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Pharmacokinetics and Therapeutic Drug Monitoring (TDM) of ARV

Jasper van der Lugt, MD
HIV-NAT, the Thai Red Cross
AIDS research Center,
Bangkok, Thailand



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Introduction

- General principles of Pharmacokinetics (PK)
- General remarks about PK in Antiretroviral Therapy (ART)
- Dose reduction in South East Asia
- Drug interaction
- TDM as a clinical tool
- Tour through our PK laboratory



General PK principles

Introduction

- Absorption, Distribution, Metabolism, Elimination (ADME)
- C_{min} , C_{max} , AUC, $T_{1/2}$
- Steady state



General PK Principles

What is PK

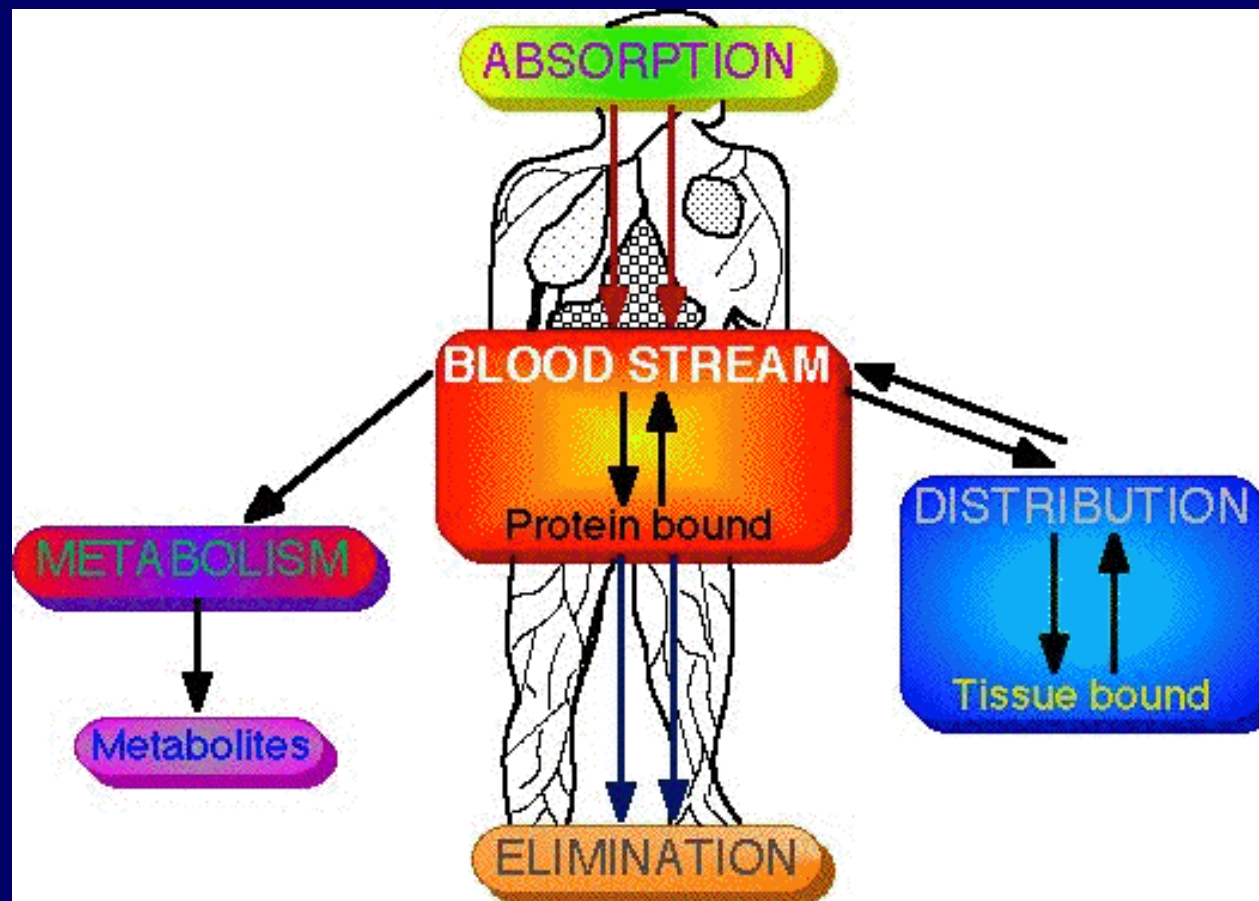
- Definition:

”PK is the mathematics of the time course of Absorption, Distribution, Metabolism, and Excretion (ADME) of drugs in the body and the relationship of these processes to the intensity and time course of therapeutic and toxicologic effect of the drug”

- Why study PK
- What are pharmacodynamics

General PK Principles

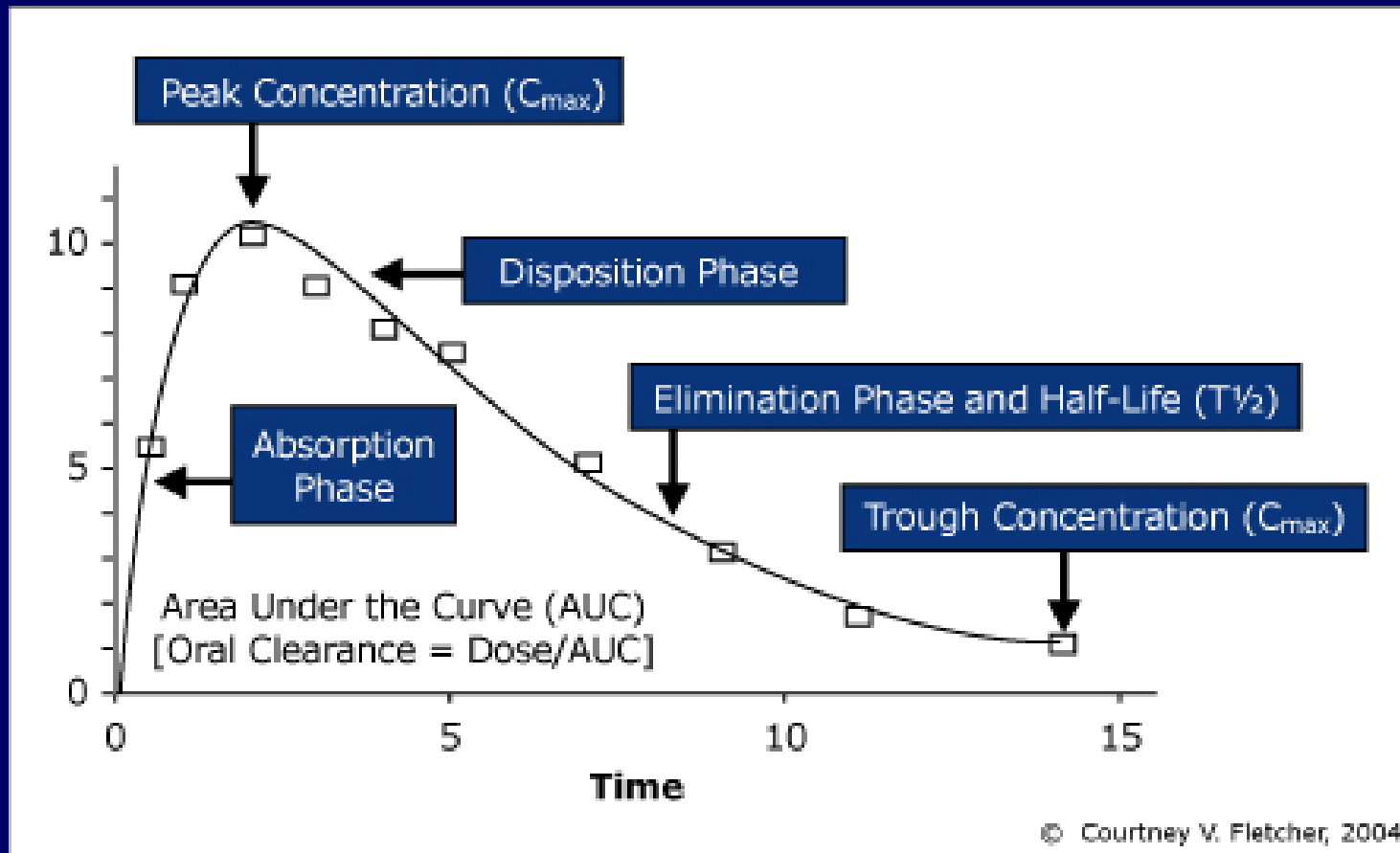
ADME





General PK Principles

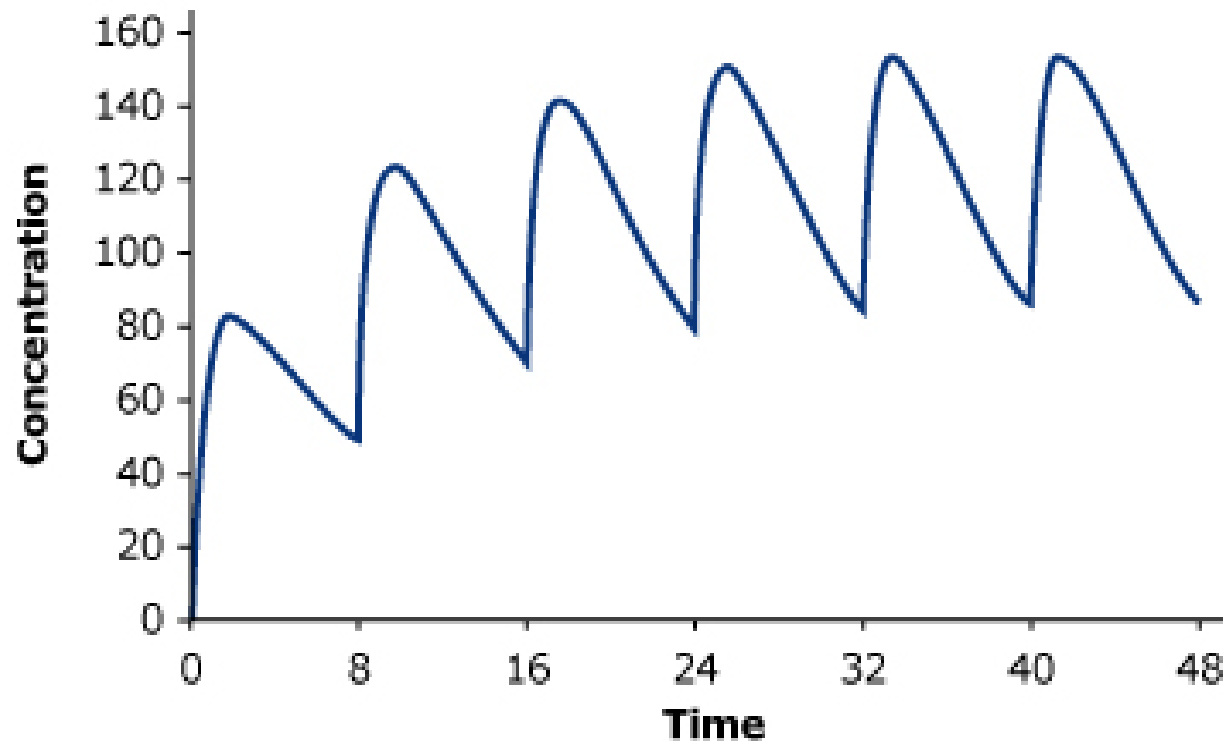
commonly used parameters





General principles

Steady state

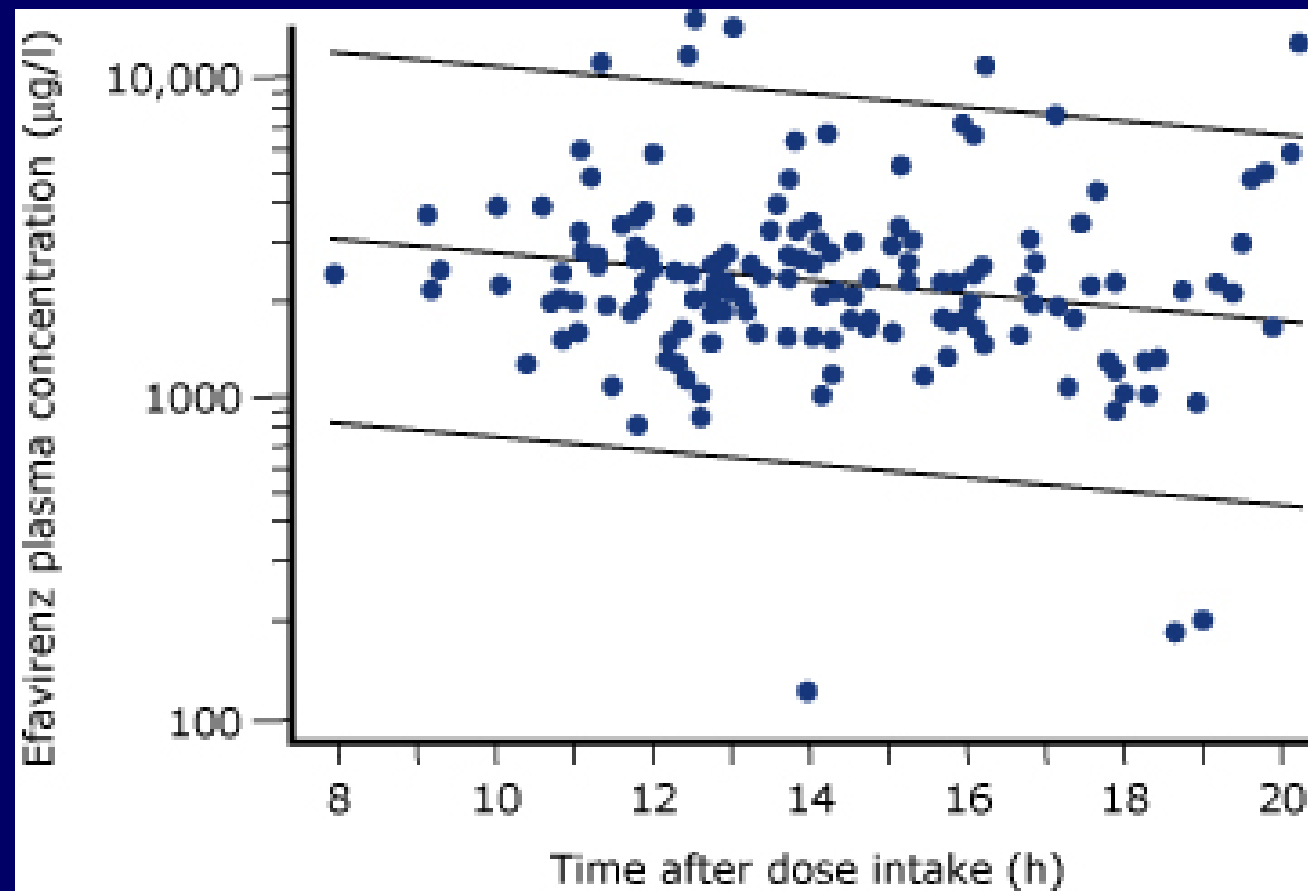




General Remarks

ARV PK

- Strong relation between dose effect
- Sensitive for interaction
- NRTIs can not be measured extra-cellular
- High interpatient variability in PK profiles



Reproduced with permission from Marzolini et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15:71-75. Copyright Lippincott Williams and Wilkins, 2001.^[43]



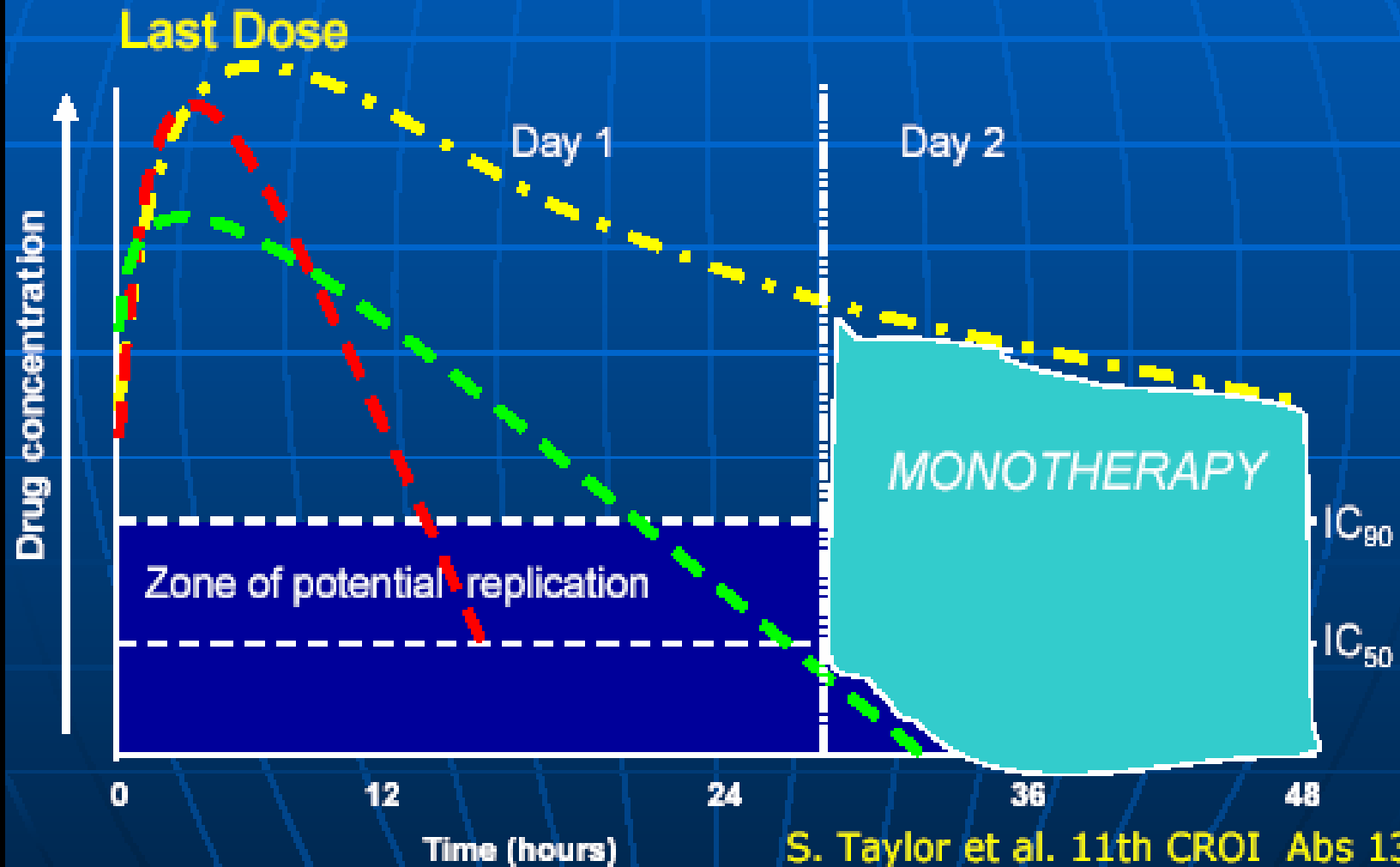
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Effects on some PK parameters

Stopping drugs with different half lives





Absorbtion

Intake with/or without food

- ddl, indinavir: without food
- saquinavir (fat), nelfinavir, lopinavir (Meltrex tablets not), atazanavir, tipranavir, darunavir: with food
- avoid high fat meal: amprenavir, efavirenz
- sometimes food improves tolerability (zidovudine, ritonavir, indinavir/ritonavir)



Distribution

- Protein binding:
 - NRTIs (except ABC): < 25%
 - ABC, NVP, IDV: 50-60%
 - APV: 90%
 - EFV, other PIs: >98%
- Most HIV drugs bind to alpha-1 acid glycoprotein or albumin; protein levels may vary between and within patients



PK trials done in South East Asia

Table 2. Pharmacokinetic parameters of saquinavir 1600 mg once daily and ritonavir 100 mg once daily, median [range]

	Saquinavir				Ritonavir			
	study 1	study 2	study 3	<i>P</i> value	study 1	study 2	study 3	<i>P</i> value
AUC (mg·h/L)	17.88 [8.92–63.16]	67.05 [46.56–92.00]	42.42 [10.53–105.07]	<0.001	6.97 [4.88–19.56]	11.61 [3.22–14.42]	11.21 [4.60–21.74]	0.05
CV ^a (%)	66	25	57		48	40	39	
<i>C</i> _{max} (mg/L)	2.84 [0.98–9.21]	7.55 [5.37–9.92]	5.68 [1.31–12.36]	0.002	0.95 [0.39–2.27]	1.22 [0.53–2.51]	1.38 [0.57–3.08]	0.04
CV	64	21	57		49	52	47	
<i>C</i> _{min} (mg/L)	0.09 [<0.01–0.64]	0.38 [0.10–1.09]	0.25 [0.06–1.07]	0.003	0.06 [<0.01–0.32]	0.03 [<0.04–0.36]	0.04 [<0.04–0.32]	0.59
CV	99	81	79		92	137	112	
<i>t</i> _{1/2} (h)	4.62 [3.26–6.30]	4.47 [2.96–6.96]	4.43 [3.84–6.44]	0.86	4.85 [3.47–6.53]	3.74 [1.50–11.34]	3.63 [1.80–14.03]	0.006
CV	18	32	16		18	70	58	

*C*_{min}, minimum observed concentration; *C*_{max}, maximum observed concentration; AUC, area under the plasma concentration-time curve.

^aCoefficient of variation (CV) expressed as standard deviation divided by the mean.

**Table 3.** Univariate and multivariate analysis with saquinavir AUC as the dependent variable

Variable	Univariate			Multivariate			
	parameter estimate	R^2	P value	parameter estimate ^a	P value	parameter estimate ^b	P value
BMI (kg/m ²)	-0.02016	0.05	0.1308				
Gender	0.20249	0.10	0.0307	-0.04430	0.6143		
Weight (kg)	-0.01160	0.24	0.0007	-0.00153	0.7055		
RTV AUC (mg·h/L)	0.03909	0.37	<0.0001	0.03116	0.0004	0.03111	0.0001
Study site	-0.34388	0.29	0.0001	-0.23664	0.0222	-0.24288	0.0021

BMI, body mass index; RTV AUC, ritonavir area under the curve.

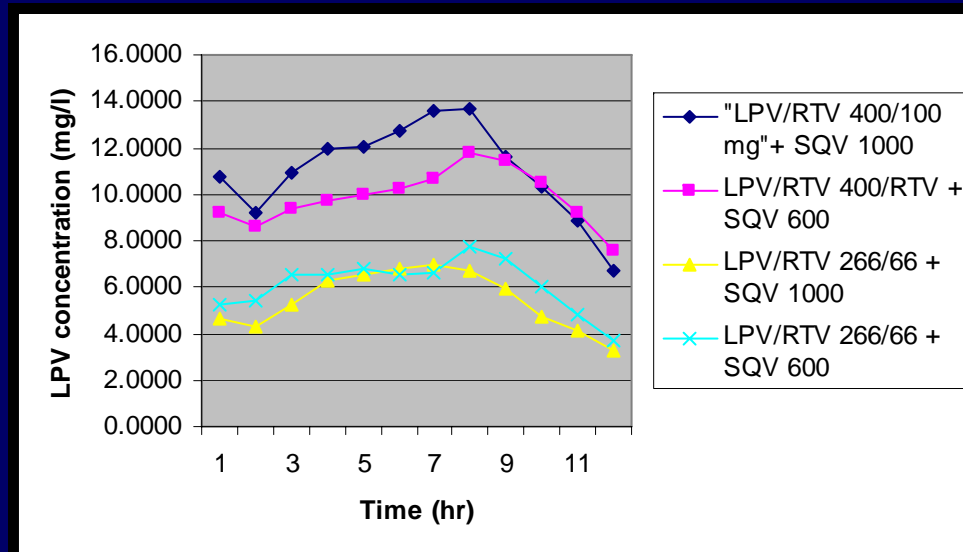
^a $R^2 = 0.50$.

^b $R^2 = 0.50$.

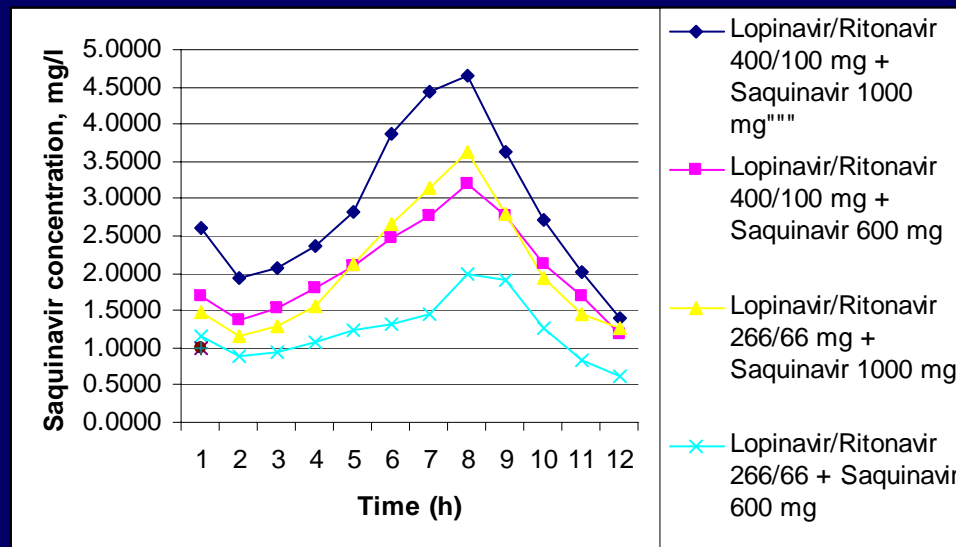


PK data of HIVNAT 019 study

Lopinavir AUC



SQV AUC





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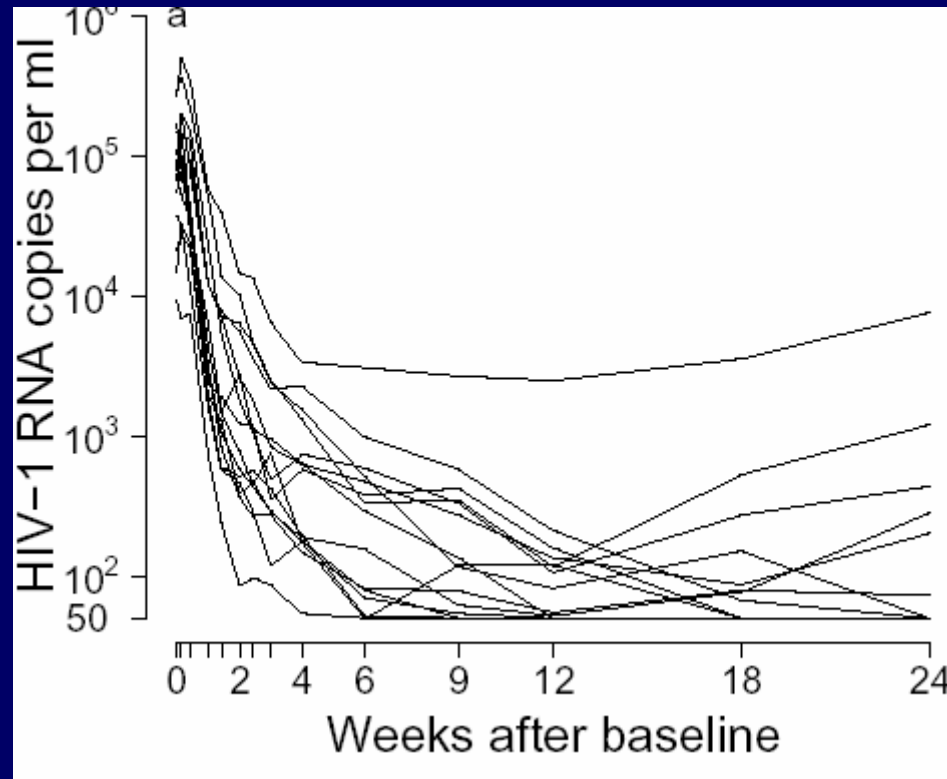
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Efficacy data of the high/high group

LPV/r 400/100mg BID

SQV 1000 mg BID





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DRUG INTERACTION





Mechanism of Interaction CYP3A

- Metabolizes all PIs and NNRTIs
- Large differences exist between patients in their CYP3A activity
- CYP3A substrates are vulnerable to many drug interactions
 - enzyme inhibition
 - enzyme induction



Drug interactions through enzyme inhibition

- Leads to higher plasma levels and possibly toxicity
- Direct effect, already after 1st dose
- Interaction stops when inhibitor is removed (cave long half-life)
- Drug interaction usually when 2 agents are metabolized by same enzyme (competition)
- Sometimes drug binds to enzyme without being metabolized (methadone – zidovudine)



Drug interactions through enzyme induction

- Leads to lower plasma levels and possibly treatment failure
- Not a direct effect, visible after several days
- Interaction does not stop when inducer is removed (7-14 days)
- Enzyme induction not very specific
- Well-known inducers: rifampin, anti-epileptics, NNRTIs, St John's Wort



Examples of HIV drug interactions

- **Anti HIV drugs itself**
- Tuberculosis drugs
- Methadone
- Ritonavir
- Oral contraceptives
- Benzodiazepines
- Herbal drugs
- Anticonvulsants



Interactions among HIV drugs itself: NRTIs

- Most important are 2 types of interactions:
- Do not combine 2 NRTIs that require same enzymes for intracellular phosphorylation:
 - d4T + AZT
 - ddC, FTC, 3TC
- Do not combine TDF with ddl
 - Increased ddl toxicity
 - Loss of immunological response



Interactions among HIV drugs itself: NNRTIs

- NNRTIs are inducers of CYP3A
- PIs are substrates of CYP3A
- When combining NNRTIs with PIs, usually the dose of the PI is increased, for example:
 - LPV/r 533/133 (4 caps) BID + EFV, or
 - LPV/r 600/150 (3 tabs) BID + EFV



Effect of rifamycins on ARV drug levels

	SQV	IDV	NFV	APV	LPV	NVP	EFV
Rifampin	-84%	-89%	-82%	-82%	-75%	-37%	-25%
Rifabutin	-40%	-32%	-32%	-15%	0	-16%	0



Efavirenz + rifampin

- Most guidelines include a recommendation to increase dose to 800mg QD (+33%) to compensate for effect of rifampin
- Patients with TB often are non-Caucasian and may already have a high EFV plasma level
- Is dose increase really necessary?
- If not: cheaper, more convenient, less toxic?



Herbal drugs (1)

- Often used by patients without informing HIV doctor
- Most herbs are (probably) safe to use, but no one knows that this is true for a specific herb
- St John's Wort: induces CYP3A (Echinacea, garlic, ginkgo, milk thistle, and St. John's wort have the potential to cause significant interactions)



Therapeutic Drug Monitoring Conditions

- Pharmacokinetic-pharmacodynamic relationship
- Small therapeutic index
- Inter- and intra-patient variability
- Parameters to guide therapy
- Intervention possibilities
- Drug assays



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TDM

Evidence From Clinical trails

- Results are conflicting
- No official guideline how to use TDM

ATHENA STUDY



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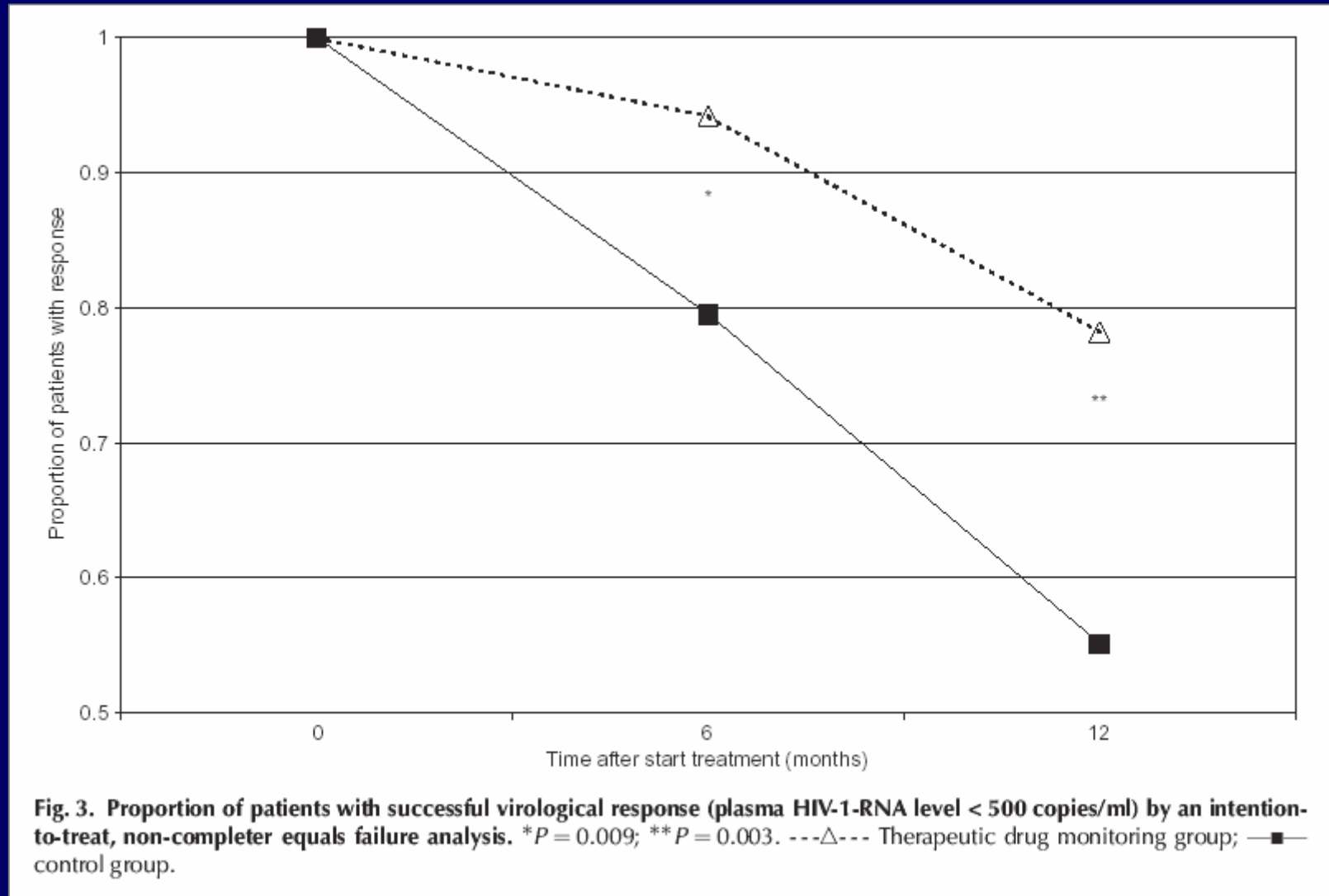




Table 1. Protease inhibitor plasma levels at weeks 4 and 8 in control and therapeutic drug monitoring arms expressed in microgram per millilitre, and the proportion of patients with optimal, partly optimal or suboptimal protease inhibitor concentrations according to our target values.

	Control arm		TDM arm	
	Week 4	Week 8	Week 4	Week 8
Saquinavir	0.61 [0.34–1.22]	0.81 [0.42–1.16]	0.16 [0.09–0.33]*	0.40 [0.09–0.72]*
Indinavir	0.76 [0.55–1.56]	1.04 [0.81–2.80]	0.53 [0.13–1.27]	0.51 [0.28–0.82]*
Ritonavir	0.84 [0.61–3.38]	2.04 [1.1–3.86]	1.64 [0.64–2.46]	2.77 [1.42–2.87]
Nelfinavir	1.83 [0.81–3.77]	1.4 [0.62–3.84]	2.01 [1.38–3.11]	1.23 [0.52–3.6]
Amprenavir	1.44 [0.85–2.08]	1.32 [0.93–2.45]	1.51 [0.81–2.63]	1.68 [1.06–2.5]
Lopinavir ^a	7.68 [2.80–10.60]	5.86 [3.15–9.72]	5.62 [4.74–9.15]	5.89 [2.97–7.59]
Optimal	72 (83%)	76 (89%)	64 (79%)	67 (84%)
Partly optimal	2 (2%)	2 (2%)	4 (5%)	0
Suboptimal	13 (15%)	8 (9%)	13 (16%)	13 (16%)

* $P \leq 0.01$.

^aPlus low-dose ritonavir.

Values presented are median [interquartile range].



TDM When?

- Virological failure
- Toxicity
- Drug-Drug interaction
- GI disease and hepatic insufficiency
- Pregnancy
- Children
- Adherence
- Ethnicity ???



TDM terminology

- IC 50
- Population curve
- Inhibitory Quotient
- Genotyping Inhibitory Quotient
- Concentration Ratio



Pediatric Case of Therapeutic Drug Monitoring (TDM)

- Thai boy, 12 y, Prajuabkirikann
- BW 28 kg, Ht 135 cm, BSA= 1 m²
- Since Jul 2000 Rx AZT, ddC
- Initially, he didn't take med on time because mother didn't understand
- ARV was stopped 3 wks before coming to HIVNAT
- Resistance testing done after 3 weeks off ARV:
4 NAMS (D67N, K70R, T215F, K219Q): resist to AZT, d4T, ddl



Pediatric Case TDM

- Last CD4 before stop ARV= 9% (185 c/ml), VL 32000
- At HIVNAT, CD4 = 4% (111c/ml)
- Cotrimoxazole started
- Switched ARV
Kaletra 2x2 (230mg/m²/dose)
IDV(400) 1x2
(400mg/m²/dose)
3TC(150) 1x2



Pediatric Case TDM

- Patient tolerated regimen well
- CD4 12wk = 10%
- CD4 24 wk = 16%
- CD4 36 wk = 13%

Week 48

- CD4 = 17%
- VL < 50
- had increased total bilirubin, TG, ALP (likely from IDV)
- IDV decreased to 200mg/m²/dose and TDM done on wk 60



Pediatric Case TDM

Date	ARV	Dose (mg/m ²)	Trough (mg/L)
Wk 4 18/05/04	LPV IDV	266.6 400	19.45 1.65
Wk 48 29/03/05	Had jaundice, increase total bilirubin, TG, ALP (likely from IDV) IDV decreased to 200mg/m ² /dose		
Wk 60 28/06/05	LPV IDV	266.6 200	27.58 0.45
07/09/05	decrease Kaletra to 1x2 when result was available		
Wk 72 05/10/05	LPV IDV	133.3 200	1.64 Not done CD4 = 24% (860)



Interaction Case

- **Thai Female, 30 y**
- **Infected since 1998**
- **History of ARV:**
 - **1998: AZT/3-TC IDV**
 - **2002: SQV/r 1600/100 TDF/FTC (STAC)**
- **Since Oct 2005: SQV/r 1500/100 + Combivir**



Interaction Case

Laboratory 22-12-05

- **VL < 50 copies**
- **CD4+ 393**
- **Safety lab: normal**

Routine TDM was performed at T24:

- **RTV 0.17 mg/l**
- **SQV 0.24 mg/l**



Interaction Case

January 2006:

- **Develops TB complains, with suspected X-ray**
- **Start:**
 - **Pyrazinamide (PZA)**
 - **Ethambutol (EMB)**
 - **Isoniazid (INH)**
 - **Rifampin (RIF)**
- **ARV: Same regimen is continued**



Interaction case

- **March Changed to RIF + INH**

TDM done:

- **SQV: 0.02 mg/l**
- **RTV: 0.00 mg/l**



TAKE HOME MESSAGES

- PK is the study of what the body does with the drug and is essential for the study of ARV
- Dose reduction is the future for South East Asia (and beyond)
- Interactions have significant effect on patients outcome
- TDM is a useful clinical tool