

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

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)	
	Lamivudine (3TC)	Food ↓Cmax but this does not significantly 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)	<u>Must</u> be taken with food
	Atazanavir (ATV)	
	Nelfinavir (NFV)	
	Ritonavir (RTV)	
	Tipranavir (TPV)	
	Darunavir (DRV)	
	Saquinavir (SQV)	
FDCs	Truvada (TDF/FC)	
	Eviplera (TDF/FTC/RPV)	<u>Must</u> 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

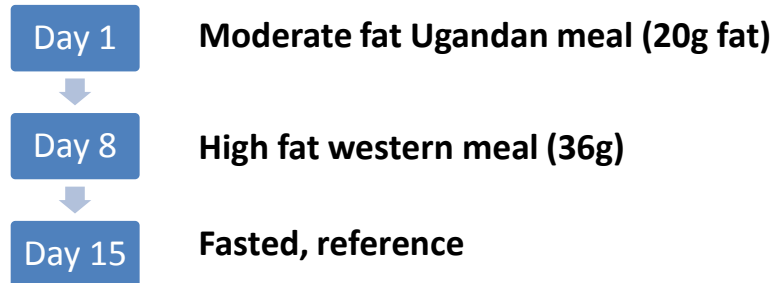
- Chelation- Didanosine, Ciprofloxacin (milk)
- Poor Acid Stability- Isoniazid
- Increase drug solubility- Saquinavir

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

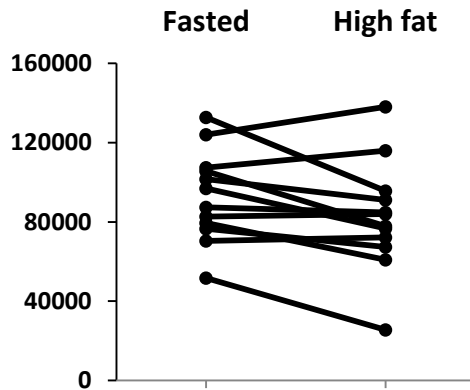
**EFFECT OF FOOD ON THE STEADY-STATE PHARMACOKINETICS
OF LOPINAVIR PLUS RITONAVIR WHEN ADMINISTERED AS A
200/50 MG FILM-COATED TABLET CO-FORMULATION IN HIV-
INFECTED ADULTS**

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

Design: Cross-over, intensive pharmacokinetic study

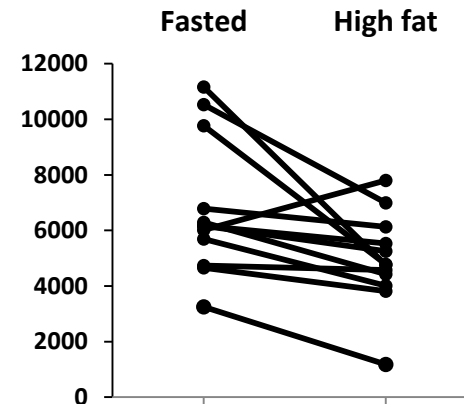


Lopinavir AUC (ng.h/mL)



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]

Conclusion Not clinically significant. Can be used without regard to meals

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**

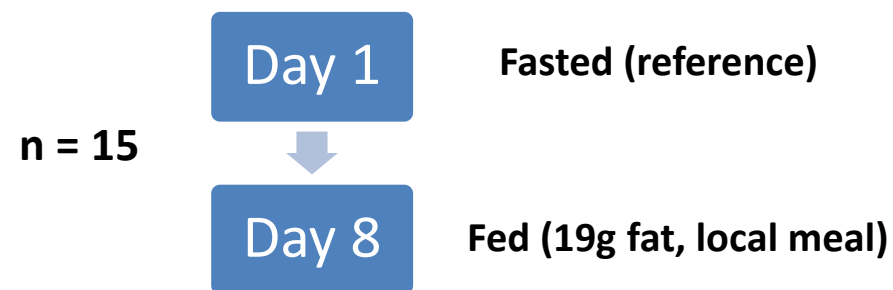
Single formulations

Tenofovir (TFV) disoproxil fumarate [**with food**]

Emtricitabine (FTC) [**not affected by food**]

Efavirenz (EFV) [**without food – CNS toxicity**]

Fixed-dose combination [**without food**]



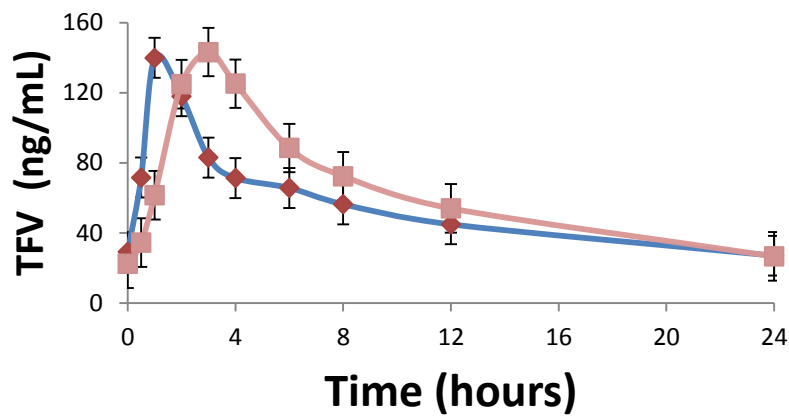
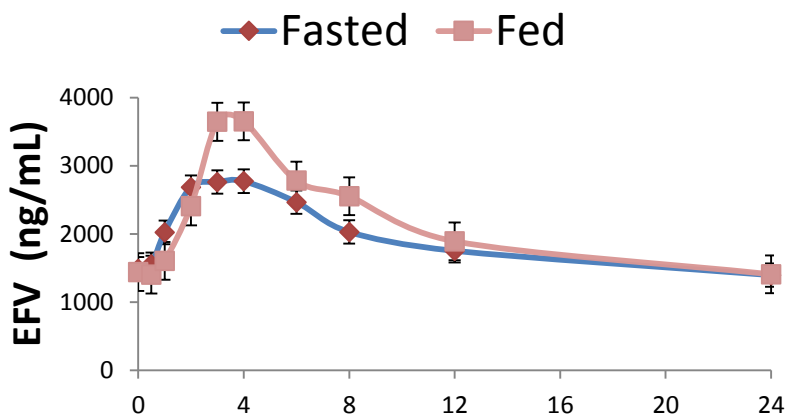
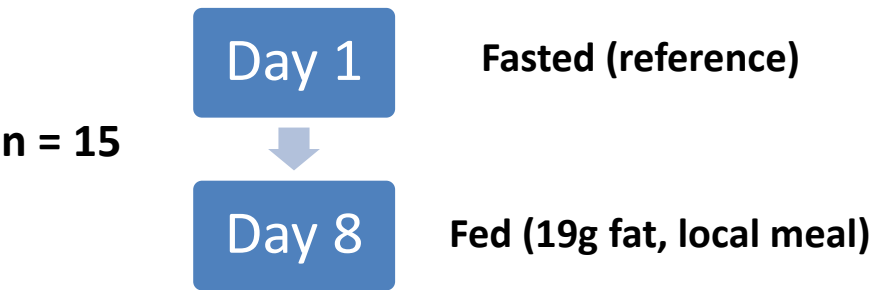
Single formulations

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Fixed-dose combination [without food]



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.

Severity of Interaction color coded

Drug Interaction Details

HIV Drug Interactions From University Of Liverpool

You can check for details at <http://www.hiv-druginteractionslite.org>

Medication

Co-Medication: Rifampicin **HIV Drug:** Nelfinavir

Interaction **High Risk**

These drugs should not be coadministered

You must enter action taken below

Quality of Evidence

High

Summary

Coadministration is contraindicated as rifampicin decreases nelfinavir virologic response and possible resistance to nelfinavir or other coadministered drugs.

[Click here for a detailed description](#)

Drug Interaction Details

HIV Drug Interactions From University Of Liverpool

You can check for details at <http://www.hiv-druginteractionslite.org>

Medication

Co-Medication: Lopinavir **HIV Drug:** Ritonavir

Interaction **Moderate Risk**

Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration

You must enter action taken below

The Client will be monitored every week for any adverse effects

Quality of Evidence

Moderate

Summary

Coadministration of ritonavir (100 mg twice daily) and lopinavir/ritonavir (400/100 mg twice daily) increased lopinavir C_{max} (28%) and AUC (46%), and C_{min} (2.2-fold). Appropriate doses of additional ritonavir in combination with Kaletra with respect to safety and efficacy have not been established.

[Click here for a detailed description](#)

Save Close

A Link to the Liverpool Web Page

The screenshot shows a web browser window with the URL www.hiv-druginteractionslite.org/InteractionDetail.aspx?CombinationId=1636&&Page=. The page title is "hiv-druginteractionslite" with a sub-link "Go to main site". A link "Click here for printable charts" is visible in the top right. The main content area is titled "Drug Interaction Details" and contains the following information:

Drug: Lopinavir	HIV Drug: Ritonavir
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Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration

Quality of Evidence: Moderate

Summary

Coadministration of ritonavir (100 mg twice daily) and lopinavir/ritonavir (400/100 mg twice daily) increased lopinavir C_{max} (28%) and AUC (46%), and C_{min} (2.2-fold). Appropriate doses of additional ritonavir in combination with Kaletra with respect to safety and efficacy have not been established.

Description

LHPG Comment: Lopinavir is co-formulated with ritonavir. Additional ritonavir will increase exposure.

Lopinavir coformulated with ritonavir as a pharmacokinetic enhancer has been approved for use at the noted doses: lopinavir/ritonavir 400/100 mg or 800/200 mg.
Norvir Summary of Product Characteristics, Abbott Laboratories Ltd, April 2012.

Coadministration of ritonavir (100 mg twice daily for 3-4 weeks) and lopinavir/ritonavir (400/100 mg twice daily for 3-4 weeks) to 8 HIV+ subjects resulted in increased of 28% and 46% for lopinavir C_{max} and AUC, and a 2.2-fold increase in C_{min} (compared to data from 21 subjects receiving lopinavir/ritonavir 400/100 mg twice daily). Appropriate doses of additional ritonavir in combination with Kaletra with respect to safety and efficacy have not been established.
Kaletra Prescribing Information, Abbott Laboratories, May 2012.

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

Acknowledgements

- Dr. Mohammed Lamorde, PhD
- University of Liverpool
- IDI Clinic Management