elvitegravi**r but also darunavir and atazanavir

# EVG Metabolism and Rationale for Boosting

- Metabolism by cytochrome P450 3A (CYP3A) and UDP-glucuronosyltransferase 1A1/3 (UGT1A1/3)




Transport of EVG not fully determined
EVG modest inducer of CYP2C9

*Ramanathan S et al Clinical Pharmacokinetics 2011; 50: 229 – 244.*

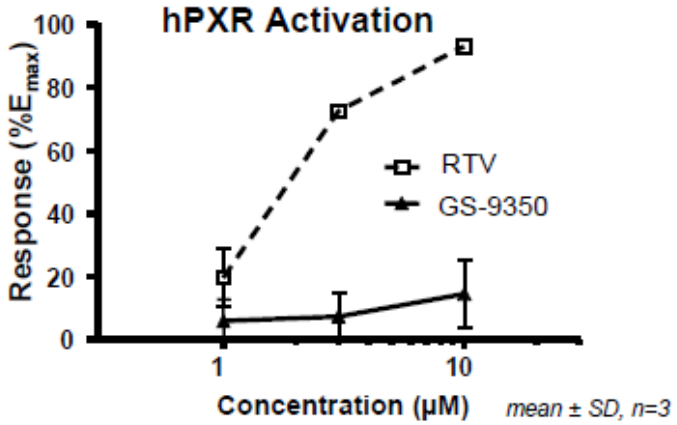
# Comparative effects of COBI (GS-9350) and RTV: *in vitro*

- Greater CYP450 enzyme inhibition specificity

| CYP450 enzyme $IC_{50}$ (μM) | 1A2 | 2B6 | 2C8 | 2C9 | 2C19 | 2D6 | 3A* |
|---|---|---|---|---|---|---|---|
| GS-9350 | >25 | 2.8 | 30 | >25 | >25 | 9.2 | **0.2** |
| RTV | >25 | 2.9 | 5.5 | 4.4 | >25 | 2.8 | **0.2** |

** midazolam 1'-hydroxylase (no preincubation)*
*mean of 3 experiments conducted in duplicate*

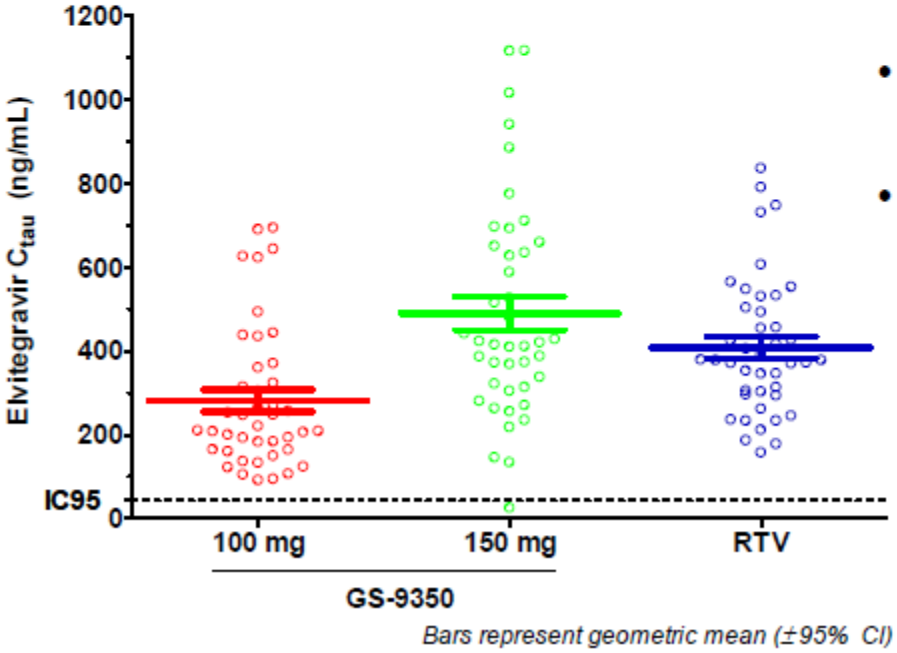
- Less induction of drug metabolizing enzymes and transporters




*Courtesy of Gilead*

# Comparative effects of COBI and RTV on Elvitegravir PK *in vivo*.

| Mean (CV%) EVG PK (n = 42) | GS-9350 100mg FDC | GS-9350 150mg FDC | EVG + RTV 100mg |
|---|---|---|---|
| $AUC_{tau}$ (ng.hr/mL) | 21100 (25.4) | 27000 (29.4) | 22500 (23.4) |
| $C_{max}$ (ng/mL) | 2250 (26.3) | 2660 (27.6) | 2500 (32.1) |
| $C_{tau}$ (ng/mL) | 282 (60.4) | 490 (52.9) | 409 (40.5) |




- GS-9350 effectively boosts EVG within FDC tablet
- High EVG trough concentrations maintained w/ GS-9350 150mg
  - 11-fold above the protein binding-adjusted $IC_{95}$ (44.5 ng/mL)
  - Low within-subject variability (15% CV)

*Courtesy of Gilead*

# Drugs contraindicated with EVG/cobi

| Drug Class | Drug Name |
|---|---|
| Alpha 1 adrenoceptor antagonist | Alfuzosin |
| Antiarrhythmics | Amiodarone, Quinine |
| Anticonvulsants | Carbamazepine, Phenobarbital, Phenytoin |
| Antimycobacterial | Rifampicin |
| Ergot derivatives | Dihydroergotamine, Ergometrine, Ergotamine |
| GI motility agent | Cisapride |
| Herbal products | St John's wort (*Hypericum perforatum)* |
| HMG CoA reductase Inhibitors | Lovastatin, Simvastatin |
| Neuroleptic | Pimozide |
| PDE 5 Inhibitor | Sildenafil (for pulmonary arterial hypertension) |
| Sedative/hypnotics | Triazolam, oral midazolam |

Please refer to the SPC for further interactions

1.Stribild SPC 2013

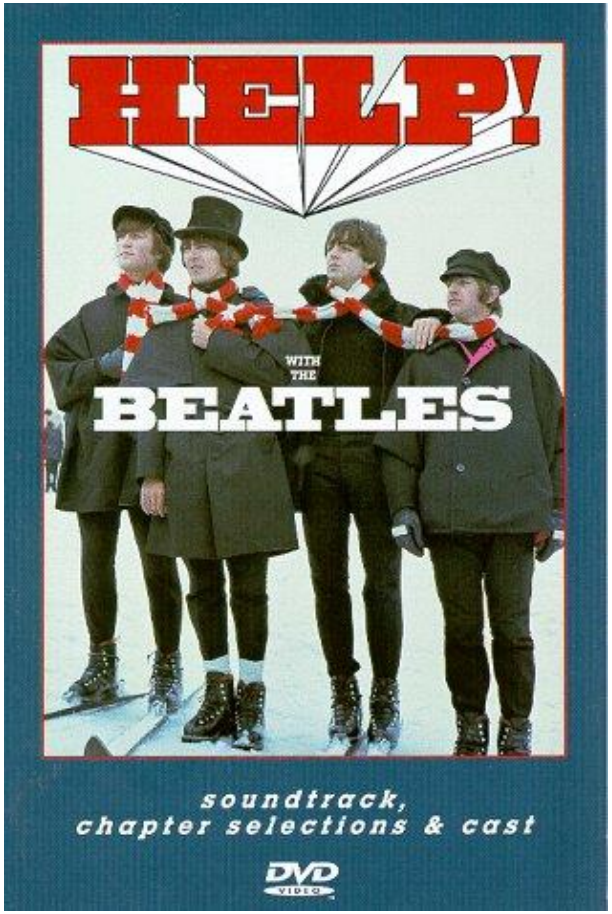
GILEAD

# Comparative effect of EVG/cobi and boosted PIs on co-administered drugs

| Effect of Antiretroviral | | | | |
|---|---|---|---|---|
| **Co-Administered Drug** | **EVG/Cobi** | **Atazanavir/r** | **Darunavir/r 800/100** | **Darunavir/r 600/100 bd** |
| **Buprenorphine** | ↑ AUC 35% | ↑ AUC 67% | ↔ AUC | ↓ AUC 11% |
| **Methadone** | ↔ AUC | ↔ AUC (unboosted) | ND | ↓ AUC 16% |
| **Rosuvastatin** | ↑ AUC 36%<br>↑ Cmax 89% | ↑ AUC 213%<br>↑ Cmax 600% | ND | ↑ AUC 48%<br>↑ Cmax 144% |
| **Norgestimate/ Ethinylestradiol** | ↑ AUC 126% (N)<br>↓ AUC 25% (E) | ↑ AUC 85% (N)<br>↓ AUC 19% (E) | ND | ↓ AUC 14% (N*)<br>↓ AUC 44% (E) |

*Data on EVG/cobi from: Bruce PD et al 52nd ICAAC, San Francisco, 2012; A-1250; Stibild Prescribing Information, Gilead Sciences, Aug 2012; Data on ATV/r and DRV/r from www.hiv-druginteractions.org*

- DDIs are complex and our understanding is evolving
- DDIs are not going away so we need…..

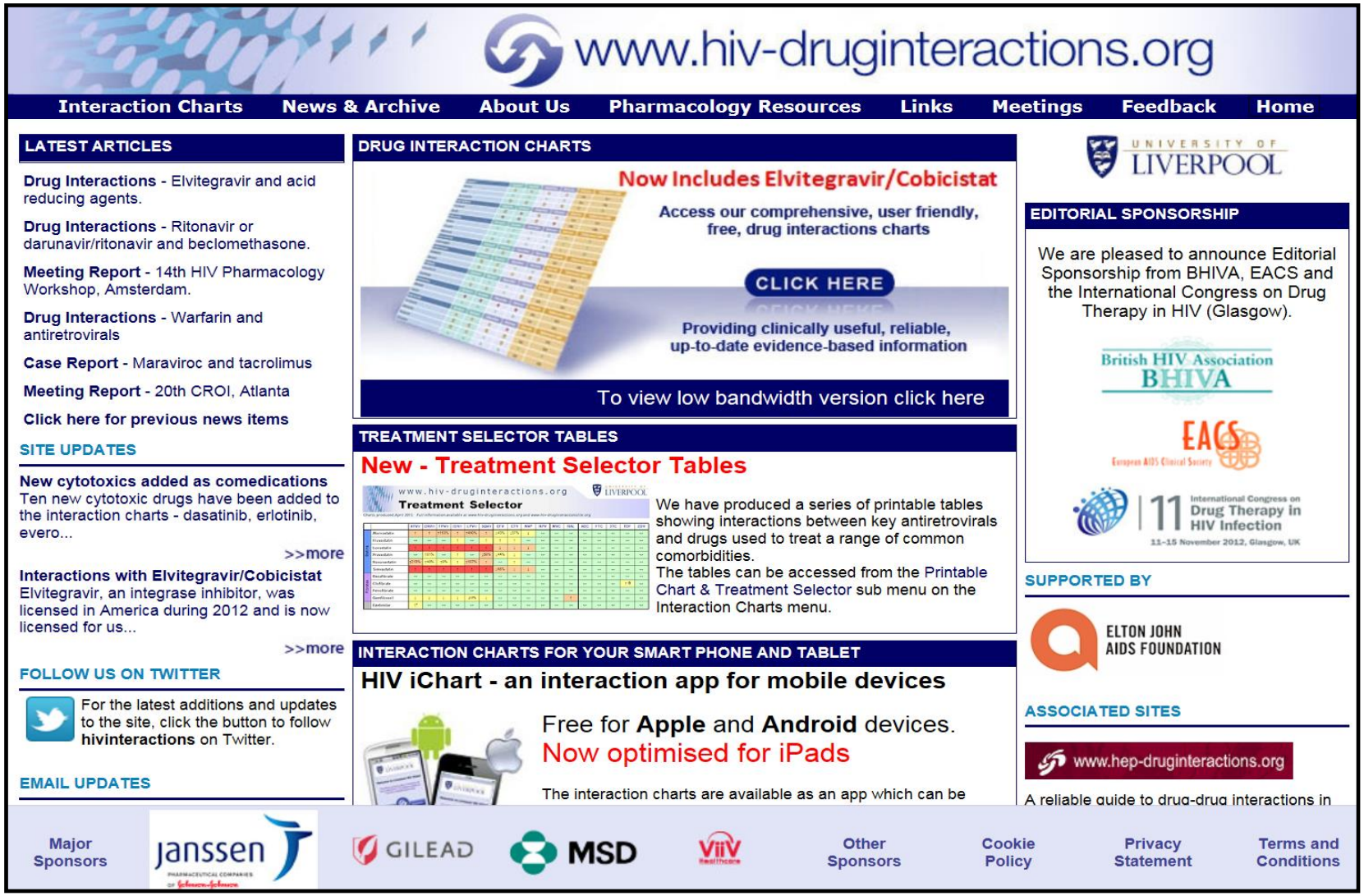


# Drug Interaction Resources

- hivinsite.ucsf.edu
  Updated drug interaction database with references and interactive tool to assess drug interactions.
- www.aidsinfo.nih.gov
  DHHS Guidelines for use of antiretroviral agents and updated drug interaction tables.
- www.hiv-druginteractions.org
  www.hep-druginteractions.org
  Downloadable drug interaction charts; interactive tools to assess interactions; updated news on published abstracts and papers
- www.hivmedicationguide.com
  Interactive drug interaction database
- Micromedex: comprehensive drug database (subscription required); an app is available

# The Liverpool Drug-drug Interactions website was updated for all DDIs for ELV/cobi: June 2013

- For the latest information, visit www.hiv-druginteractions.org
- Refer to the Stribild SPC for further information.



# Treatment Selectors (Updated August 2013 to include elvitegravir/cobicistat)

We have produced a series of printable tables showing interactions between key antiretrovirals and drugs used to treat a range of common comorbidities. The tables are designed to immediately tell which antiretrovirals and co-medications are 'more risky' in relation to drug interactions.

| | |
|---|---|
| Analgesics<br>(Updated August 2013) |  |
| Antidepressants<br>(Updated August 2013) |  |
| Anti-Diabetics<br>(Updated August 2013) |  |
| Antipsychotics<br>(Updated August 2013) |  |
| Anti-Tuberculosis Drugs<br>(Updated August 2013) |  |
| Anxiolytics & Hypnotics<br>(Updated August 2013) |  |
| Cytotoxics<br>(Updated August 2013) |  |
| Hypertensives<br>(Updated August 2013) |  |
| Lipid Lowering<br>(Updated August 2013) |  |

www.hiv-druginteractions.org

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# Lipid-Lowering Treatment Selector

*Charts revised August 2013. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org*

| | | ATV/r | DRV/r | FPV/r | IDV/r | LPV/r | SQV/r | EFV | ETV | NVP | RPV | MVC | EVG/c | RAL | ABC | FTC | 3TC | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Statins | Atorvastatin | ↑ | ↑ | ↑153% | ↑ | ↑490% | ↑ | ↓43% | ↓37% | ↓ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Fluvastatin | ↔ | ↔ | ↔ | ↑ | ↔ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Lovastatin | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Pravastatin | ↔ | ↑81% | ↔ | ↑ | ↔ | ↓50% | ↓44% | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Rosuvastatin | ↑213% | ↑48% | ↑8% | ↑ | ↑107% | ↑ | ↔ | ↑ | ↔ | ↔ | ↔ | ↑ 48% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Simvastatin | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓68% | ↓ | ↓ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Fibrates | Bezafibrate | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Clofibrate | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑⇑ | ↔ |
| | Fenofibrate | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Gemfibrozil | ↓ | ↓ | ↓ | ↓ | ↓41% | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Ezetimibe | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Colour Legend**

- No clinically significant interaction expected
- These drugs should not be coadministered.
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity (<2 fold ↑AUC or <50% ↓AUC). No *a priori* dosage adjustment is recommended.

**Text Legend**

↑ Potential increased exposure of the lipid-lowering drug
↓ Potential decreased exposure of the lipid-lowering drug
↔ No significant effect

⇑ Potential increased exposure of HIV drug
⇓ Potential decreased exposure of HIV drug

a Unboosted atazanavir

# Anti-tuberculosis Treatment Selector

*Charts revised August 2013. Full information available at* ***www.hiv-druginteractions.org*** *and* ***www.hiv-druginteractionslite.org***

| | | ATV/r | DRV/r | FPV/r | IDV/r | LPV/r | SQV/r | EFV | ETV | NVP | RPV | MVC | EVG/c | RAL | ABC | FTC | 3TC | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First Line and Second Line Durgs | Amikacin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[a] | ↔[a] | ↔[b] | ↔ |
| | Capreomycin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑?[a] | ↑?[a] | ↑?[b] | ↔ |
| | Clofazimine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Cycloserine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Ethambutol | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Ethionamide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Isoniazid | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Kanamycin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[a] | ↔[a] | ↔[b] | ↔ |
| | Moxifloxacin | ↑[c] | ↔ | ↔ | ↔ | ↔[c] | ↔[d] | ↔ | ↔ | ↔ | ↔[e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Para-aminosalicylic acid | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑? | ↔ | ↔ | ↔ | ↔ | ↑? | ↑? | ↑? | ↔ |
| | Pyrazinamide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Rifabutin | ↑ | ↑ ⇑50% | ↑ | ↑ | ↑ | ↑ | ↓38% | ⇓37% | ↑17% | ⇓ | f | ↑ ⇓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Rifampicin | ⇓72% | ⇓ | ⇓90% | ⇓80% | ⇓ | ⇓ | ⇓26% | ⇓ | ⇓58% | ⇓80% | ⇓[g] | ⇓ | ⇓40% | ⇓ | ↔ | ↔ | ↔ | ⇓47% |
| | Rifapentine | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓[g] | ⇓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Streptomycin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[b] | ↔ |

**Colour Legend**

- No clinically significant interaction expected
- These drugs should not be coadministered.
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity (<2 fold ↑AUC or <50% ↓AUC). No *a priori* dosage adjustment is recommended.

**Text Legend**

↑ Potential increased exposure of the anti-tuberculosis drug
↓ Potential decreased exposure of the anti-tuberculosis drug
↔ No significant effect

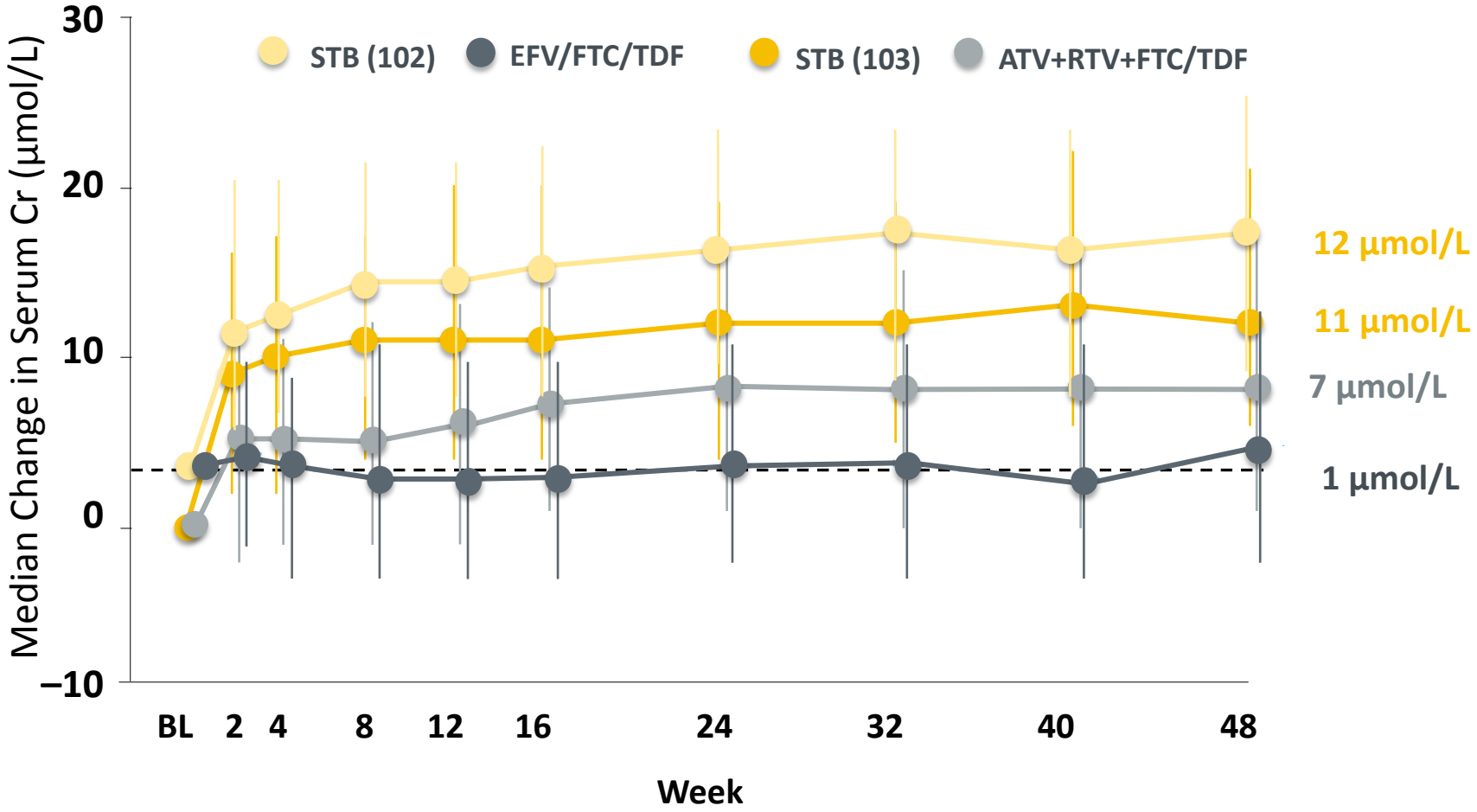
⇑ Potential increased exposure of HIV drug
⇓ Potential decreased exposure of HIV drug

a Aminoglycosides are nephrotoxic (risk is dose and treatment duration related). Renal function should be monitored periodically and the dosage of NRTI adjusted accordingly.
b Coadministration should be avoided due to the risk of additive tubular toxicity, but if such use is unavoidable, closely monitor renal function.
c Both drugs can potentially prolong the QT interval, ECG monitoring recommended.
d Both drugs can potentially prolong the QT interval. Coadministration with such drugs is contraindicated in the European SPC and US Prescribing Information.
e Rilpivirine's manufacturer recommends caution when coadministering with another drug susceptible to prolong QT interval as supratherapeutic dose of rilpivirine (75 and 300 mg once daily) were shown to prolong QT interval.
f No dose adjustment for MCV in absence of PI. With PI (except TPV/r, FPV/r), give MVC 150 mg twice daily.

# Renal effects of Stribild

## Median Change From Baseline in Serum Creatinine

*Combined GS-102 and -103 Stribild vs. EFV/FTC/TDF or ATV+RTV+FTC/TDF*



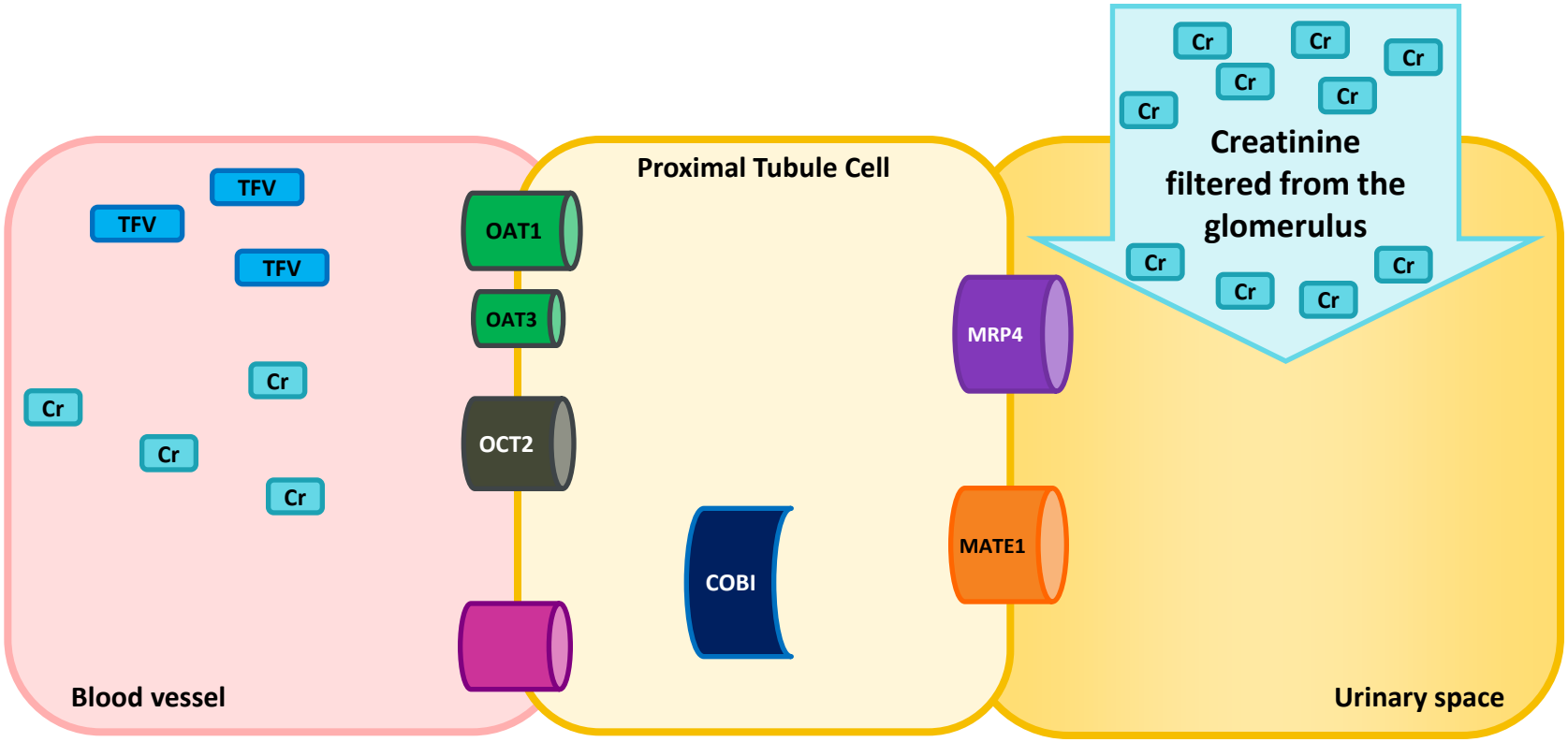

p<0.001 STB vs. EFV/FTC/TDF

*DeJesus E et al. Lancet 2012;379:2429–38*
*Sax PE et al. Lancet 2012;379:2439–48*

*GILEAD – with permission*

# Cobicistat Inhibits Active Tubular Secretion of Creatinine - *Resulting in Increased Serum Creatinine*

- Preclinical studies indicate that cobicistat blocks a transport pathway used for creatinine secretion from the proximal tubule




*German P et al. J Acquir Immune Defic Syndr 2012;61:32–40*
*Lepist EI, Ray AS. Expert Opin Drug Metab Toxicol 2012;8:433–48*

*GILEAD – with permission*

Clin Pharmacokinet
DOI 10.1007/s40262-013-0093-2

REVIEW ARTICLE

# Clinical Pharmacokinetic, Pharmacodynamic and Drug-Interaction Profile of the Integrase Inhibitor Dolutegravir

Mackenzie L. Cottrell · Tanja Hadzic · Angela D. M. Kashuba

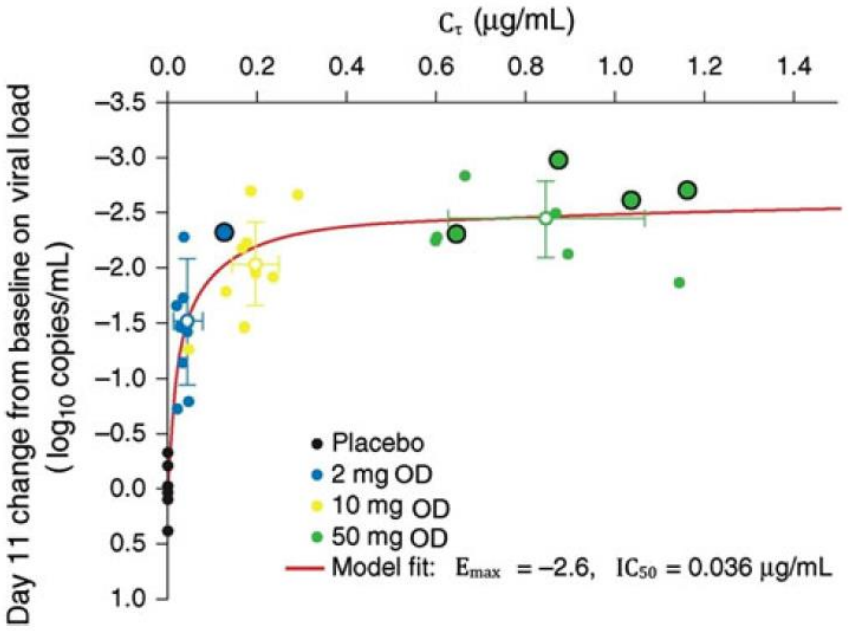
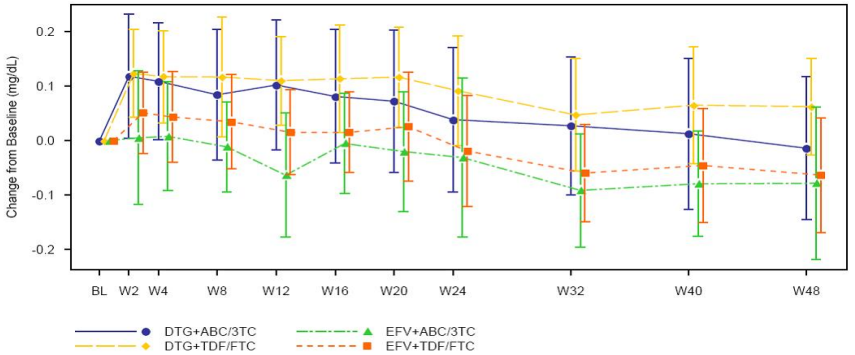



**Fig. 2** Mean change from baseline in HIV-1 RNA. $C_\tau$ concentration at the end of the dosing interval, $E_{max}$ maximum effect, $IC_{50}$ concentration producing 50 % inhibition, *OD* once daily. (reproduced with permission from Min et al. [12])

**Metabolised by**:
UGT1A1 (major); CYP3A4 (minor)

Does **not** induce or inhibit CYP enzymes or UGT1A1 at clinically relevant concentrations.

Has modest DDI profile




*Van Lunzen J et al IAS Rome July 2011*

# Corticosteroids

- Cushing's syndrome and adrenal suppression reported in a patient on ATV/r and **dexamethasone 0.1% eye drops** (1)

- Cases of Cushing's syndrome reported with use of **intra articular triamcinolone injections** in patients on boosted PIs (2-5)

- Cases of Cushing's syndrome and adrenal suppression in patients on inhaled **budesonide** & boosted PIs (6-8).

- Numerous cases of Cushing's syndrome with inhaled **fluticasone** and boosted PI

CLINICAL CASE SEMINAR

**Iatrogenic Cushing's Syndrome with Osteoporosis and Secondary Adrenal Failure in Human Immunodeficiency Virus-Infected Patients Receiving Inhaled Corticosteroids and Ritonavir-Boosted Protease Inhibitors: Six Cases**

Katherine Samaras, Sarah Pett, Andrew Gowers, Marilyn McMurchie, and David A. Cooper

*1, Molloy A et al AIDS 2011; 25: 1337-1339; 2, Dort K et al AIDS Res Ther 2009; 6: 10; 3, Yombi JC et al Clin Rheumatol 2008; 27 (Suppl 2); S79-82; 4, Danaher PJ et al Orthopedics 2009; 32: 450; 5, Ramanathan R et al Clin Infect Dis 2008; 47: e97-99; 6, Kedem e et al J Asthma 2010; 47: 830-831; Gray D et al S Afr Med J 2010; 100: 296-297; Frankel JK & Packer CD. Ann Pharmacother 2011; 45: 823-824.*

# Corticosteroids

| Drug | Oral | Inhaled | Topical | Eye/Ear drops | Injection | Rectal |
|---|---|---|---|---|---|---|
| **Budesonide** ***CYP3A4*** | ✓ | ✓ | | | | ✓ |
| **Dexamethasone** ***CYP3A4*** | ✓ | | ✓ | ✓ | ✓ | |
| **Fludrocortisone** ***CYP3A4*** | ✓ | | | | | |
| **Fluticasone** ***CYP3A4*** | | ✓ | ✓ | | | |
| **Hydrocortisone** ***CYP3A4*** | | | ✓ | ✓ | ✓ | ✓ |
| **Prednisolone** ***CYP3A4*** | ✓ | | ✓ | ✓ | ✓ | ✓ |
| **Beclomethasone** ***Esterase to active met*** | | ✓ | | | | |
| **Triamcinolone** ***CYP3A4*** | ✓ | ✓ | ✓ | | ✓ | |
| **Mometasone** ***CYP3A4*** | | ✓ | ✓ | | | |

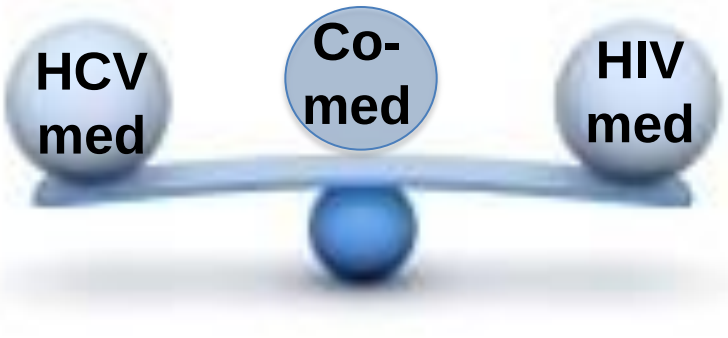
*All information taken from relevant SmPC's: accessed October 2012*

# HIV-HCV Co-infection

***Toxicity***

**Telaprevir**
**Boceprevir**
**Ribavirin**

**Drugs in pipeline**

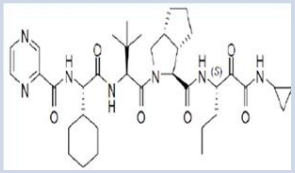
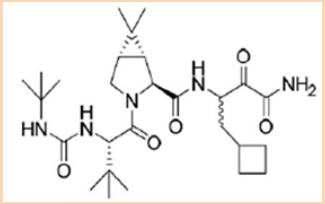



**ATV/r**
**DRV/r**
**LPV/r**
**Efavirenz**
**Rilpivirine**
**Etravirine**
**Raltegravir**
**Elvitegravir/cobi**
**Maraviroc**
**NRTIs**

***Reduced Efficacy***

In a co-infected patient we now need to manage the interactions between the HCV and HIV medication as well as other co-meds

# Clinical Pharmacology of DAAs

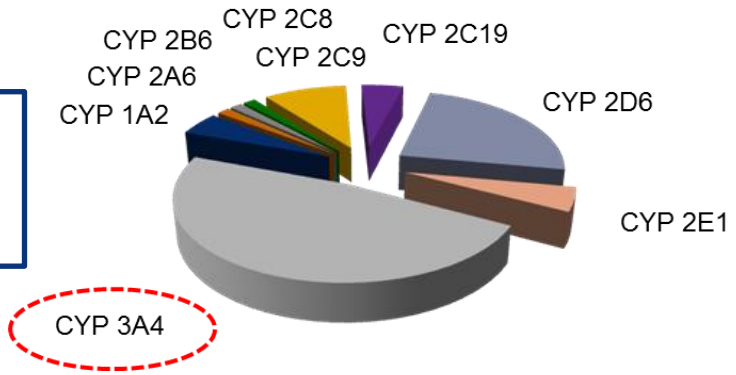
| DRUG | CYP450 | Non-CYP450 | Transport Proteins |
|---|---|---|---|
| Telaprevir  | CYP3A4<br>• Substrate<br>• Inhibitor | | • Transported by P-gp<br>• Inhibits P-gp<br>• Inhibits OATP1B1 |
| Boceprevir  | CYP3A4<br>• Substrate<br>• Inhibitor | AKR substrate | • Transported by P-gp<br>• Inhibits P-gp<br>• Inhibits OATP1B1; OCT1/2 |

*Kessara C et al 18th CROI, Abs 118; Garg V et al 18th CROI, Abs 629; Telaprevir SmPC, 2013; Boceprevir SmPC, 2013; Kiser JJ et al Hepatology 2012; 55: 1620-1628; Kunze A et al Biochem Pharmacol 2012; 84: 1096-1102.*

# Telaprevir & Boceprevir increase exposure to CYP3A substrates: *Perpetrator*

| Drug | TVR effect on the AUC (exposure) | BOC effect on the AUC (exposure) |
|---|---|---|
| **Cyclosporine A** | 4.6-fold increase | 2.7-fold increase |
| **Tacrolimus** | 70-fold increase | 17-fold increase |
| **Midazolam** | 3.4-fold increase (i.v)<br>9-fold increase (oral) | 6.3-fold increase (oral) |
| **Atorvastatin** | 7.9-fold increase | 2.3-fold increase |

CYP 3A isozymes are involved in the metabolism of ~50% drugs

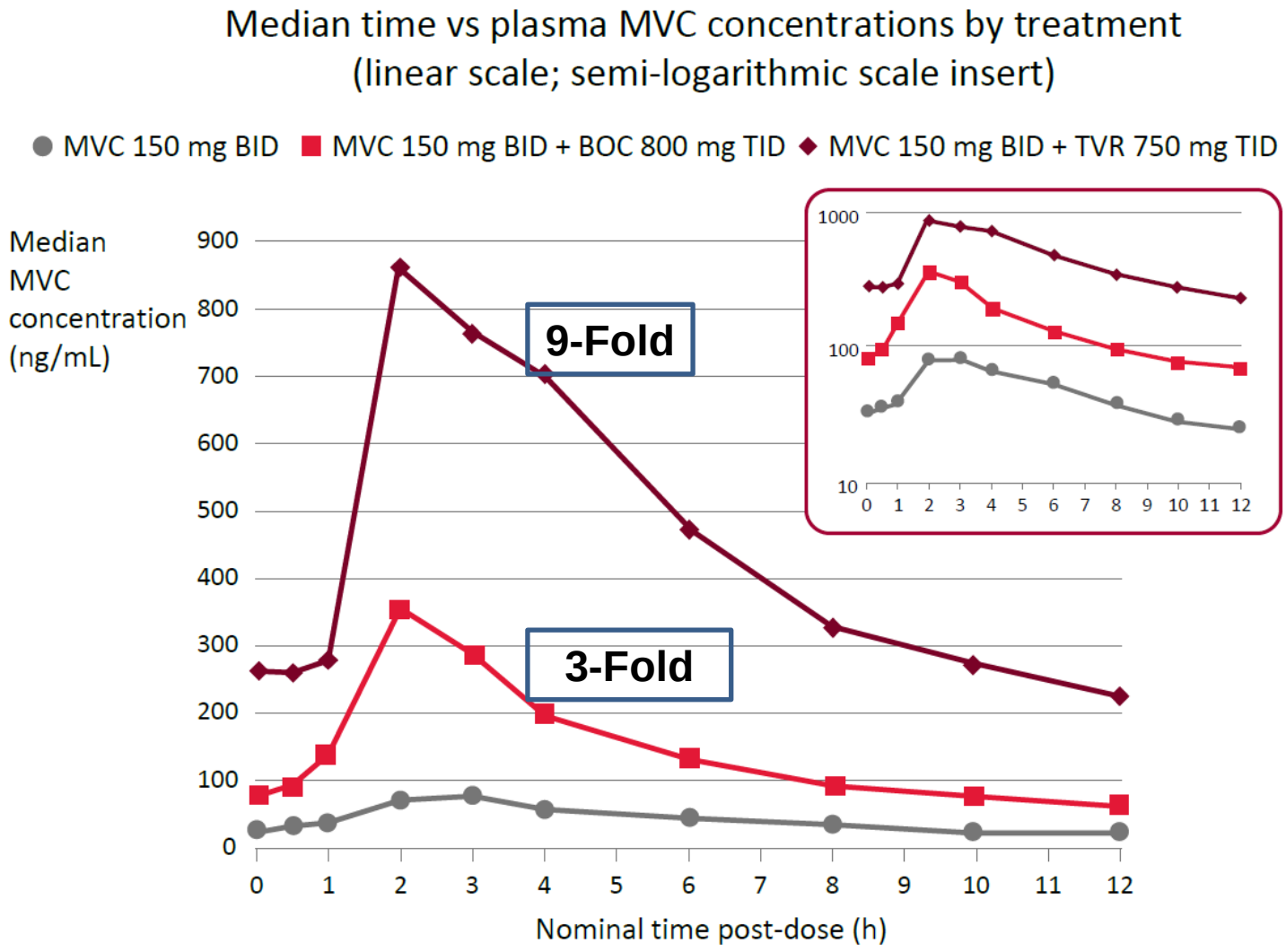



Garg V, et al. Heptatology 2011:54:20–27; Garg V, et al. J Clin Pharmacol 2012 ; Lee JE, et al. Antimicrob Agents Chemother 2011;55:4569–74; Telaprevir SmPC; Hulskotte EGJ et al HEPDart 2011; Abs 122 and Abs 123; Kessara C et al, CROI 2011, Abs 118; Boceprevir SmPC

# Relevance to HIV-HCV Co-infection

- If clearance involves just CYP3A4 – co-med levels will *increase.*
- But if other additional metabolic pathways – co-med levels *could decrease.*
- Also note *other interaction mechanisms.*

# Effect of Boceprevir and Telaprevir on the PK of Maraviroc (a CYP3A4 drug) - *Predictable*




*Vourvahis M et al. IWCPHT 2013 Abs O-17*

# Effect of TVR & BOC on PK of Rilpivirine (*CYP3A4*) and Raltegravir (*UGT1A1; CYP3A4 minor*) - *Predictable*

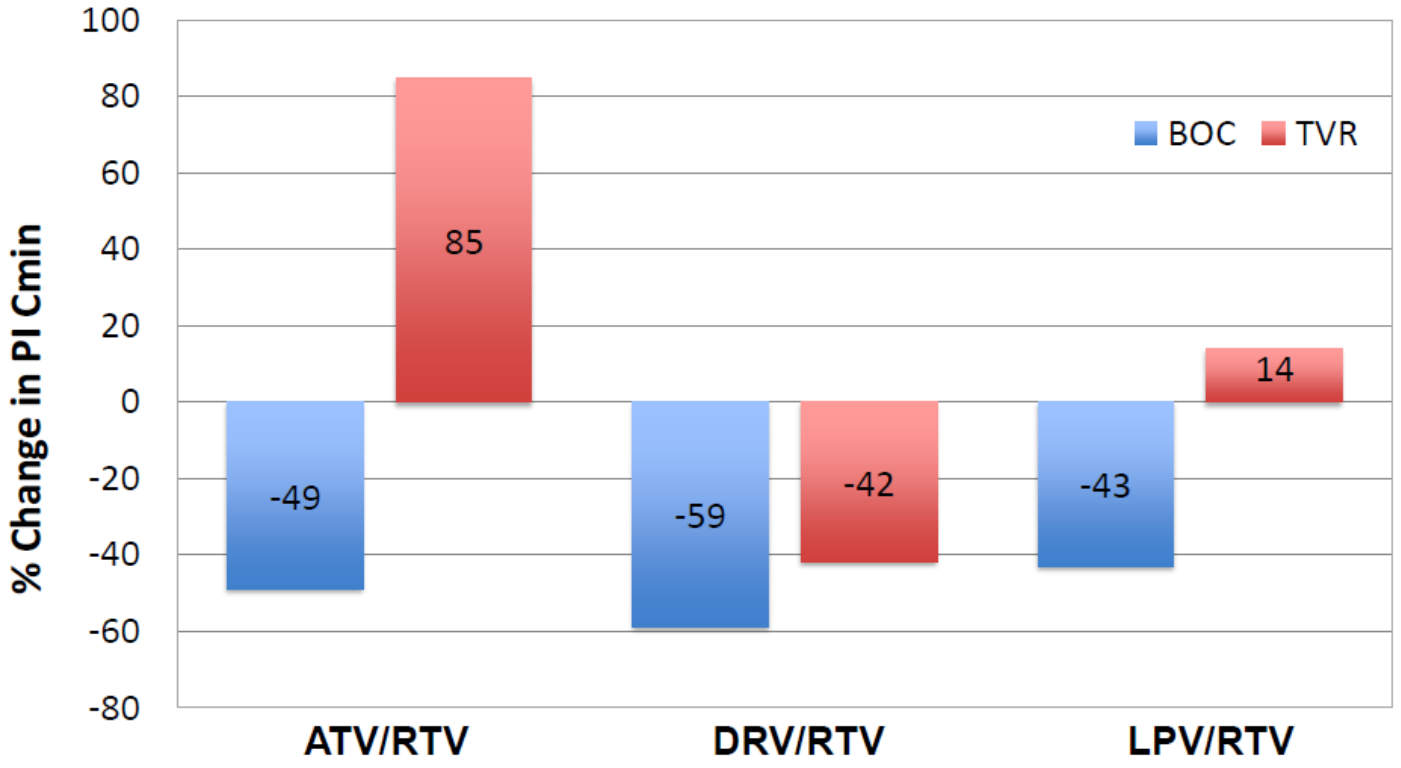
| Parameter | Effect of TVR | Effect of BOC |
|---|---|---|
| **Rilpivirine AUC** ng.h/mL | ↑ **78%** | ↑ **39%** |
| **Raltegravir AUC** ng.hr/mL | ↑ **31%** | ↑ **4%** |

- Finding consistent with CYP3A inhibition
- Increase in RPV exposure *probably not* clinically significant and no dose adjustment recommended.
- Increase in RAL exposure not clinically significant

Rhee EG, et al. CROI 2013; Atlanta, GA. #537; Kakuda T et al; IWCPHT, 2012, Barcelona, #O-18
De Kanter C et al CID 2013; 56: 300-306 van Heeswijk R et al; ICAAC 2011.

**So why does the exposure of boosted HIV PIs mainly *decrease* in healthy volunteer studies?**

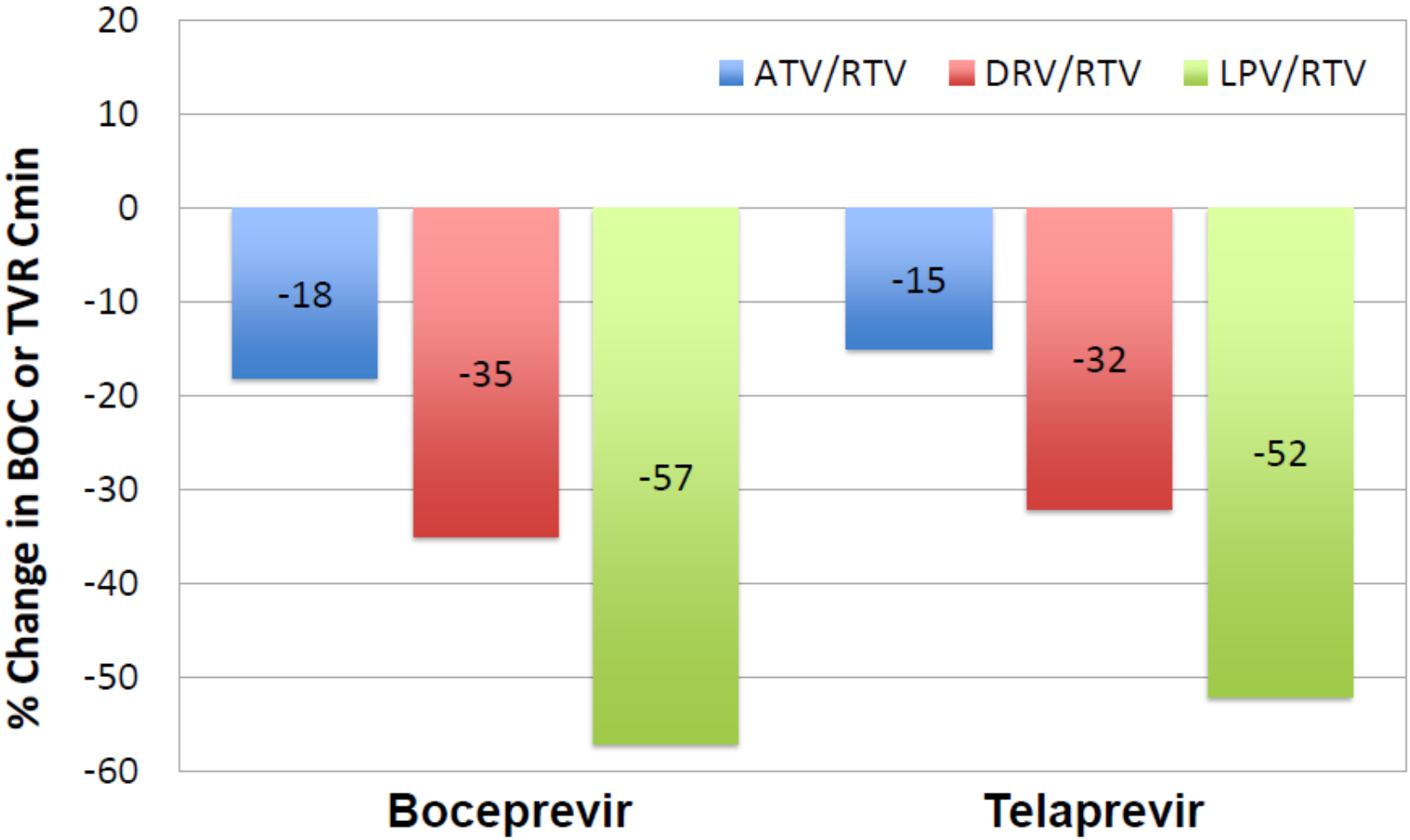
# Effect of Boceprevir and Telaprevir on the HIV Boosted PI concentrations




**But remember ritonavir boosting inhibits ~95% of CYP3A activity so Telaprevir and Boceprevir exert other effects.**

*Fletcher CV IAPAC 2013*

# Effect of Ritonavir boosted HIV PIs on Boceprevir and Telaprevir concentrations




*Fletcher CV IAPAC 2013*

# Telaprevir: Summary of key interactions with HIV antiretrovirals *(data Healthy subjects)*

| HIV antiretroviral | Recommendation |
|---|---|
| Atazanavir/r | Clinical and laboratory monitoring for hyperbilirubinemia is recommended |
| Darunavir/r<br>Fosamprenavir/r<br>Lopinavir/r | Not recommended |
| Efavirenz | TVR dose increase necessary (1125 mg q8h) |
| Maraviroc | MVC dose reduced to 150 mg bid (or qd?).+ |
| Etravirine | No dose adjustment required* |
| Rilpivirine | No dose adjustment required* (but 79% increase in RPV AUC) - monitor |
| Raltegravir (non CYP) | No dose adjustment required** (but 31% increase in RAL AUC) |
| Dolutegravir (non CYP) | No dose adjustment required$ (but 30% increase in DOL AUC) |
| Tenofovir | Increase in TFV (30%). Clinical and laboratory monitoring is warranted |

* Data presented by Kakuda et al at 13th HIV Pharmacology Workshop, Barcelona, April 2012; ** van Heeswijk R et al; ICAAC 2011; Abs A1-1738a; +Vourvahis M et al IWCHPT, April 2013; $Johnson M et al IWCPHT, April 2013.

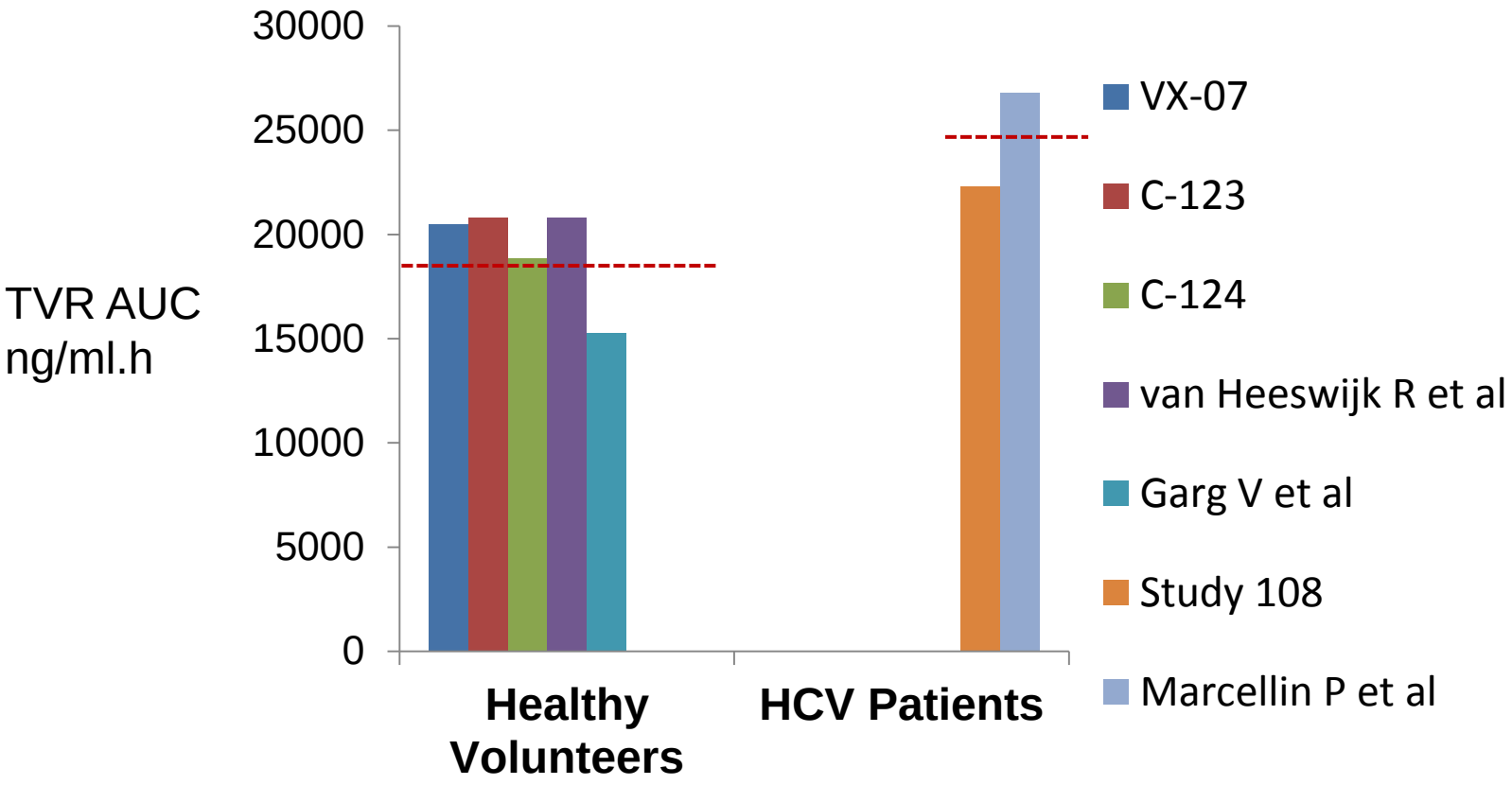
# Boceprevir: Summary of key interactions with HIV antiretrovirals *(data healthy subjects)*

| HIV antiretroviral | Recommendation |
|---|---|
| Atazanavir/r<br>Darunavir/r<br>Lopinavir/r | Not recommended |
| Efavirenz | Reduction in boceprevir levels; clinical outcome not directly assessed – not recommended |
| Maraviroc | MVC dose reduced to 150 mg bid (or qd?)[+] |
| Etravirine | No dose adjustment required* |
| Raltegravir (non CYP) | No dose adjustment required** |
| Dolutegravir (non CYP) | No dose adjustment required [$] |
| Tenofovir | No change in TFV AUC but Cmax increased by 32%. No dose adjustment but clinical/laboratory monitoring warranted |

*De Kanter C, et al. CROI 2012. Abstract 772LB; **Hammond K et al, IWCPHT 2012; Abs O-15 Abs Victrlelis SmPC; $Johnson M, IWCPHT April 2013; +Vourvahis M et al IWCPHT April 2013.

# What if drug interactions were ‘significantly’ different in HCV patients compared to healthy volunteers?

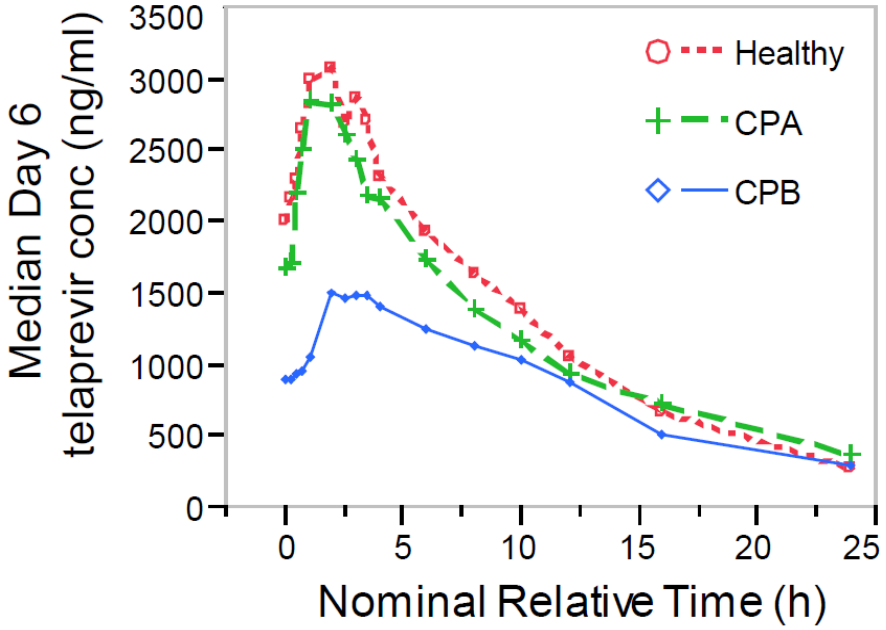
# Telaprevir Exposure (AUC) in Healthy Volunteers and HCV Patients



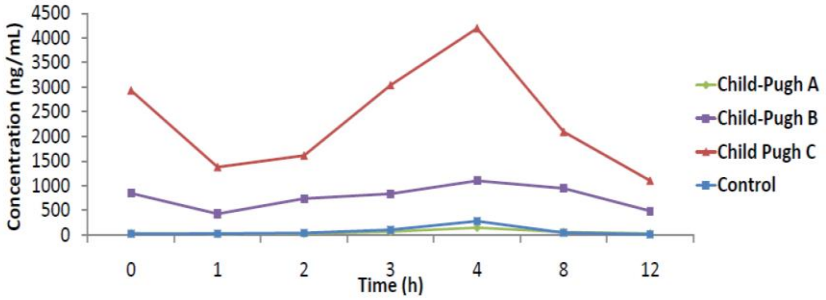

*FDA Briefing Document April 2011; van Heeswijk R et al; IWCPHep Ther 2011; Ab 12; Garg V et al Br J Clin Pharmacol 2012; 75: 431-439; Marcellin P et al Gastroenterology 2011; 140: 459-468. Ingliz P Fut Virololgy 2013; 8: 735-743.*

# Impact of Hepatic Impairment on PK of Telaprevir and Asunaprevir

***Both drugs metabolised by CYP3A4 and transported by OATP1B1***




*6th Int Workshop on Clin Pharm Hep Ther June2013.*




- AUC ↑ 9.8-fold and 32-fold in moderate and severe impairment

Eley T et al. AASLD 2012, #1873

- **<u>Reduced</u> Absorption**
- **<u>Increased</u> clearance due to reduced protein binding**

- **<u>Increased</u> Absorption**
- **<u>Decreased</u> clearance due to inhibition of CYP3A4**

# So...

- The magnitude of a drug interaction may be different in HCV patients?

  *Emerging evidence to support this*

- Also in co-infection – HIV VL suppressed when starting HCV tx – *so does a decrease in plasma exposure of one drug matter so much?*
- Get ~0.8 log suppression of HIV from Peg INF.
- Complex DDIs – a role for **monitoring?**

# British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011

## 17.1 Recommendations

There is insufficient evidence to recommend routine use of TDM in the management of ART (I).

- TDM may be useful in individual patients (IV):
  - to assess and manage drug–drug or drug–food interactions;
  - if there is coexistent kidney or liver disease;
  - to assess and manage suboptimal adherence;
  - to assess reasons for regimen failure and to optimize treatment if resistance is present;
  - to manage drug-related toxicity.

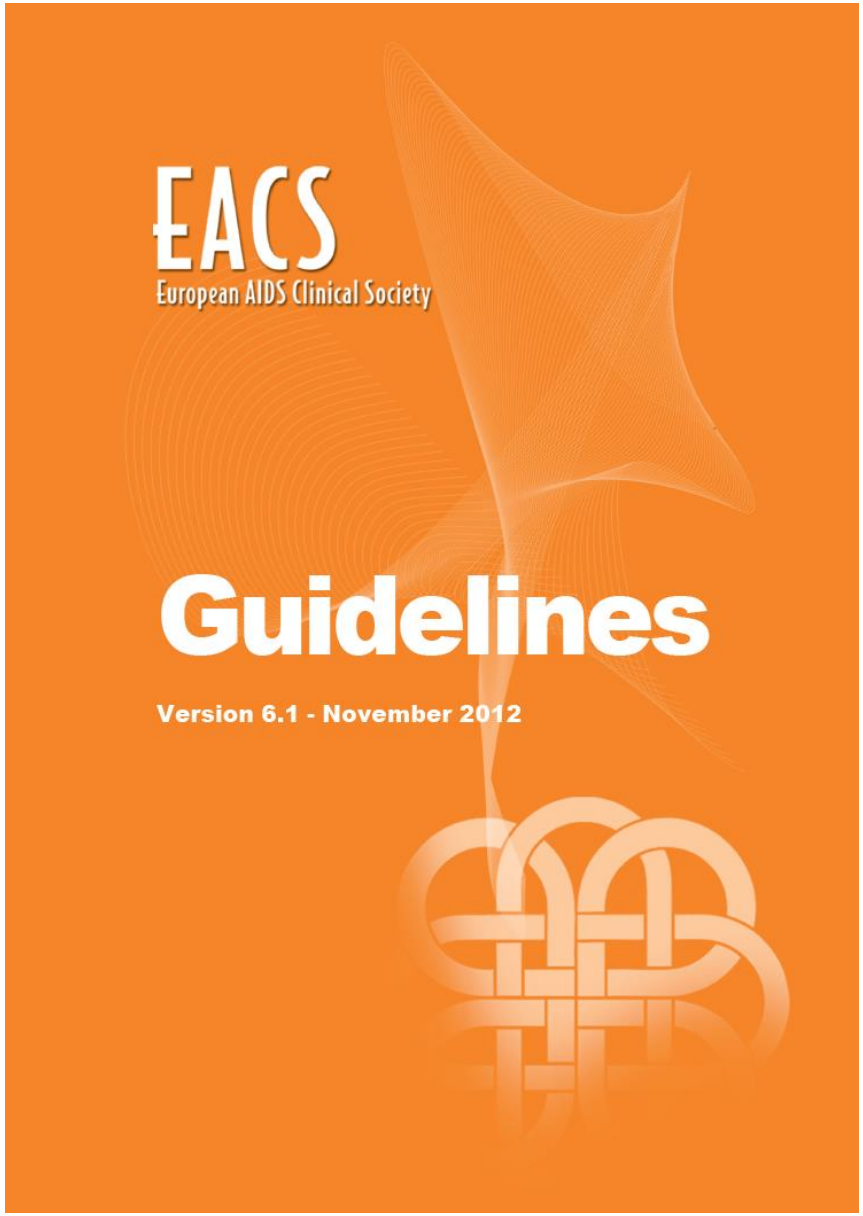
*Asboe D et al HIV Med 2012; 13: 1-44.*

# Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

## Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents (Last updated January 10, 2011; last reviewed January 10, 2011)

| Panel's Recommendations |
| --- |
| • Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult **(CIII)**.<br>• TDM may be considered in selected clinical scenarios, as discussed in the text below. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional* |
| ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion* |

- Drug-drug interactions; drug-food interactions
- Change in pathophysiology
- Pregnant women in later stages
- Heavily pre-treated patients with VF
- Use of alternate dosing regimens
- Concentration related toxicities
- Lack of VR in adherent patient.




**Virologic Failure:**

*Consider TDM*

**ART in TB/HIV co-infection:**

*TDM recommended (EFV + Rif; PI/r + RFB)*

# Role of Clinical Pharmacology in future

- Drug penetration and compartments
  *(Virologic Failure; toxicity; cure)*
- PreP – oral and long acting
- Dose optimisation (Encore – EFV 400 v 600 mg)
- Nanoformulations
- Novel formulations – including generics

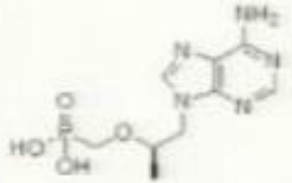
# Poor Early Virologic Performance and Durability of Abacavir-based First-line Regimens for HIV-infected Children

*Karl-Günter Technau, MSc(Med),* Erica Lazarus, MB ChB,† Louise Kuhn, PhD,‡ Elaine J. Abrams, MD,§ Gillian Sorour, FCPaed,* Renate Strehlau, MBBCH,* Gary Reubenson, FCPaed,* Mary-Ann Davies, MMed,¶ and Ashraf Coovadia, FCPaed**

(*Pediatr Infect Dis J* 2013;32: 851–855)

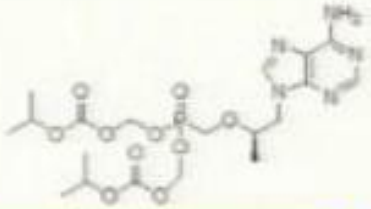
# Tenofovir Alafenamide (TAF)

## Next Generation Prodrug of Tenofovir



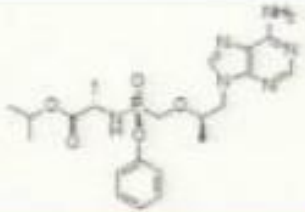
**TFV**

Tenofovir



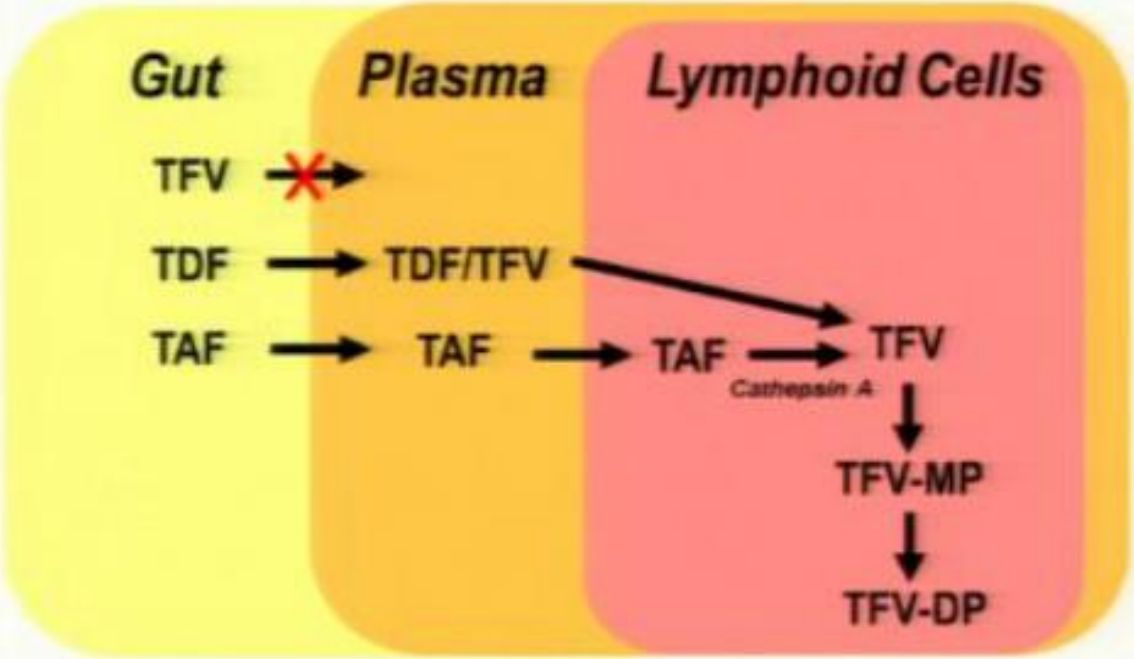
**TDF**

Tenofovir Disoproxil Fumarate



**TAF**

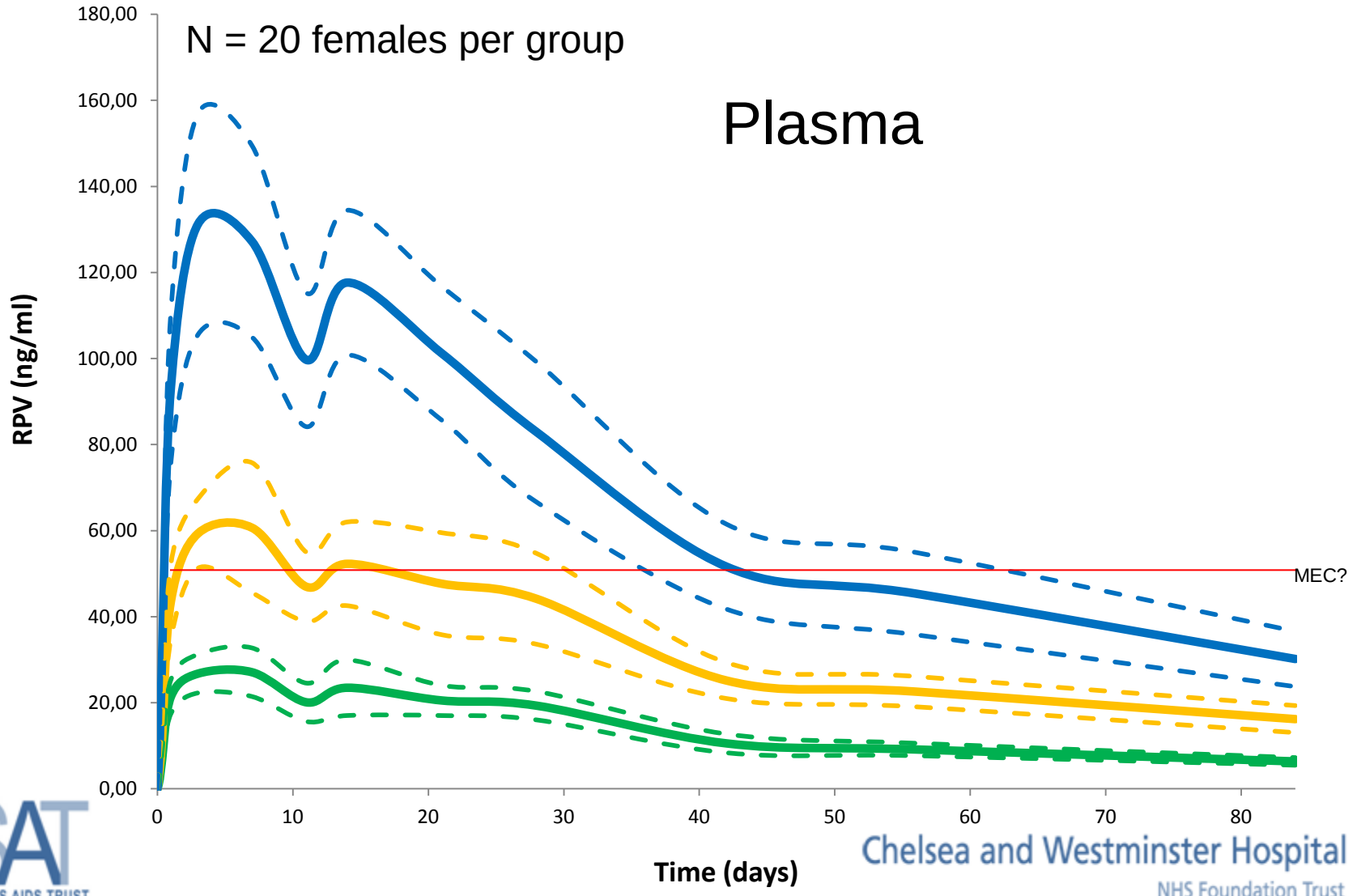
Tenofovir Alafenamide




Zolopa, et al., CROI 2013; Paper # 99LB

# Rilpivirine Long Acting

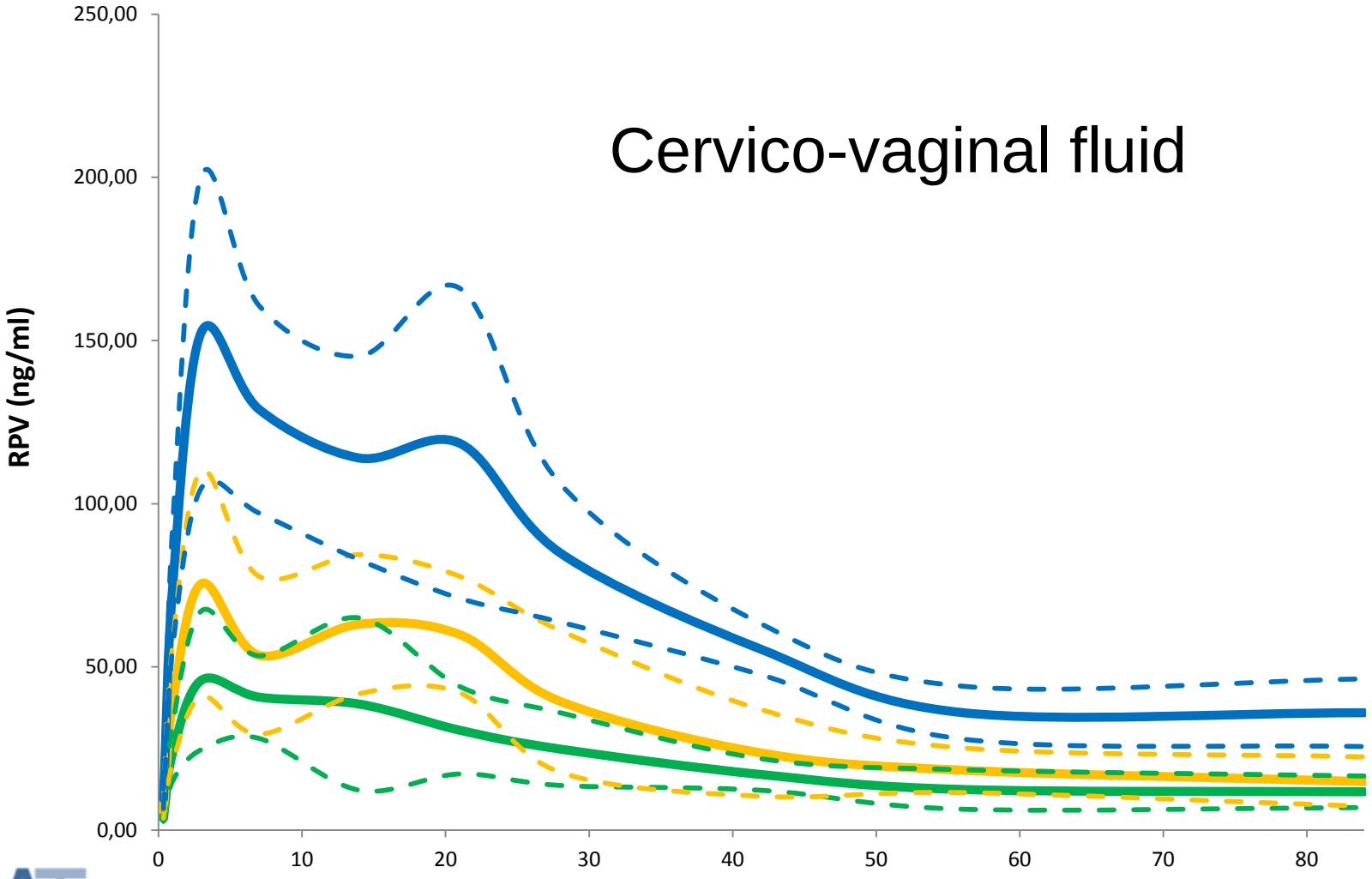
## 300, 600 & 1200 mg i.m.




Jackson et al, CROI 2012.

# Rilpivirine Long Acting

## 300, 600 & 1200 mg i.m.




ST STEPHEN'S AIDS TRUST

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

# ENCORE1 Study: EFV 400 v 600 mg in tx-naïve patients. Week 48 outcomes

- **EFV 400 mg + FTC/TDF**
  - **Non-inferior to EFV 600 mg**
    - **No difference in proportion achieving HIV RNA <200 cps/mL:**
  - **Significantly greater increase in CD4 cells (*P*=0.009)**
    - **Difference: 25 cells/mm$^3$**
  - **Trend towards a reduced incidence of EFV-related Aes**

- **EFV 400 mg may be considered an option for initial ART?**

| Efavirenz + 2 NRTIs: Week 48 Outcomes | 400 mg (n=321) | 600 mg (n=309) |
|---|---|---|
| Virologic failure (%) | 1.6 | 2.3 |
| HIV RNA <200 copies/mL (%) | | |
| Overall | 94.1 | 92.2 |
| HIV RNA <$10^5$ | 94.9 | 92.9 |
| HIV RNA ≥$10^5$ | 92.7 | 91.1 |
| Adverse events (%) | | |
| CNS | 44 | 51 |
| Psychiatric | 4 | 4 |
| Rash | 19 | 28 |
| Gastrointestinal | 15 | 18 |
| Respiratory | 6 | 7 |
| Hepatology | <1 | 0 |

Puls R, et al. 7th IAS Conference. Kuala Lumpur, 2013. Abstract WeLBB01.

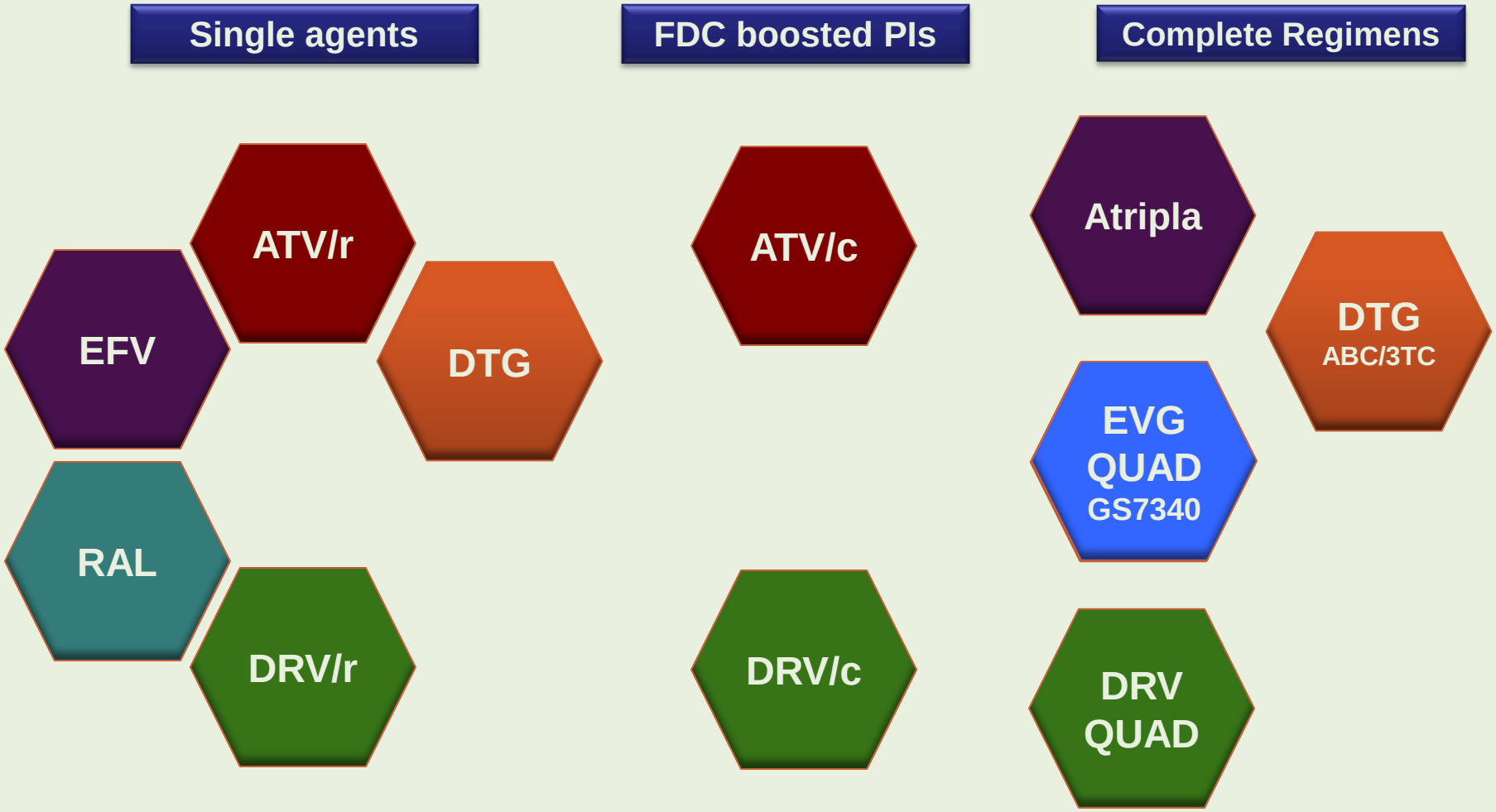
# Nanomedicines for HIV therapy

Heterogeneity in response to HIV treatments has been attributed to several causes including variability in pharmacokinetic exposure. Nanomedicine applications have a variety of advantages compared with traditional formulations, such as the potential to increase bioavailability and specifically target the site of action.

*Studies ongoing with EFV and LPV*

# Thank you

# Future Preferred Regimens




ATV=atazanavir; c=cobicistat; DRV=darunavir; DTG=dolutegravir; EVG=elvitegravir; GS7340=TDF pro-drug; r=ritonavir; RAL=raltegravir; TDF/FTC=tenofovir+emtricitabine as Truvada

# Tenofovir Alafenamide (TAF)

## Background (formerly GS-7340)

- **TAF is a prodrug of tenofovir (TFV) with increased delivery to lymphoid cells and hepatocytes**
- **Relative to TDF 300 mg, TAF 25 mg has[1]:**
  - Increased anti-HIV-1 activity in Phase 1
  - Increased intracellular TFV-DP levels by ~7-fold
  - Decreased circulating plasma TFV levels by ~90%
  - Lower levels of TFV in kidney and bone tissue expected
- **TAF formulated into a single tablet regimen as E/C/F/TAF**
  - Elvitegravir 150mg
  - Cobicistat 150mg
  - FTC (emtricitabine) 200mg
  - TAF 10mg
- **TAF 10mg in E/C/F/TAF has PK comparable to TAF 25mg alone[2]**
  - COBI ↑ TAF levels ~2.2-fold

[1] *P Ruane, et al. CROI 2012; Paper # 103*

[2] *S Ramanathan, et al. IWCPHT 2012; Abstract O_13*

Zolopa, et al., CROI 2013; Paper # 99LB

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# Antidepressant Treatment Selector

*Charts produced April 2013. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org*

| | | ATV/r | DRV/r | FPV/r | IDV/r | LPV/r | SQV/r | EFV | ETV | NVP | RPV | MVC | RAL | ABC | FTC | 3TC | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SSRI | Citalopram | ↑[a] | ↑ | ↑ | ↑ | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Escitalopram | ↑[a] | ↑ | ↑ | ↑ | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Fluvoxamine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Fluoxetine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Paroxetine | ↑↓? | ↓39% | ↓50% | ↑↓? | ↑↓? | ↑↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Sertraline | ↓ | ↓49% | ↓ | ↓ | ↓ | ↓ | ↓39% | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| SNRI | Duloxetine | ↑↓ | ↑↓ | ↑↓ | ↑↓ | ↑↓ | ↑↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Venlafaxine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ⇓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| TCA | Amitriptyline | ↑ | ↑ | ↑ | ↑ | ↑ | ↑[b] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Clomipramine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑[b] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Desipramine | ↑ | ↑ | ↑ | ↑ | ↑5% | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Doxepin | ↑ | ↑ | ↑ | ↑ | ↑ | ↑[b] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Imipramine | ↑[a] | ↑ | ↑ | ↑ | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Nortriptyline | ↑[a] | ↑ | ↑ | ↑ | ↑[a] | ↑[ab] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Trimipramine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| TeCA | Maprotiline | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Mianserine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Mirtazapine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Others | Bupropion | ↓ | ↓ | ↓ | ↓ | ↓57% | ↓ | ↓55% | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Lamotrigine | ↓32% | ↓ | ↓ | ↓ | ↓50% | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Nefazodone | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓⇑ | ↓ | ⇑ | ⇑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | St John's wort | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Trazodone | ↑ | ↑ | ↑ | ↑ | ↑ | ↑[b] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Colour Legend**

- No clinically significant interaction expected
- These drugs should not be coadministered.
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity (<2 fold ↑AUC or <50% ↓AUC). No *a priori* dosage adjustment is recommended.

LHPG

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# Anti-hypertensive Treatment Selector

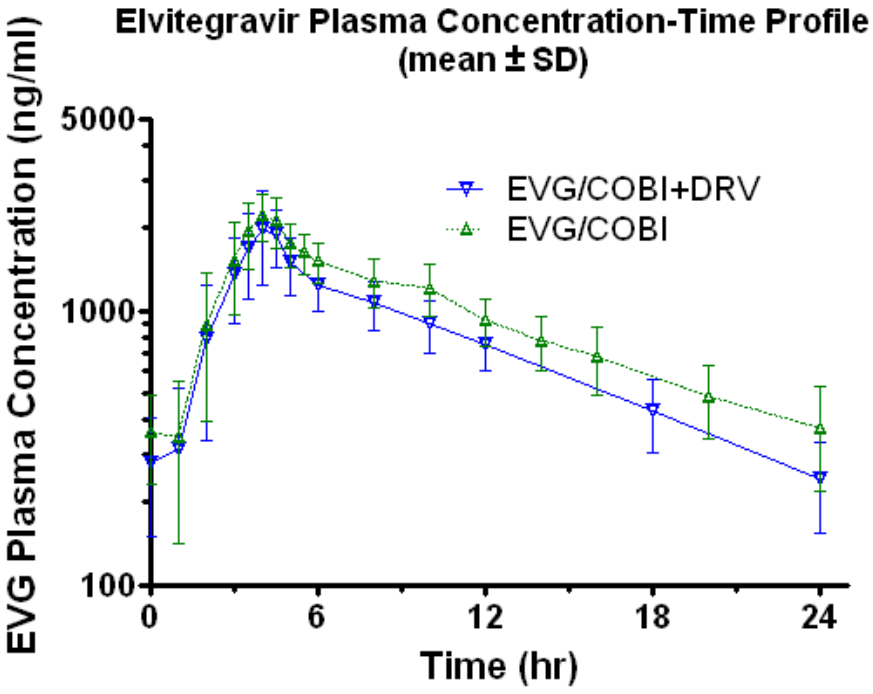
*Charts produced April 2013. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org*

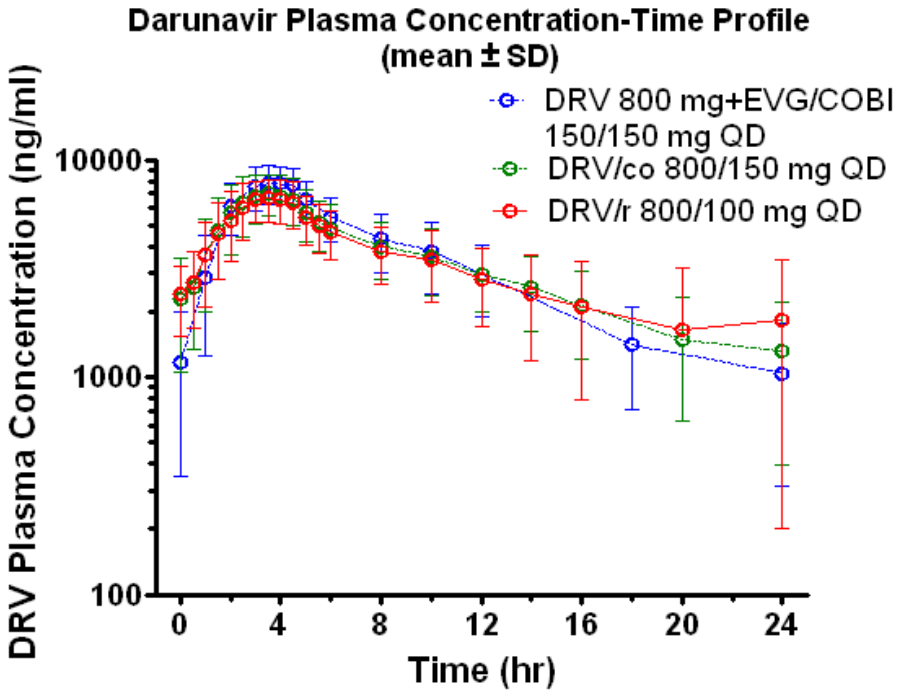
| | | ATV/r | DRV/r | FPV/r | IDV/r | LPV/r | SQV/r | EFV | ETV | NVP | RPV | MVC | RAL | ABC | FTC | 3TC | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACE Inhibitors | Cilazapril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Enalapril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Lisinopril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Perindopril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Quinapril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Ramipril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Trandolapril | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Angiotensin Antagonists | Candesartan | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Irbesartan | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Losartan | ↓[a] | ↓[a] | ↓[a] | ↓[a] | ↓[a] | ↓[a] | ↑[b] | ↑[b] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Olmesartan | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Telmisartan | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Valsartan | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| β Blockers | Atenolol | ↔[d] | ↔ | ↔ | ↔ | ↔[d] | ↔[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Bisoprolol | ↑[d] | ↑ | ↑ | ↑ | ↑[d] | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Carvedilol | ↑↓[d] | ↑↓ | ↑↓ | ↑↓ | ↑↓[d] | ↑↓[d] | ↑↓ | ↑↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Metoprolol | ↑[d] | ↑ | ↑ | ↑ | ↑[d] | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Propanolol | ↑[d] | ↑ | ↑ | ↑ | ↑[d] | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Calcium Channel Agonists | Amlodipine | ↑[c] | ↑ | ↑ | ↑80% | ↑ | ↑[c] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Diltiazem | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓69% | ↓⇑ | ↓ | ⇑ | ⇑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Felodipine | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Lacidipine | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Lercanidipine | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Nicardipine | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓ | ↓⇑ | ↓ | ⇑ | ⇑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Nifedipine | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Nisoldipine | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Verapamil | ↑[c] | ↑ | ↑ | ↑ | ↑ | ↑[c] | ↓ | ↓⇑ | ↓ | ⇑ | ⇑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Diuretics | Amiloride | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Bendroflumethiazide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Chlortalidone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | Furosemide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ⇑ | ↔ |
| | Indapamide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

# Drug-Drug Interactions: Management Concepts

- Some interactions are useful eg boosting - *ritonavir, cobicistat*
- Some interactions are recognised and then managed clinically
- Some interactions are so profound that concomitant administration should be avoided.
- Some interactions are of unknown clinical significance.

# EVG/COBI + DRV QD PK

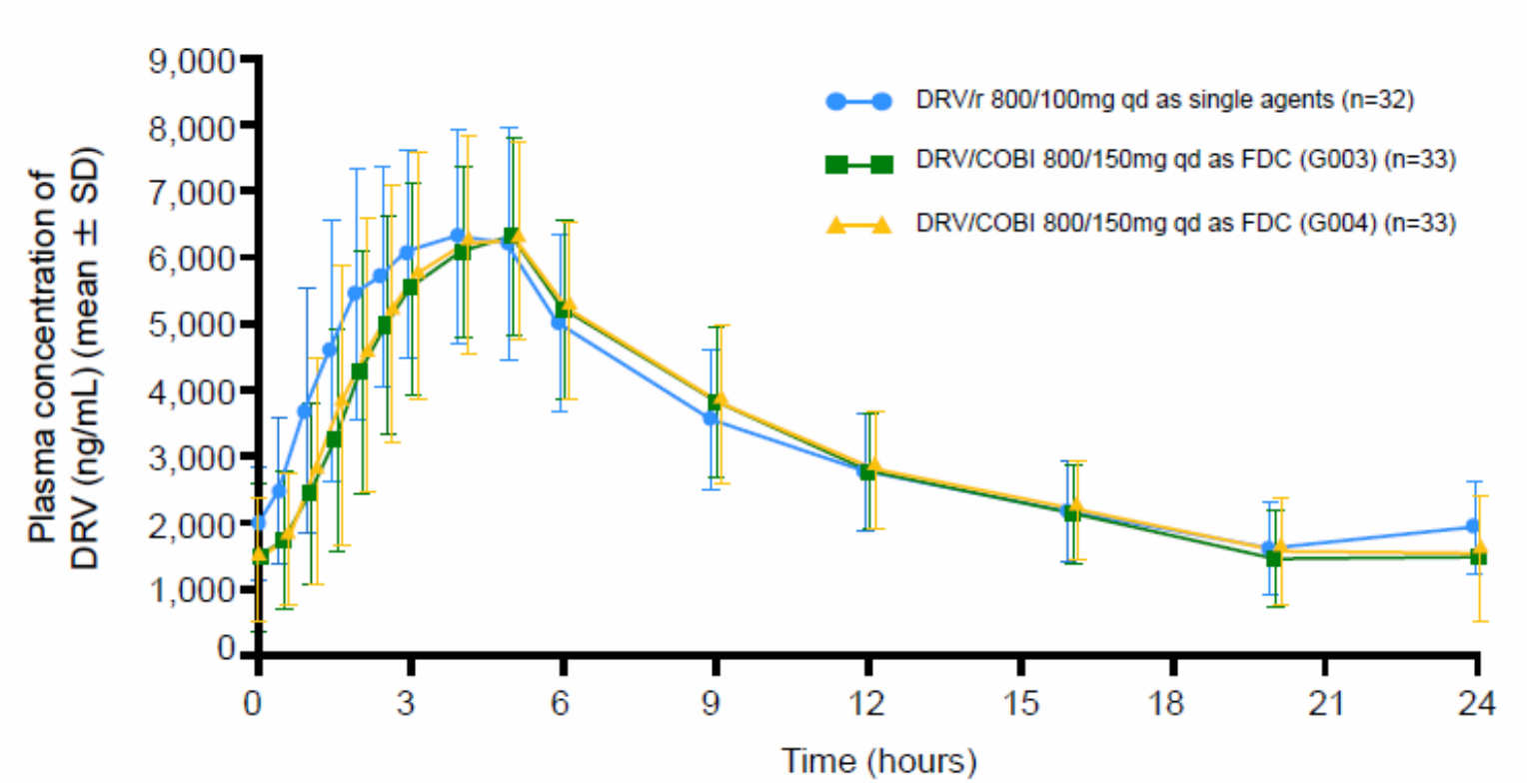



- EVG Ctrough **lower** with EVG/COBI + DRV vs EVG/COBI
- DRV Ctrough **lower** with EVG/COBI + DRV vs DRV/COBI

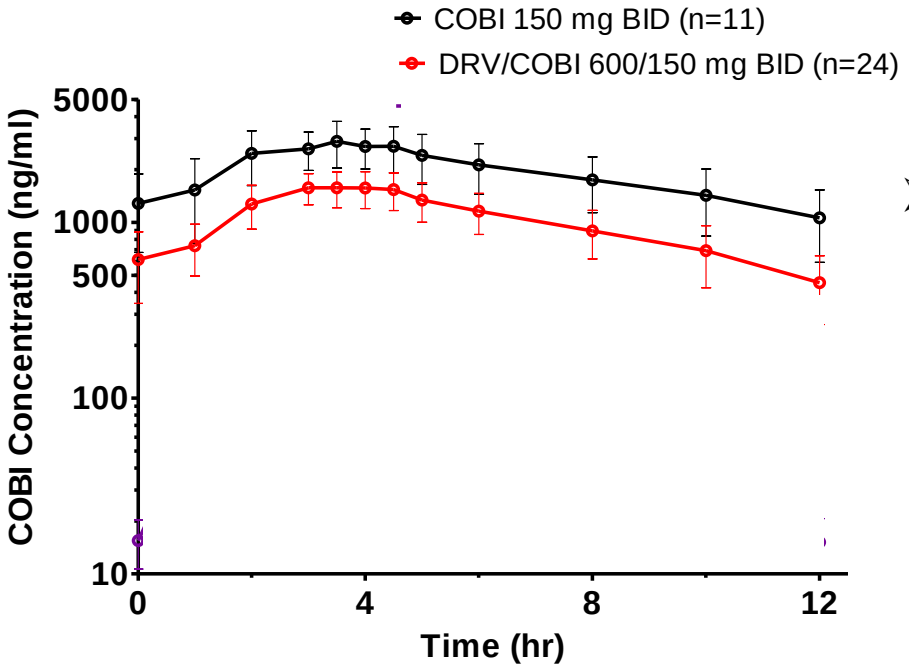
Ramanathan S et al IWCPHT April 2012 O-8

# PK of DRV 800 mg with Cobi 150 mg (FDC) or RTV 100 mg




*Kakuda T et al IWCHPT Barcelona , April 2012; IAS Kuala Lumpur, July 2013*

# COBI 150 mg BID PK Alone and with DRV




- COBI BID exposures ~-2-fold lower with DRV

| COBI BID PK | Alone (Mean CV N=11) | DRV BID (Mean CV N=24) |
|---|---|---|
| $AUC_{0-12}$ (ng.h/ml) | 23100 (33) | 12200 (26) |
| $C_{max}$ (ng/ml) | 2990 (28) | 1700 (21) |

Ramanathan S et al IWCPHT April 2012 O-8

# Management of Hepatitis C Virus/HIV Coinfection Among People Who Use Drugs in the Era of Direct-Acting Antiviral–Based Therapy

CID 2013:57 (Suppl 2) • S119

**Lynn E. Taylor,[1] Tracy Swan,[2] and Gail V. Matthews[3,4]**

[1]Department of Medicine, Brown University, Providence, Rhode Island; [2]Treatment Action Group, New York, New York; [3]Viral Hepatitis Clinical Research Program, The Kirby Institute, The University of New South Wales, and [4]Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney, Australia

Failure to perform drug–drug interaction studies that facilitate inclusion of high-prevalence patient groups in clinical trials perpetuates a vicious cycle; after approval, treatment is often withheld due to lack of information on safety, efficacy, and tolerability. Clinicians treating coinfected patients on stable OST with advanced liver disease—individuals most likely to benefit from successful HCV treatment—often do so without adequate data. To date, drug–drug interaction studies with ARVs and HCV PIs have been performed only in healthy volunteers. Drug levels may be different in HIV-infected and HCV/HIV-coinfected patients, especially those with hepatic impairment.