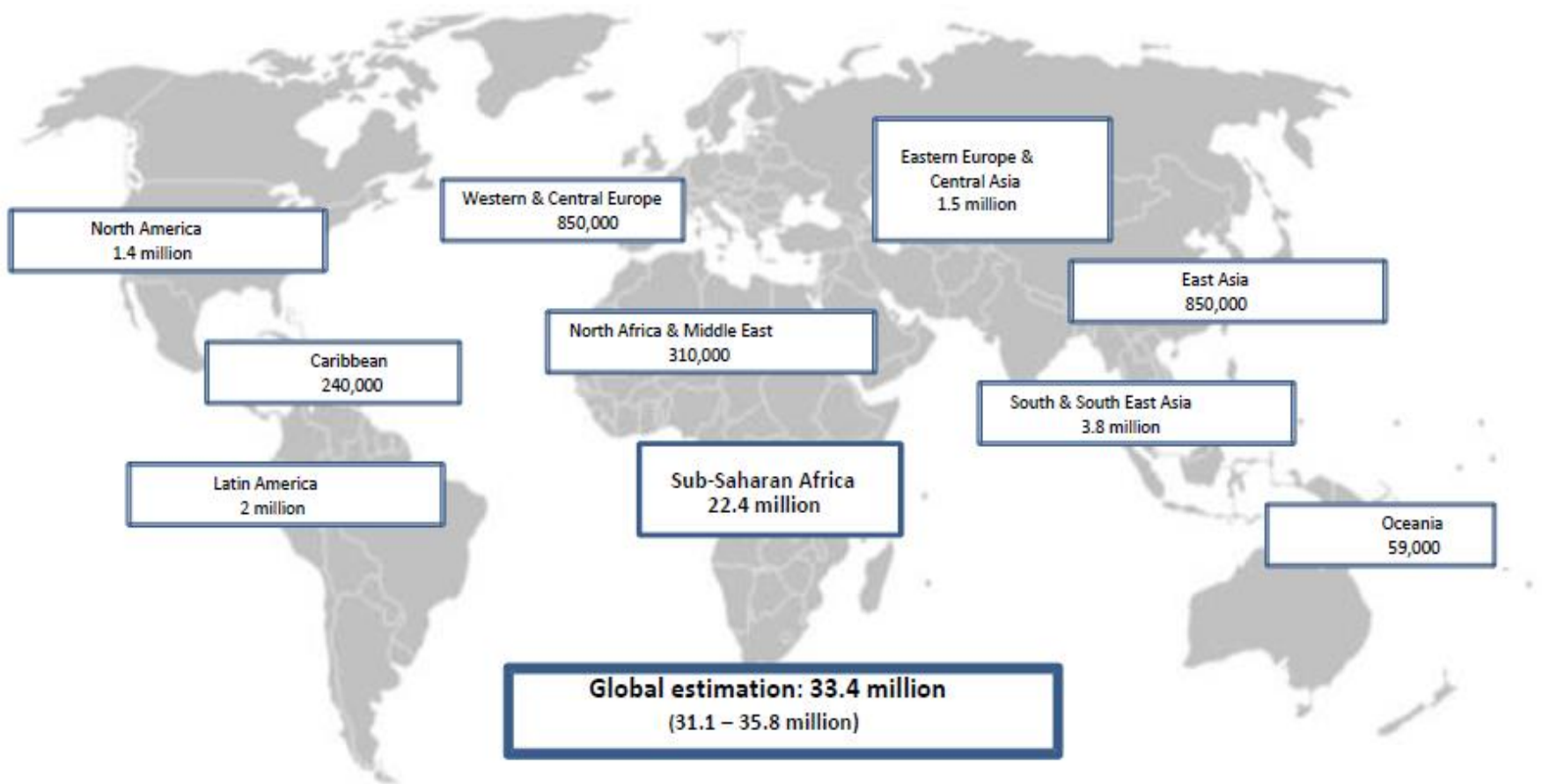
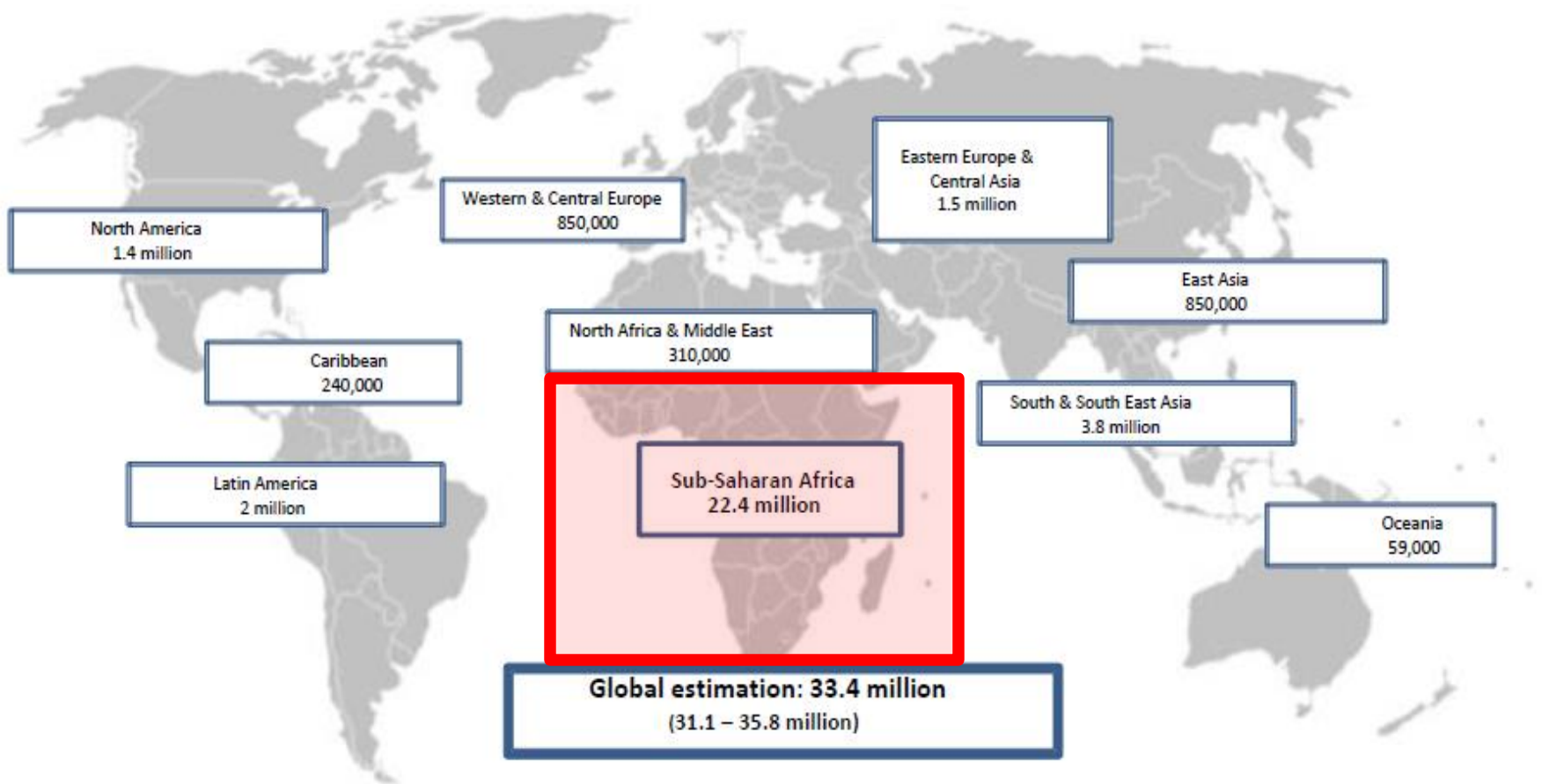


Role of Clinical Pharmacology in Developing Countries

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"Africa (orthographic projection)" by Martin23230 - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - [http://commons.wikimedia.org/wiki/File:Africa_\(orthographic_projection\).svg#mediaviewer/File:Africa_\(orthographic_projection\).svg](http://commons.wikimedia.org/wiki/File:Africa_(orthographic_projection).svg#mediaviewer/File:Africa_(orthographic_projection).svg)



<http://atlas Mara.com/>



Uganda

1985: HIV identified in “Slim” samples

1990: Adult HIV prevalence 25%

2001: 1 million deaths (cumulative)

2001: AU declares state of emergency



2003 – First ART guidelines released

Public health approach

2013: 1,600,000 People living with HIV

2013: Adult prevalence 7.4%

2013: 40% receiving ART

2013: 60,000 deaths

2013: 10,000 vertical transmissions

Initial Regimen

N(t)RTI	NNRTI
d4T + 3TC	EFV or NVP
TDF + 3TC (FTC), or AZT + 3TC	



2013: TDF + 3TC (or FTC) + EFV *

Preferred for adults (women, pregnancy, BF, TB co-infection)

Second-line Regimen

N(t)RTI	PI
AZT + ddI	ATV/r or LPV/r
TDF + 3TC, or AZT + 3TC	



2013: If TDF + 3TC used in first line, switch to AZT+3TC, and vice versa

Ethnic Factors and Impact on Drug Therapy

Intrinsic factors

- Gender
- Age
- Race
- Polymorphism
- Height
- Body weight
- Diseases
- Food habits

Extrinsic factors

- Culture
- Socioeconomic factors
- Medical practice
- Drug compliance

Ethnic Factors and Impact on Drug Therapy

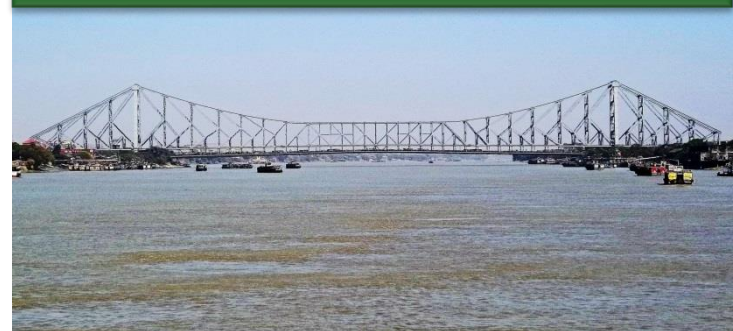
Intrinsic factors

- Gender
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- Food habits

Extrinsic factors

- Culture
- Socioeconomic factors
- Medical practice
- Drug compliance

BRIDGING STUDIES



Women and HIV



Non-pregnant

- Contraception plus ART?



Pregnancy/PMTCT

- Are my ARVs safe in pregnancy?
- Dose adjustments in pregnancy?



Post-partum/Breastfeeding

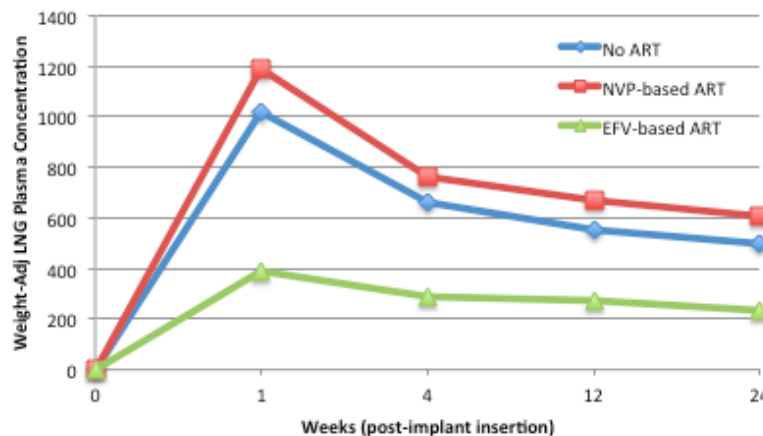
- Should I stop ART?



Contraception plus ART?

Levonorgestrel Implant (Jadelle)

K Scarsi et al. J Int
AIDS Soc 2014



**Levonorgestrel levels
reduced 40 - 54% with
efavirenz ART**

Etonorgestrel Implant (Implanon)

Vieira C, et al.
JAIDS 2014

**Etonogestrel AUC
reduced 63% with
efavirenz ART**

**Etonogestrel AUC
increased 52% with
lopinavir/r ART**



Efavirenz and teratogenicity

EFAVIRENZ & TERATOGENICITY Nathan Ford et al, AIDS 2011

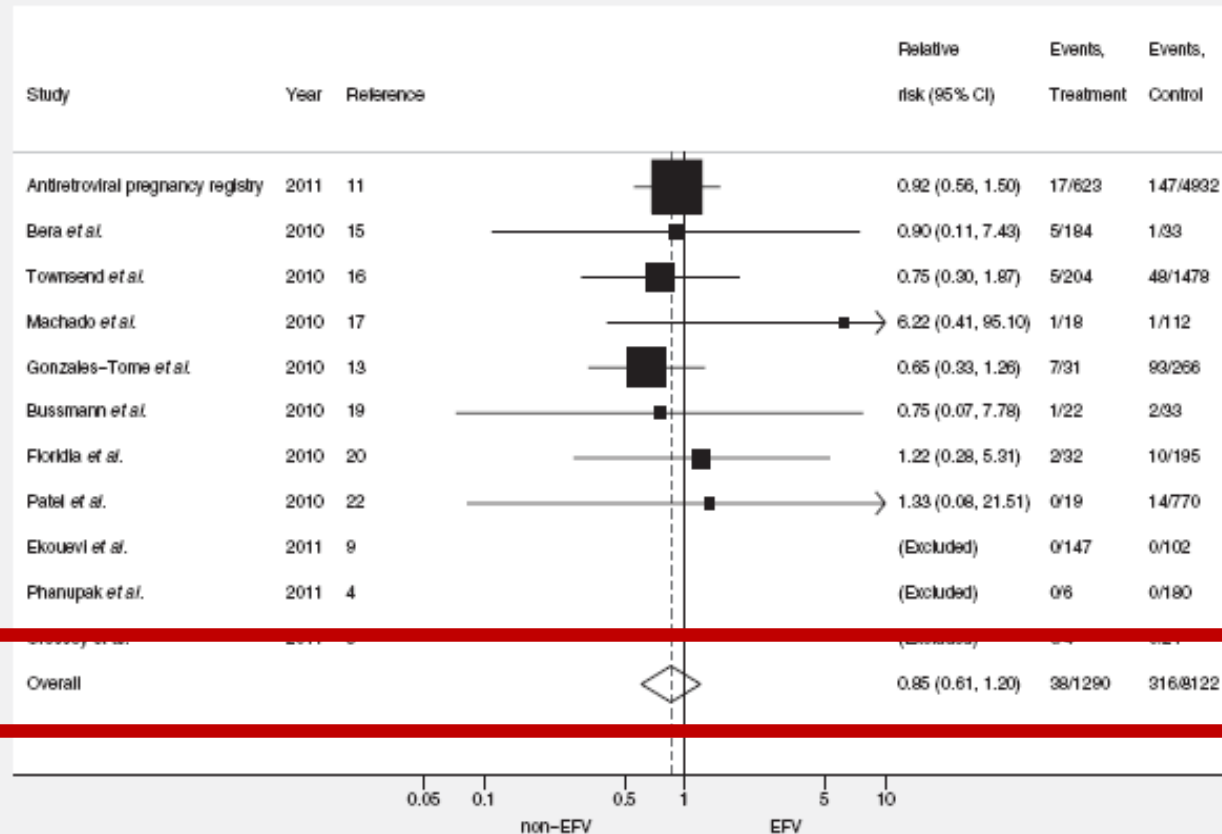
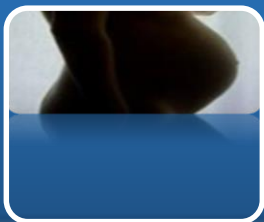


Fig. 1. Relative risk of birth defects on efavirenz vs. nonefavirenz regimens. CI, confidence interval; EFV, efavirenz.



Intrapartum

Are dose adjustments necessary?

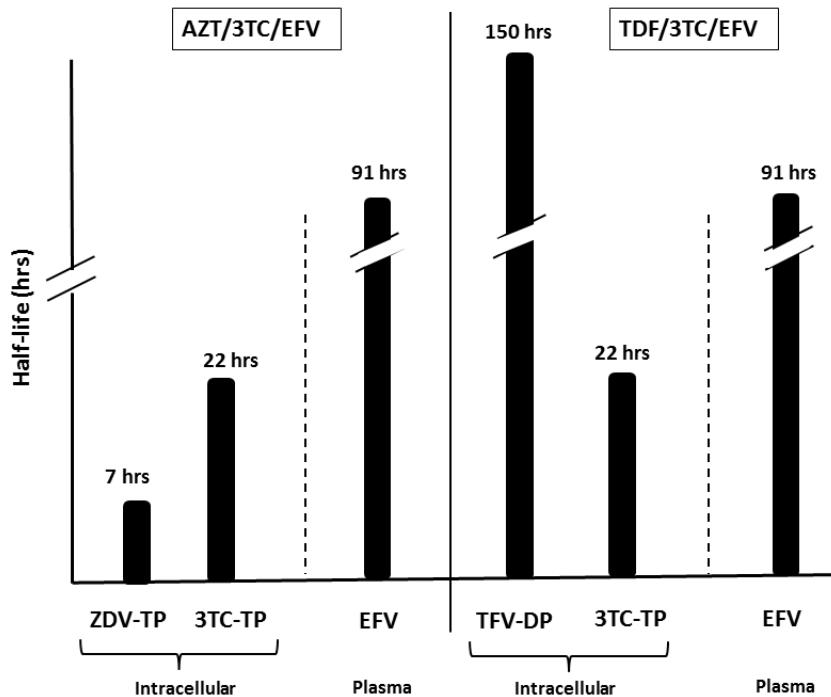
Antiretroviral drug	T3 reduction	Dose adjustment?	Reference
EFV	NA	No	Hill et al. AIDS 2014
NVP	20% (AUC)	No	Lamorde et al. JAIDS 2012
LPV	NA	No*	Cressey et al. JAC 2015
ATZ	34% (AUC)	No ⁺	Colbers et al. Antivir Ther 2014

* Increased doses may be needed for >100kg, adherence problems, prior use of LPV/r
+ Some subjects may require increase of ATZ/r 400/100 mg.



Post-partum

- Interruption of ART for PMTCT
 - Programmatic (Option B)
 - Non-adherence/loss to follow-up in Option B+



Stopping strategy to minimise risk of resistance:

AZT/3TC/EFV – NRTI tail for 2 weeks

TDF/3TC/EFV – No data to inform recommendation

Lamorde et al. AIDS 2014; 28



Post-partum/Breastfeeding

- Breastfeeding recommended for first 6 months
- Scarce data on TDF/3TC/EFV in breastmilk
- Ongoing studies
 - Validate breast milk assays, characterize pharmacokinetics and HIV virology in maternal blood, breast compartment and infant blood

Diseases



Tuberculosis



Malaria



Neglected Tropical
Diseases



Tuberculosis



PMTCT

IYCF

PAED

ADULT

The Integrated National Guidelines

on

Antiretroviral Therapy

Prevention of Mother to Child
Transmission of HIV

Infant & Young Child Feeding

2012

First-line ART

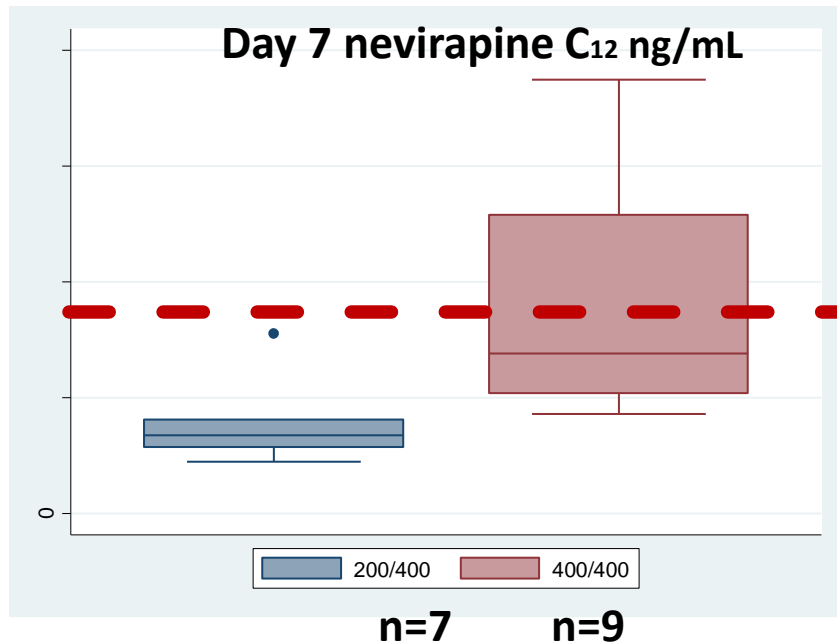
- **Recommends efavirenz-based ART + rifampicin**
- Avoid nevirapine + rifampicin

Second-line ART

- Consider rifabutin + PI-based ART
- Avoid rifampicin + PIs



Tuberculosis



Lamorde *et al.* JAC 2011

First-line ART

- Recommends efavirenz-based ART + rifampicin
- **Avoid nevirapine + rifampicin**

CARINEMO RCT for TB/HIV Co-infection
Week 48 VL <50 copies/ml

- **NVP (no-lead in) 60%**
- **EFV 68.4%**

Bonnet *et al.* Lancet ID 2013

2013 CDC Guidelines: efavirenz is preferred but if nevirapine must be used, avoid lead-in dosing



Tuberculosis



THE REPUBLIC OF UGANDA

PMTCT

IYCF

PAED

ADULT

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First-line ART

- Recommends efavirenz-based ART + rifampicin
- Avoid nevirapine + rifampicin

Second-line ART

- Consider rifabutin + PI- ART

Rifabutin 150 mg X 3 weekly or 150 mg daily?

Low rifabutin levels reported with 150 mg X 3 weekly
Boulanger et al, CID, 2009; Ramachandran IJTLD, 2013

CDC suggests 150 mg once daily



Malaria

Co-administered drug	Effect on artemether-lumefantrine exposure		
	artemether	DHA	lumefantrine
rifampicin ¹	89% ↓	85% ↓	68% ↓
nevirapine ²	72% ↓	37% ↓	21% ↓
efavirenz ²	77% ↓	75% ↓	55% ↓
LPV/r ³	43% ↓	Not affected	386 ↑

Simulations suggest **artemether-lumefantrine** dose increases required⁴

- **250% dose increase** with efavirenz
- **75% dose increase** with nevirapine

¹Lamorde et al AIDS 2013 ²Byakika-Kibwika et al JAC 2012 ³Byakika-Kibwika JAC 2012 ⁴Hoglund BJCP 2014

NTD

Neglected Tropical Diseases

		Drugs used in Neglected Tropical Diseases																	
		Atazanavir	Darunavir	Fosamprenavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir	Zidovudine	Abacavir	Didanosine	Emtricitabine	Lamivudine	Raltegravir	Rilpivirine	Stavudine	Tenofovir
Antiretrovirals	PIs	ATV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		DRV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		FPV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		IDV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		LPV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		NFV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		RTV	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		SQV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		TPV/r	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	NNRTIs	EFV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		ETV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		NVP	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		Ril	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	NRTIs	ABC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		ddI	4	4	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		d4T	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		FTC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		3TC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		TDF	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		ZDV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Entry-I	MVC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Int-I	RAL	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

Interactions between ART and NTD drugs

Evidence for all recommendations: low quality or very low quality

Seden et al. AIDS 2013

3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; d4T, stavudine; ddI, didanosine; DRV/r, darunavir/ritonavir; EFV, efavirenz; Entry-I, entry inhibitor; ETV, etravirine; FPV/r, fosamprenavir/ritonavir; FTC, emtricitabine; IDV, indinavir; Int-I, integrase inhibitor; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NFV, nelfinavir; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PIs, protease inhibitors; RAL, raltegravir; Ril, rilpivirine; RTV, ritonavir; SQV/r, saquinavir/ritonavir; TDF, tenofovir; TPV/r, tipranavir/ritonavir; ZDV, zidovudine. ● No clinically significant interaction expected. ● Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration. ● These drugs should not be coadministered. Quality of Evidence [12]. 1. High, 2. Moderate, 3. Low, 4. Very Low.

Food habits & Culture



Food

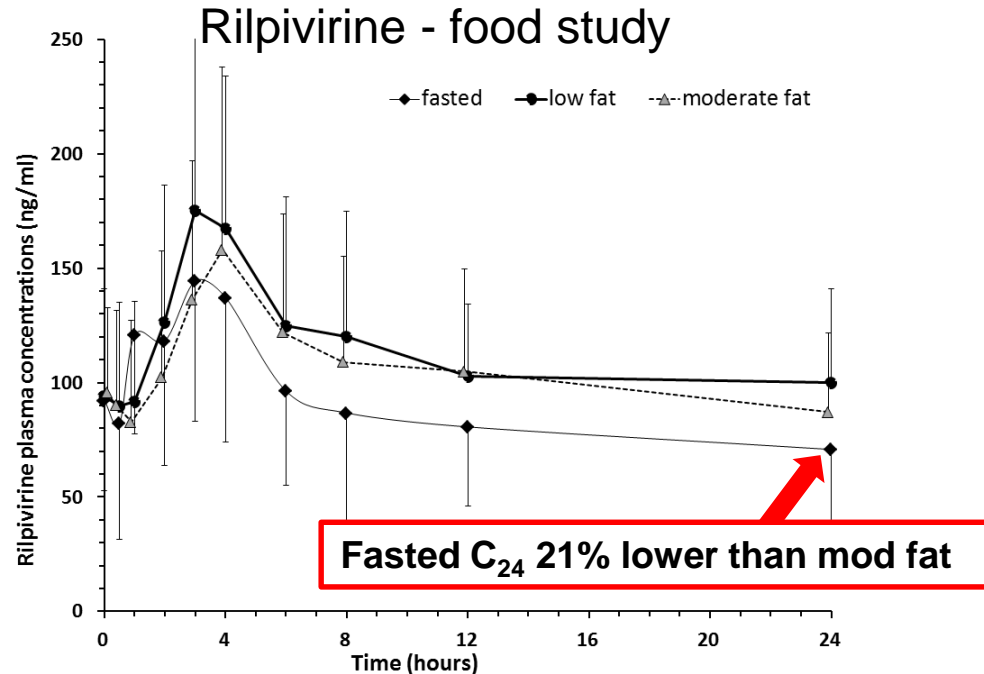


Traditional medicine



Food drug interactions

- Culture of taking drugs with food
- Reality of lack of food
- Study design issues
 - Single dose versus steady state
 - Simulation of a missed meal (for drugs requiring food)



Fasted AUC_{0-24} 16% lower than mod fat

Lamorde et al. JAC 2015 (in press)



Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda

Mohammed Lamorde^{a,b,*}, John R.S. Tabuti^c, Celestino Obua^d, Collins Kukunda-Byobona^e, Hindam Lanyero^d, Pauline Byakika-Kibwika^{a,b,f}, Godfrey S. Bbosa^d, Aloysius Lubega^d, Jasper Ogwal-Okeng^d, Mairin Ryan^b, Paul J. Waako^d, Concepta Merry^{a,b,f,g}



- 103 plant species were reported by 25 traditional medicine practitioners
- Treatments were oral decoctions containing several plants
- 1 in 5 traditional medicine practitioners treated children

Medical Practice



Drug Quality

- Hosseinipour et al. AIDS 2007
- Byakika-Kibwika et al. JAC 2008
- Byakika-Tusiime et al. PLoS One 2009



TDM

- L'Homme et al CID 2008
- Lamorde et al. BMC 2014

Study participants

Investigators and study teams

Ceppie Merry
David Back
Elly Katabira
Harriet Mayanja-Kizza
Harriet Tikakabikoba
John Tabuti
Jonathan Mayito
Jonson Magoola
Jamila Nakku
Lillian Nabukeera
Mairin Ryan
Marta Boffito
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Niklas Lindegardh
Paul Waako
Pauline Byakika-Kibwika
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Yuka Manabe
AIDS Treatment Information Centre
IDI Research Department and Clinic staff

MU-JHU Core Lab staff

Collaborating Institutions

Haughton Institute; Dublin and Trinity College Dublin
University of Liverpool
Northwestern University, Chicago
University of Nebraska
Mahidol University Thailand
University of Amsterdam
University of Turin
University of Nijmegen

Capacity building

Infectious Diseases Network for Treatment and
Research in Africa (INTERACT)

Funding

European and Developing Countries Clinical Trials
Partnership
Health Research Board, Ireland
INTERACT
Janssen Pharmaceutica
Gilead Foundation
University of Liverpool
HIV Research Trust



Thank you