ARVs on an Empty Stomach: Food Interaction Studies in a resource Limited Setting

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Outline of Discussion

- Key Definitions
- Mechanisms for Food-Drug Interactions
- Recommendation for specific ARVs Drugs
- Selected Food-PK Studies in Ugandan Patients
- IT tools for clinical support: An IDI Example

Setting the Stage: Definitions

- ***An empty stomach:*** Taking an oral medication as one hour before eating or two hours after.

- ***Bioavailability (aspect of food-drug interactions):*** specific physical interference of drug absorption due to the presence or absence of food or specific food components in the gastrointestinal tract.

Reference: http://www.iuphar.org/pdf/hum_55.pdf

Mechanisms of Food (nutrients) & Drug Interactions

PROCESS	MECHANISM -Factors

Raiten DJ , Grinspoon Arpadi SS , Conference Report 10−13 April 2005

With or Without Food?

	With or Without Food	
SINGLE AGENT PREPS	**Abacavir (ABC)**	Food delays absorption (and ↓Cmax) but does not affect overall exposure
	Emtricitabine (FTC)	
	Lamividine (3TC)	Food ↓Cmax but this does not significanlty reduce overall absorption
	Zidovudine (AZT)	
	Nevirapine* (NVP)	
	Raltegravir (RAL)	Overall food effect uncertain but co-administration ↑ PK variability
	Maraviroc (MVC)	
	Fosamprenavir (FPV)	
	Lopinavir/ritonavir (LPV/r)	No significant
FDCs	**AZT/3TC**	
	ABC/3TC	
	ABC/3TC/AZT	

** includes prolonged release viramune ®*

	On Empty Stomach	
SINGLE AGENT PREPS	**Didanosine (DDI)**	EC Capsules-at least 2 hours before/after meals; Tablets-30 mins before meal
	Stavudine (D4T)	
	Efavirenz (EFV)	Administration with food may lead to increased drug levels and toxicities
FDCs	**Atripla**	Effavirenz effect as above with single agents prep. TDF exposure may be reduced by

Adapted from http://www.hiv-druginteractions.org/data/NewsItem/100_ARV_Food_Final.pdf

With or Without Food?

	With Food	
SINGLE AGENT PREPS	**Tenofovir (TDF)**	
	Etravirine (ETV)	Systemic exposure is reduced in fasting state
	Rilpivirine (RPV)	Must be taken with food
	Atazanavir (ATV)	
	Nelfinavir (NFV)	
	Ritonavir (RTV)	
	Tiprinavir (TPV)	
	Darunavir (DRV)	
	Saquinavir (SQV)	
FDCs	**Truvada (TDF/FC)**	
	Eviplera (TDF/FTC/RPV	Must be taken with food

Adapted from: http://www.hiv-druginteractions.org/data/NewsItem/100_ARV_Food_Final.pdf

Food Interaction Mechanisms for Specific ARVs/OI Drugs

- Chelation- Didanosine, Ciprofloxacin (milk)
- Poor Acid Stability- Isoniazid
- Increase drug solubility- Saquinavir

Food-PK Studies at the IDI Makerere, Uganda-1

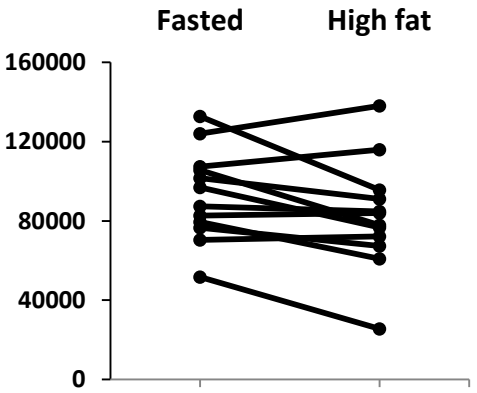
EFFECT OF FOOD ON THE STEADY-STATE PHARMACOKINETICS OF LOPINAVIR PLUS RITONAVIR WHEN ADMINISTERED AS A 200/50 MG FILM-COATED TABLET CO-FORMULATION IN HIV-INFECTED ADULTS

Patients - HIV-infected patients (n = 12) on LPV/r tablets 400 mg twice daily

Design: Cross-over, intensive pharmacokinetic study

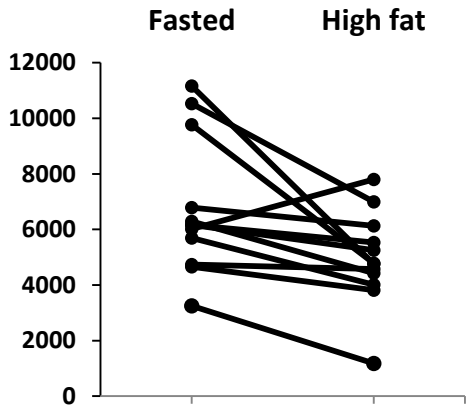
- Day 1 — Moderate fat Ugandan meal (20g fat)
- Day 8 — High fat western meal (36g)
- Day 15 — Fasted, reference

Lopinavir AUC (ng.h/mL)



High fat meal - 14% lower
GMR 0.86 [0.77 – 0.95]

Ritonavir AUC (ng.h/mL)



High fat meal - 29% lower
GMR 0.71 [0.61 – 0.84]

<u>Conclusion</u> Not clinically significant. Can be used without regard to meals

Lamorde M *et al*. J Acquir Immune Defic Syndr. 2012 Jul 1;60(3):295-8

Food-PK Studies at the IDI Makerere, Uganda-2

EFFECT OF FOOD ON THE STEADY-STATE PHARMACOKINETICS OF TENOFOVIR, EMTRICITABINE AND EFAVIRENZ WHEN ADMINISTERED AS A FIXED-DOSE COMBINATION TABLET IN HIV-1 INFECTED UGANDAN ADULTS

Single formulations

Tenofovir (TFV) disoproxil fumarate [with food]

Emtricitabine (FTC) [not affected by food]

Efavirenz (EFV) [without food – CNS toxicity)

Fixed-dose combination [without food]

n = 15

Day 1 — **Fasted (reference)**

Day 8 — **Fed (19g fat, local meal)**

Single formulations

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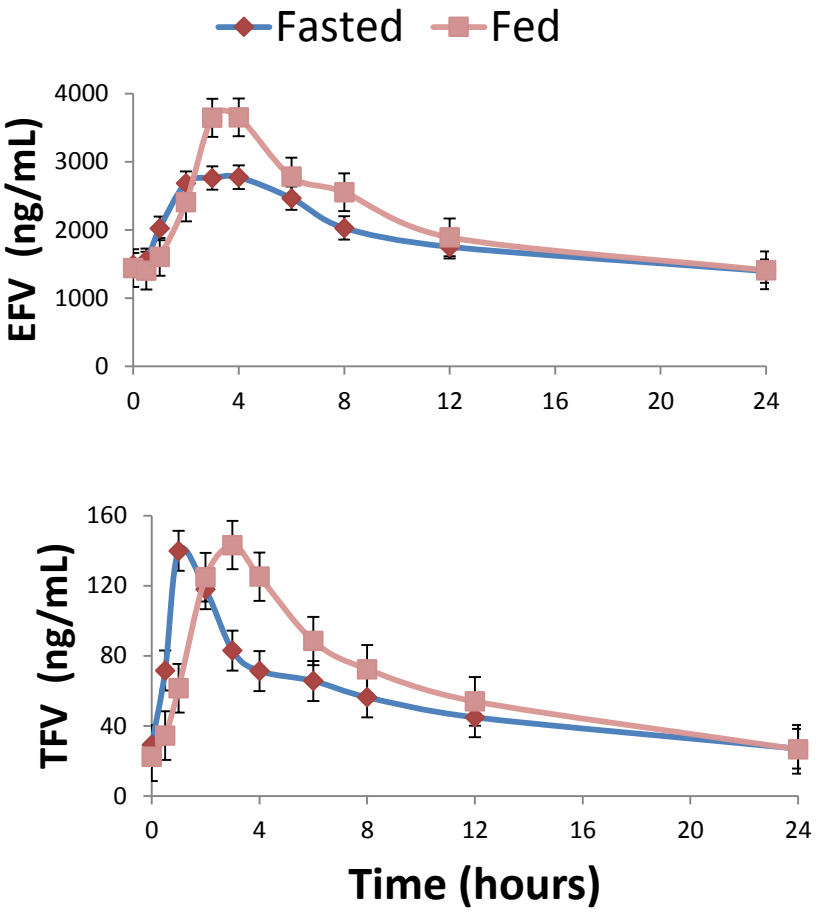
Parameter	TFV	FTC	EFV
C_{max}	1.04 (0.84 -1.27)	0.83* (0.76-0.92)	1.47* (1.24–1.75)
AUC_{0-24}	1.19* (1.10-1.29)	0.87* (0.78 – 0.97)	1.13* (1.03–1.23)
C_{24}	0.99 (0.82-1.19)	0.91 (0.73-1.14)	1.01 (0.91-1.11)

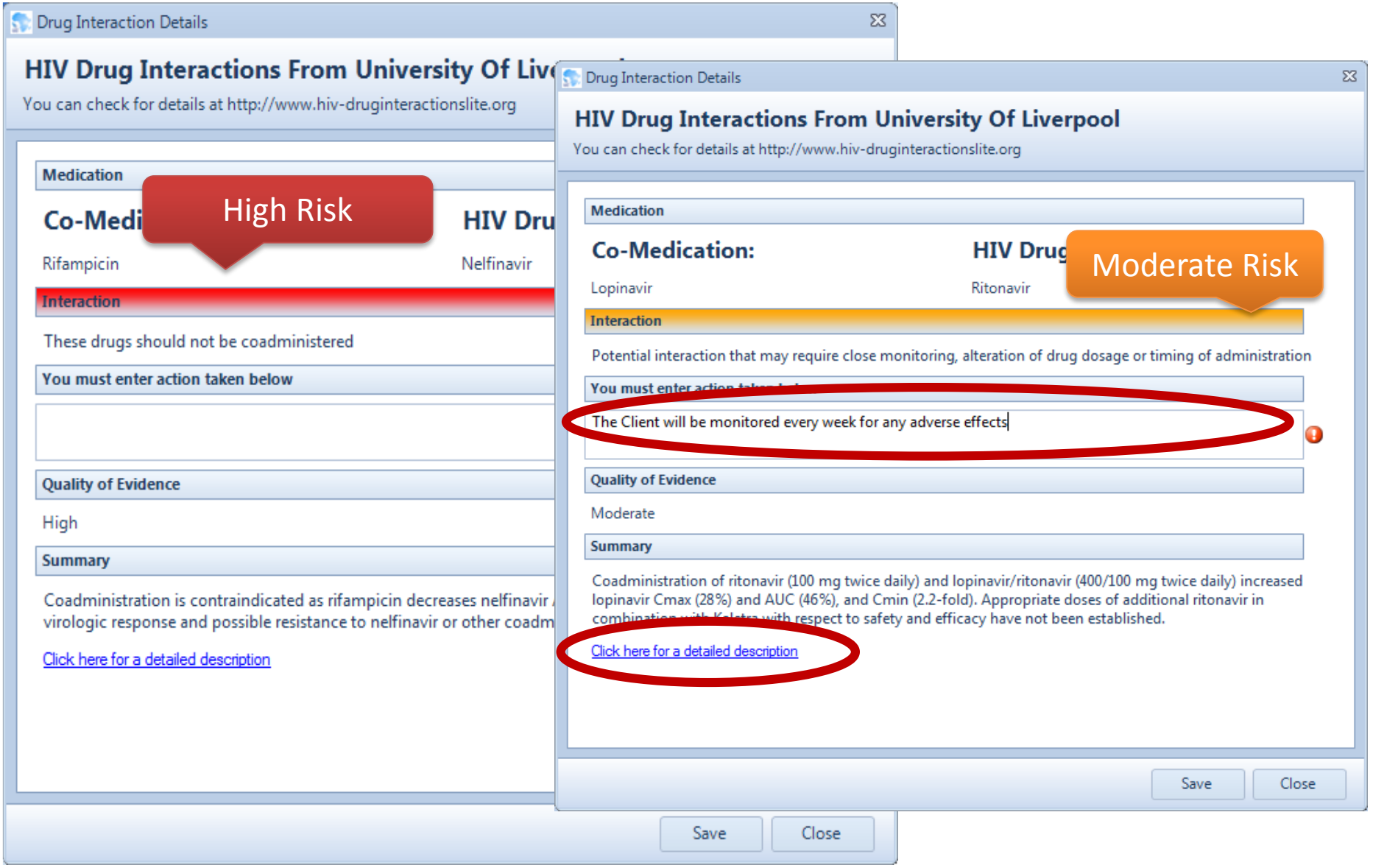


The same 2 patients had EFV concentrations above 4,000 ng/mL under both meal conditions at 12 hours post-dosing.

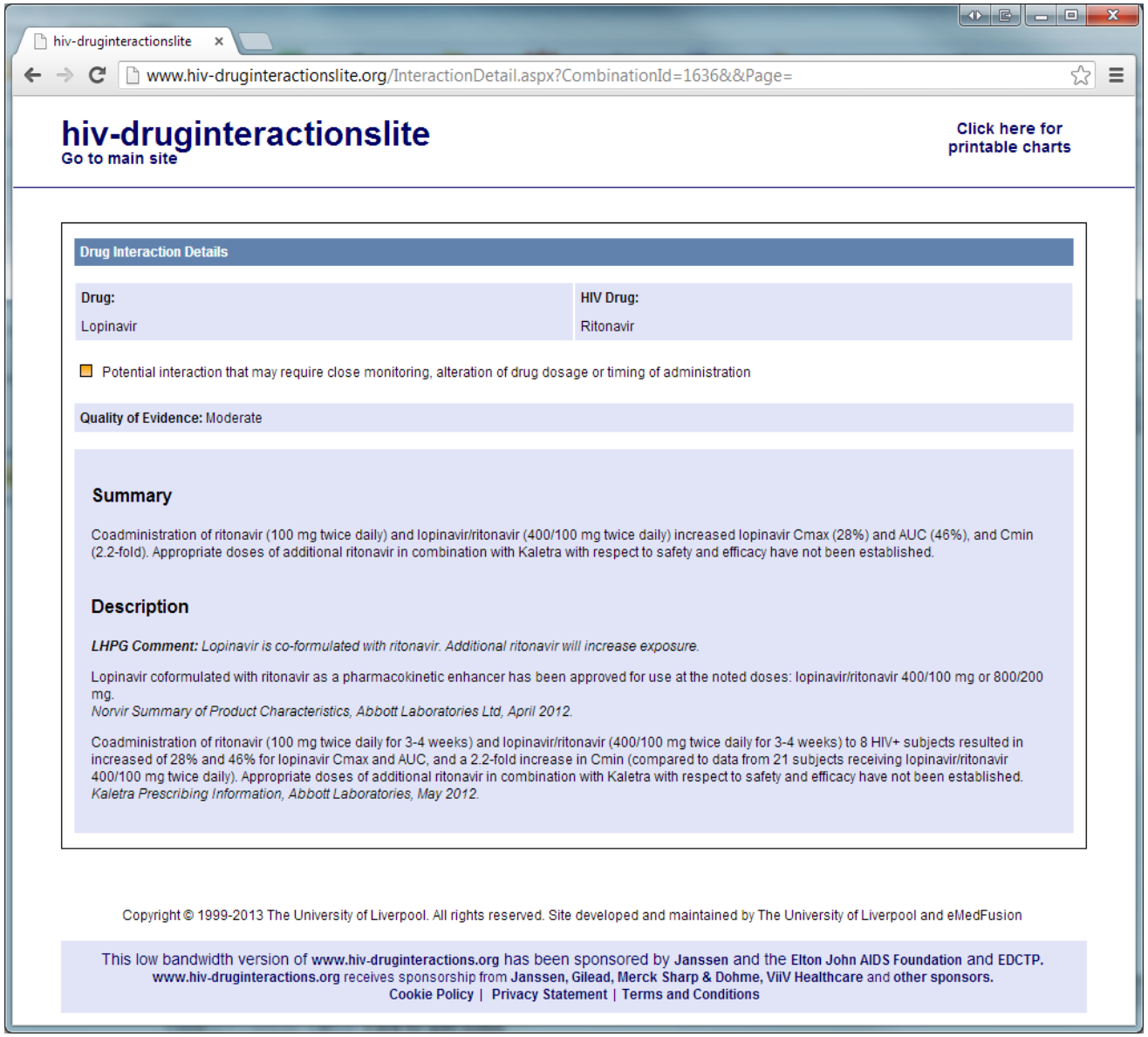
Conclusion Can be used without regard to meals among stable patients.

Lamorde M et al. AIDS Res Treat. 2012;2012:105980

Severity of Interaction color coded



A Link to the Liverpool Web Page



Links to the Liverpool University HIV-drug charts for updates and detailed information about Drug Interactions.

Acknowledgements

- Dr. Mohammed Lamorde, PhD
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