Plasma measurement of antivirals in the clinical setting: which role in 2021?

16th Residential Course on Clinical Pharmacology of Antiretrovirals, Torino, January 13-15, 2021 (virtual)

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Disclosure

- DM Burger has served on an advisory board for Merck
- DM Burger has received grant funding/research support from Merck, Janssen, Gilead, ViiV

- All payments have been invoiced by the financial department of Radboud University Medical Centre Nijmegen

Contents

- Therapeutic Drug Monitoring: how it all started (1995 - 2010)
- Therapeutic Drug Monitoring: the dark years (2010-2020)
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- Therapeutic Drug Monitoring: a bright future? (2021 - ?)

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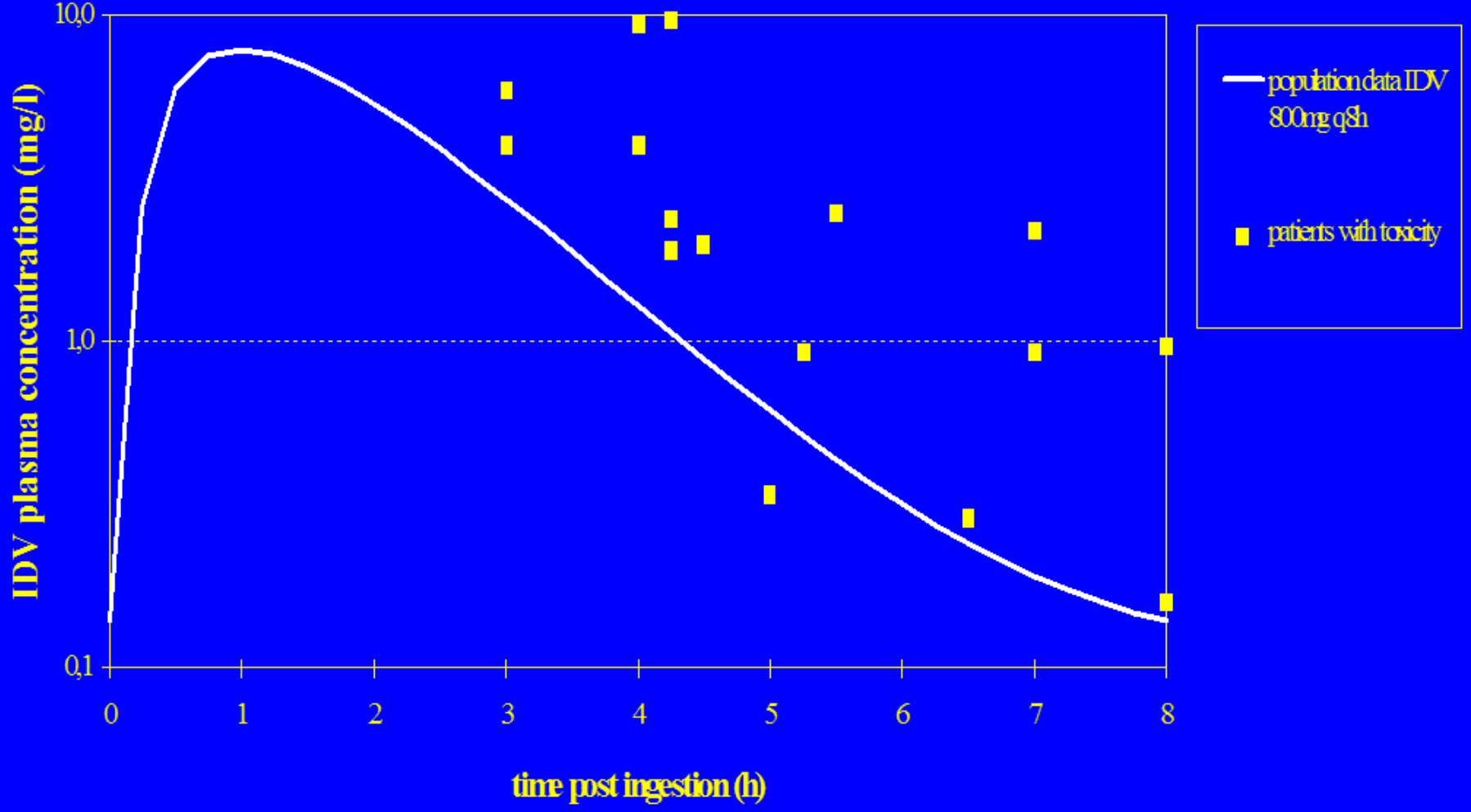
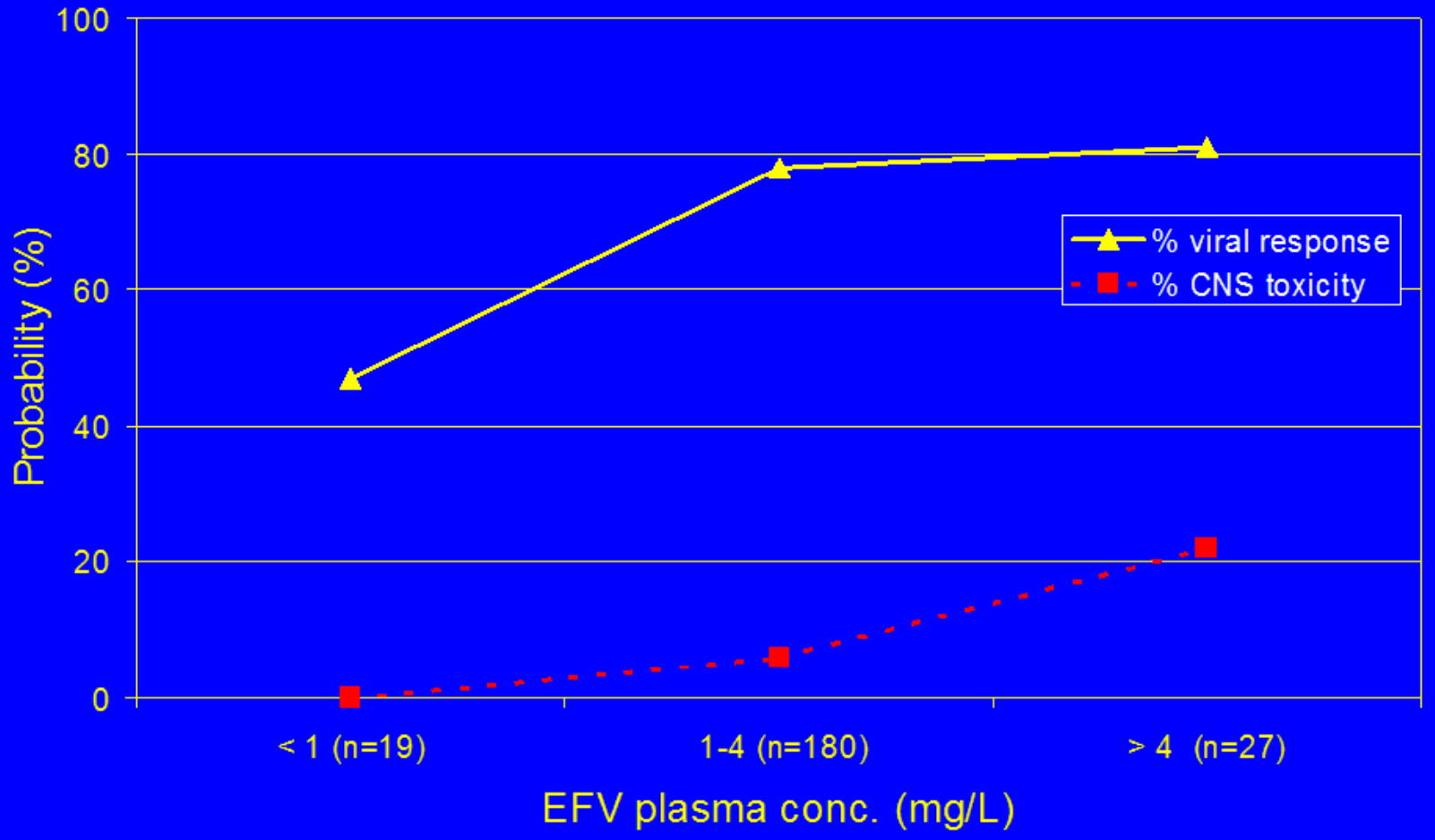
Nephrotoxicity and IDV concentrations



Dieleman, AIDS 1999

Efavirenz PK-PD (Marzolini et al. AIDS 2001)



de Vries-Sluijs et al (Clin Pharmacokinetics, 2003):

Low nevirapine plasma concentrations predict virological failure in an unselected HIV-1-infected population

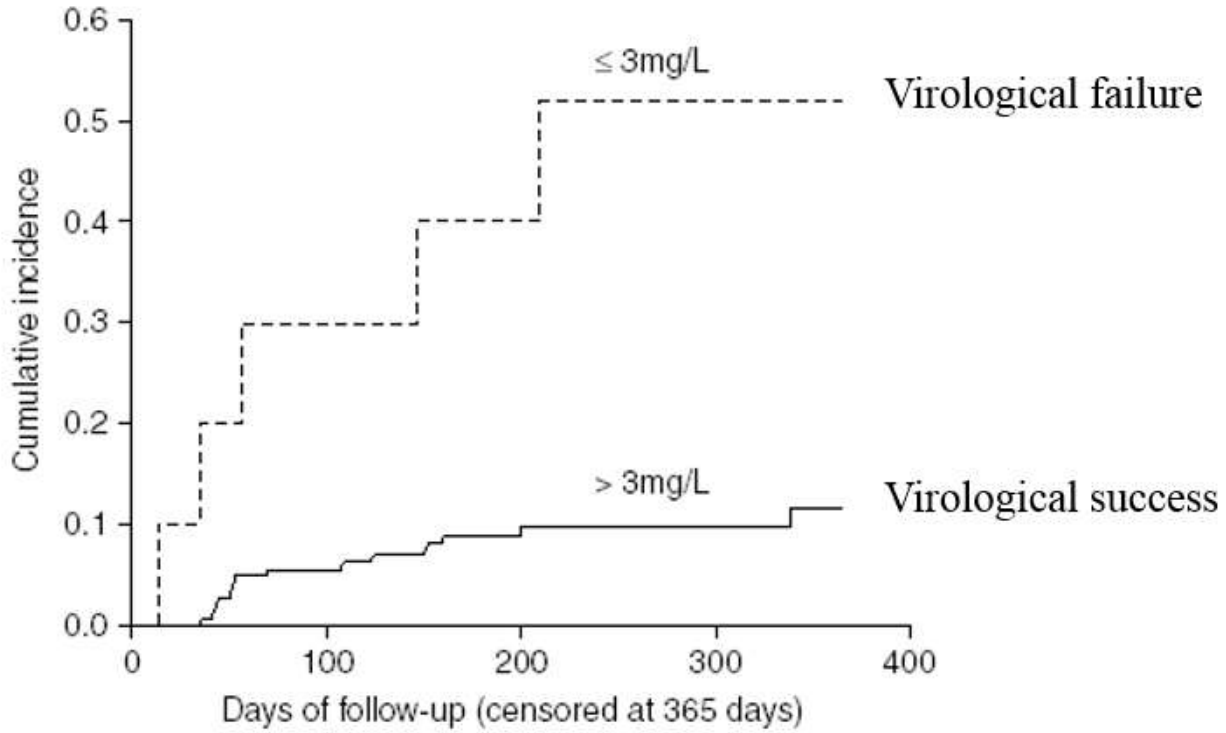
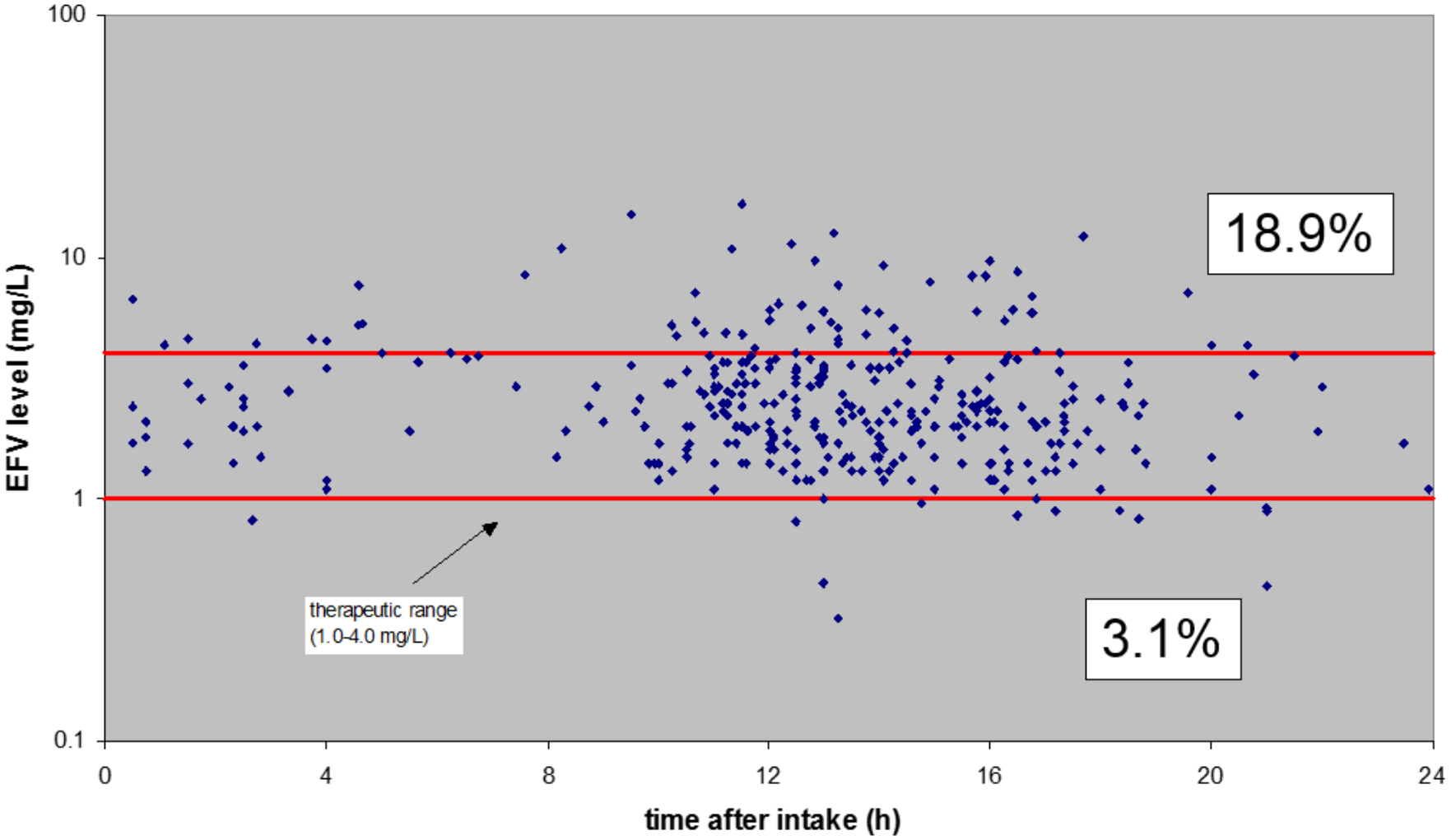


Fig. 2. Cumulative incidence of virological failure according to nevirapine plasma concentration measured at the start of follow-up.

Interpatient variability of efavirenz



Burger et al. Br J Clin Pharmacol 2006

PIs & NNRTIs fulfill all requirements for TDM

- ✓ A relationship exists between drug level and pharmacological response
- ✓ There is a wide interpatient variability in pharmacokinetics
- ✓ The drug has a narrow therapeutic window
- ✓ The pharmacological response is not directly measurable
- ✓ The drug can be measured in the desired biological matrix
- ✓ The patient is on the best drug
- ✓ A relationship exists between drug level and pharmacological response for a specific patient
- ✓ The duration of therapy is long enough for the patient to benefit from TDM
- ✓ TDM results influence the decision-making process

Ensom et al. Clin Pharmacokinet 1998

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TDM became out of fashion….

- Newer ARVs had better PK profiles:
  - PI boosting
  - Long elimination half-life
  - More forgiving (missed dose less of a problem)
- Virological failure with resistance development became rare
- Newer ARVs had a better safety profile (at least we were told…)
- We had learnt how to deal with DDIs

TDM became out of fashion….

TDM had to reinvent itself (1)

Antiviral Therapy 2014; 19:765–771 (doi: 10.3851/IMP2761)

Original article

Long-term treatment with tenofovir: prevalence of kidney tubular dysfunction and its association with tenofovir plasma concentration

*Marieke Ezinga[1,2], Jack FM Wetzels[3], Marjolein EW Bosch[4], André JAM van der Ven[2,4], David M Burger[1,2]**

TDM had to reinvent itself (2)

MAJOR ARTICLE HIV/AIDS

Raltegravir in HIV-1–Infected Pregnant Women: Pharmacokinetics, Safety, and Efficacy

Maren I. Blonk,[1] Angela P. H. Colbers,[1] Carmen Hidalgo-Tenorio,[2] Kabamba Kabeya,[3] Katharina Weizsäcker,[4] Annette E. Haberl,[5] José Moltó,[6] David A. Hawkins,[7] Marchina E. van der Ende,[8] Andrea Gingelmaier,[9] Graham P. Taylor,[10] Jelena Ivanovic,[11] Carlo Giaquinto,[12] and David M. Burger[1]; for the Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women (PANNA) Network

Clinical Infectious Diseases® 2015;61(5):809–16

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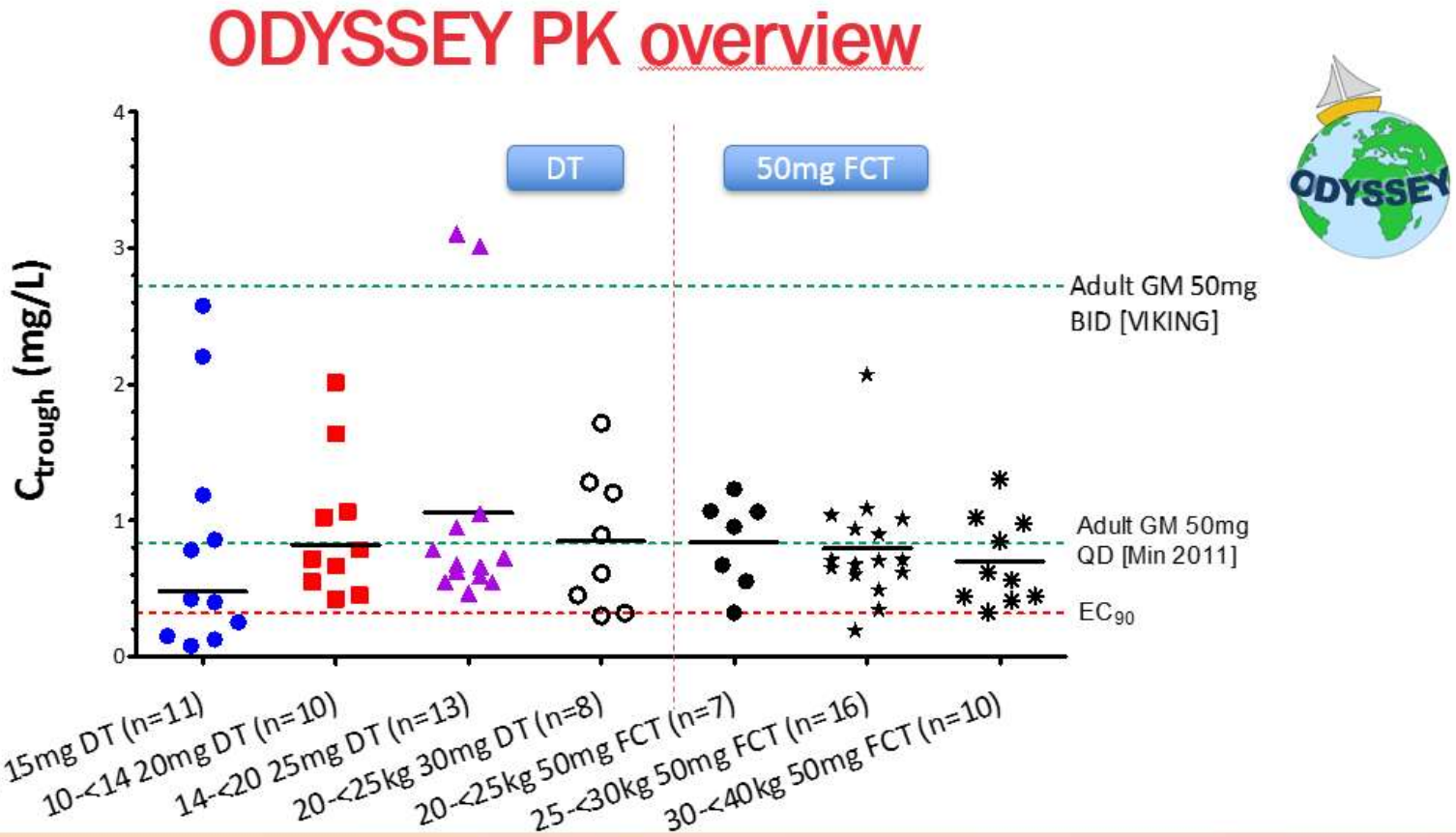
TDM had to reinvent itself (3)



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TDM of ARVs anno 2021 (1)

- Everyone agrees there is no need to do this on a routine basis

- One can think of many indications that HIV treatment is not optimal:
  - Suspicion of nonadherence
  - Undetected drug-drug interaction
  - Uncertainty of correct dose (children, pregnancy, organ dysfunction, obesity, gastric bypass, etc.)
  - Unexplained suboptimal virological response (EACS)
  - Etc.

TDM of ARVs anno 2021 (2)

Virological Failure

Definition	**INCOMPLETE SUPPRESSION**: HIV-VL > 200 copies/mL at 6 months[1] after starting therapy in PLWH not previously on ART **REBOUND**: confirmed HIV-VL > 50 copies/mL in PLWH with previously undetectable HIV-VL
General measures	Review expected potency of the regimen
	Evaluate adherence, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues
	Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 200-500 copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations
	Tropism testing if considering MVC
	Consider TDM
	Review ART history
	Identify treatment options, active and potentially active drugs/combinations
Management of virological failure (VF)	**If HIV-VL > 50 and < 200 copies/mL:**
	Check for adherence
	Check HIV-VL 1 to 2 months later[2]
	If genotype not possible, consider changing regimen based on past treatment and resistance history
	If HIV-VL confirmed > 200 copies/mL:
	Change regimen as soon as possible. What to change will depend on the resistance testing results
	If no resistance mutations found: re-check for adherence, perform TDM
	If resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised
	Goal of new regimen: HIV-VL < 50 copies/mL within 6 months

https://www.eacsociety.org/files/guidelines-10.1_5.pdf

TDM of ARVs anno 2020 (3)

Research letters

J Antimicrob Chemother 2018; **73**: 826–827
doi:10.1093/jac/dkx461
Advance Access publication 12 December 2017

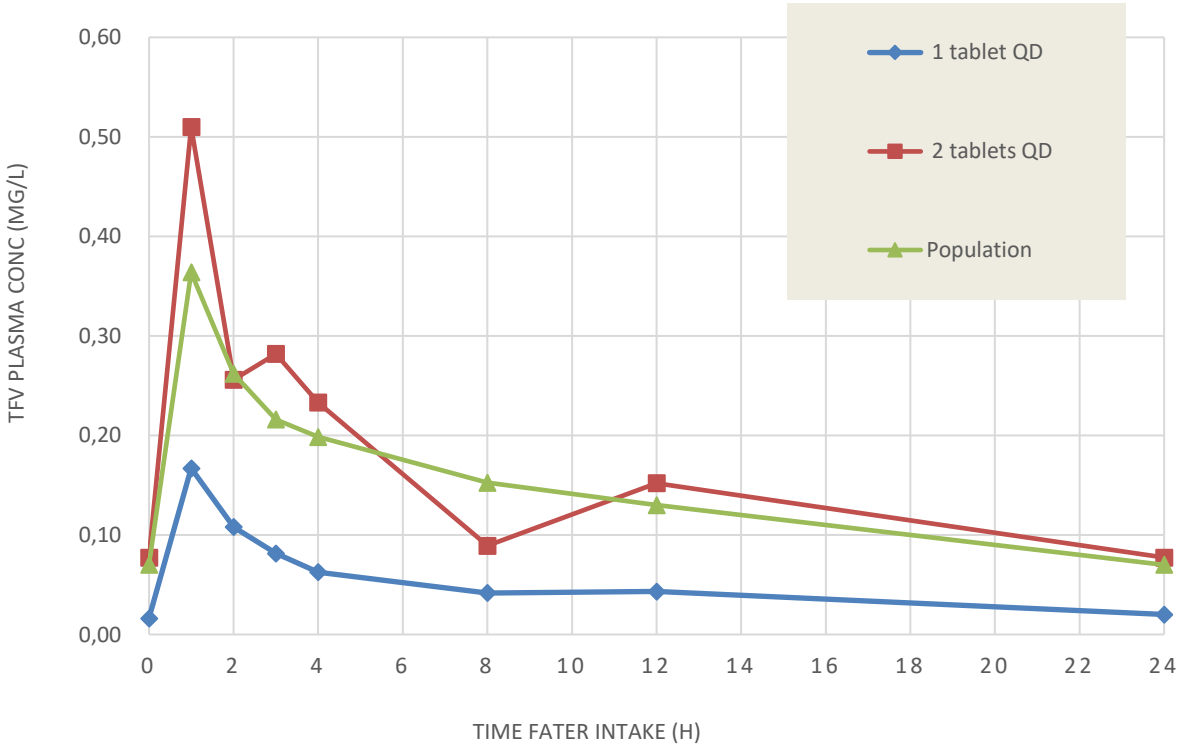
Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid

Annagloria Palazzo*, Mattia Trunfio, Veronica Pirriatore, Maurizio Milesi, Amedeo De Nicolò, Chiara Alcantarini, Antonio D'Avolio, Stefano Bonora, Giovanni Di Perri and Andrea Calcagno

Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

TDM of ARVs anno 2020 (4)

TFV levels in a PrEP client with gastrectomy

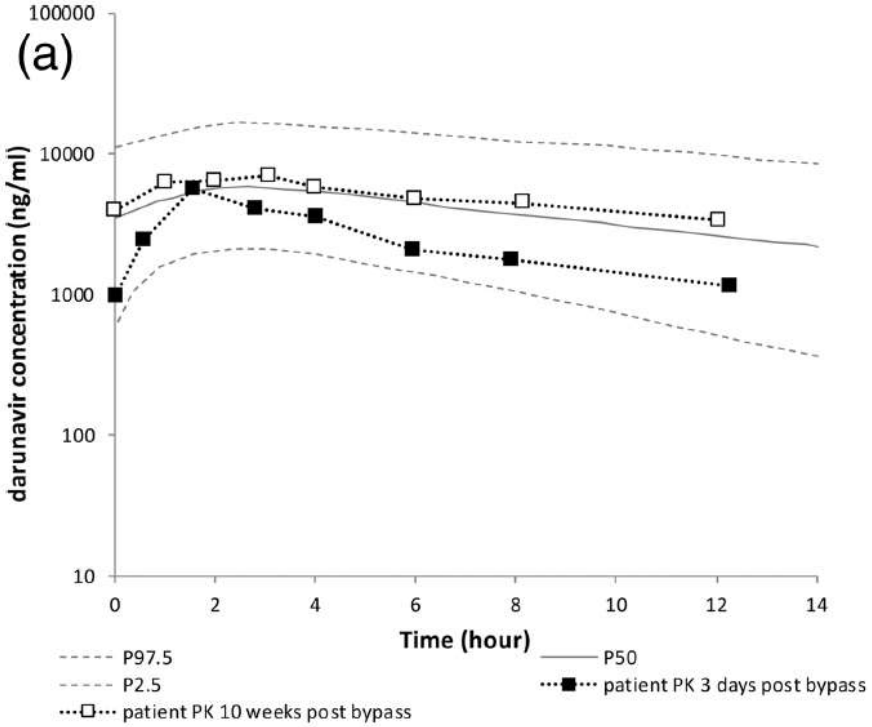


Roelofsen et al. AIDS 2020

TDM of ARVs anno 2020 (5)

Boosted darunavir, emtricitabine and tenofovir pharmacokinetics in the early and late postgastric bypass surgery periods

Veronika Baettig[a,b], Perrine Courlet[c], Tarik Delko[b,d], Manuel Battegay[a,b] and Catia Marzolini[a,b], [a]Division of Infectious Diseases and Hospital Epidemiology,



AIDS 2018, **32**:1903–1907

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TDM of ARVs anno 2020 (6)

REVIEW ARTICLE

OPEN

Optimizing Pediatric Dosing Recommendations and Treatment Management of Antiretroviral Drugs Using Therapeutic Drug Monitoring Data in Children Living With HIV

Hylke Waalewijn, Msc, Anna Turkova, PhD,†‡ Natella Rakhmanina, PhD,§¶‖ Tim R. Cressey, PhD,**††‡‡ Martina Penazzato, PhD,§§ Angela Colbers, PhD,* and David M. Burger, PhD,* on behalf of the Pediatric Antiretroviral Working Group (PAWG)*

(*Ther Drug Monit* 2019;41:431–443)

TDM of ARVs anno 2020 (6)

TABLE 1. Current Plasma Drug Targets for TDM of ARV Drugs

Drug	Plasma Target	Toxicity Considerations
NNRTI		
Efavirenz (EFV)	Mid-dose level ≥1 mg/L[29]	Mid-dose level <4 mg/L[30]
Nevirapine (NVP)	C_{trough} ≥3.0 mg/L[41]	No relation found between PK parameters and toxicity
Rilpivirine (RPV)	C_{trough} ≥0.042 mg/L[52,53]	C_{max}: <0.60 mg/L[52,53]
PIs		
Atazanavir (ATV)	C_{trough} ≥0.23 mg/L[55,56]	C_{trough}: 0.50–0.76 mg/L[58–60]
Darunavir (DRV)	C_{trough} ≥0.55 mg/L[73]	No relation found between PK parameters and toxicity
Lopinavir (LPV)	C_{trough} ≥1.0 mg/L[7,84]	No relation found between PK parameters and toxicity
InSTI		
Dolutegravir (DTG)	C_{trough} ≥0.324 mg/L[112]	No relation found between PK parameters and toxicity
Raltegravir (RTG)	C_{trough} ≥0.045 mg/L[115]	No relation found between PK parameters and toxicity
Elvitegravir (EVG)	C_{trough} ≥0.13[121]	No relation found between PK parameters and toxicity

(*Ther Drug Monit* 2019;41:431–443)

Journal of Tropical Pediatrics, 2019, 0, 1–10
doi: 10.1093/tropej/fmz077
Original paper

OXFORD

Pediatric Antiretroviral Therapeutic Drug Monitoring: A Five and a Half Year Experience from a South African Tertiary Hospital

Anton E. Engelbrecht, MBChB,[1] Lubbe Wiesner, PhD,[2] Jennifer Norman, MSc,[2] Helena Rabie, MMed Paed[3*] *and* Eric H. Decloedt, PhD[1*]

"LPV TDM confirmed non-adherence in 25% (4/16) of the cases where other measurements of adherence did not match with the clinical picture"

What about antivirals beyond HIV?

Successful HCV treatment of patients on contraindicated anti-epileptic drugs: Role of drug level monitoring

Table 1. Characteristics of the studied subjects and exposure of daclatasvir, sofosbuvir and GS-331007 in combination with anti-epileptic drugs.

Patient		AED	HCV				DAA exposure AUC_{0-24h} (h * g/L)^		
Gender	Age (yr)	Drug and daily dose	Genotype	Cirrhosis	Pre-treated	Treatment	DAC	SOF	GS-331007
Ref[1,2]							**14.12**	**1.01**	**7. 20**
#1 Male	56	CBZ: 400 mg	1	No	No	SOF: 400 mg QD DAC: 60 mg BID 12 weeks	4.75	0.913	7.60
#2 Male	71	CBZ: 1,000 mg	1b	No	Yes	SOF: 400 mg QD DAC: 60 mg BID	1.48	0.347	12.70
						DAC: 60 mg TID[¥] 24 weeks	4.38	0.383	13.16
#3 Male	45	CBZ: 1,200 mg PHB: 225 mg	3a	Yes	No	SOF: 400 mg QD DAC: 60 mg TID RBV: 600 mg BID 24 weeks	3.98	–	–
#4 Male	53	CBZ: 1,200 mg	1a	No	No	SOF: 400 mg QD DAC: 60 mg TID 12 weeks	3.09	0.328	4.42
#5 Female	70	PHE: 225 mg	1b	Yes	Yes	SOF: 400 mg QD DAC: 60 mg TID 12 weeks	18.32	–	–
#6 Female	47	PHB: 100 mg	1b	No	No	SOF: 400 mg QD DAC: 60 mg TID 12 weeks	42.57	2.327	10.18

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Journal of Hepatology **2019** vol. 70 | 548–577

Crushing of DAAs: is it possible?

Treatment of chronic hepatitis C virus infection with crushed ledipasvir/sofosbuvir administered through a percutaneous endoscopic gastrostomy tube in a patient with HIV coinfection

Vanessa Huffman, PharmD, Department of Pharmacy, Memorial Hospital West, Memorial Healthcare System, Pembroke Pines, FL

Diana C. Andrade, PharmD, BCPS, BCIDP, Department of Pharmacy, Memorial Hospital West, Memorial Healthcare System, Pembroke Pines, FL

Elizabeth Sherman, PharmD, AAHIVP, Division of Infectious Disease, Memorial Regional Hospital, Memorial Healthcare System, Hollywood, FL, and College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL

Jianli Niu, MD, PhD, Office of Human Research, Memorial Healthcare System, Hollywood, FL

Paula A. Eckardt, MD, FACP, AAHIVS, Division of Infectious Diseases, Memorial Regional Hospital, Memorial Healthcare System, Hollywood, FL

This case report describes our initial experience with crushable ledipasvir/sofosbuvir tablets in the treatment of an HIV/HCV coinfected patient with high-grade soft tissue sarcoma of the throat who was unable to swallow tablets. Crushable ledipasvir/sofosbuvir tablets provide a viable option to successfully achieve SVR when PEG tube administration is the only option.

Am J Health-Syst Pharm. 2020;78:36-40

PK of crushed LPV/r in Covid-19 patients

Research Letter

Crushing lopinavir/ritonavir tablets does not result in lower exposure to lopinavir/ritonavir in adult patients with Covid-19

Shaghayegh Mohsenian Naghani[a], Mark Jansen[a], Tessa Jaspers[a], Diane Bastiaans[b], David Burger[c]

Table 1. An overview of measured plasma samples with patients characteristics, therapy duration with LPN/RTN, time between last administrated LPN/RTN dose and measured plasma concentration LPV/RTV

Patient no.	Sample	Gender	Age (years)	Weight (kg)	Duration LPV/RTV therapy (days)	Time between last dose LPV/RTV and measurement (hours)	Plasma concentration LPV (mg/L)	Plasma concentration RTV (mg/L)	Constipation	Gastric retention
1	1	M	57	85	5.5	10	>30	0.65	Yes	Yes
2	1*	M	67	90	5.5	10	10.8	0.19	Yes	Yes
2	2*	M	67	90	7.5	12.5	7.1	0.28	Yes	Yes
3	1	M	77	73	6.5	10	19.05	0.53	Yes	Yes
4	1	F	65	95	3.5	10.5	9.9	0.20	Yes	Yes
5	1	M	52	99	4.0	9.5	20.1	0.64	Yes	No
6	1*	M	70	102	4.0	9	29.8	0.46	Yes	No
6	2*	M	70	102	6.5	9.5	23.7	0.37	No	No
7	1	M	65	107	3.0	11.5	28.8	0.53	Yes	No
8	1	F	70	129	2.5	11	9.8	0.37	Yes	Yes
9	1	M	52	93	2.0	9.5	>30	1.05	Yes	Yes
10	1*	M	50	128	2.5	9.5	28.4	0.52	Yes	No
10	2*	M	50	128	4.5	10.5	>30	0.44	Yes	No
11	1	F	64	104	2.0	9.5	19.7	1.92	Yes	Yes

LPV: Lopinavir; RTV: Ritonavir; M: male; F: Female; *samples from same patient, applies for patient no. 2, 6 and 10.

Submitted

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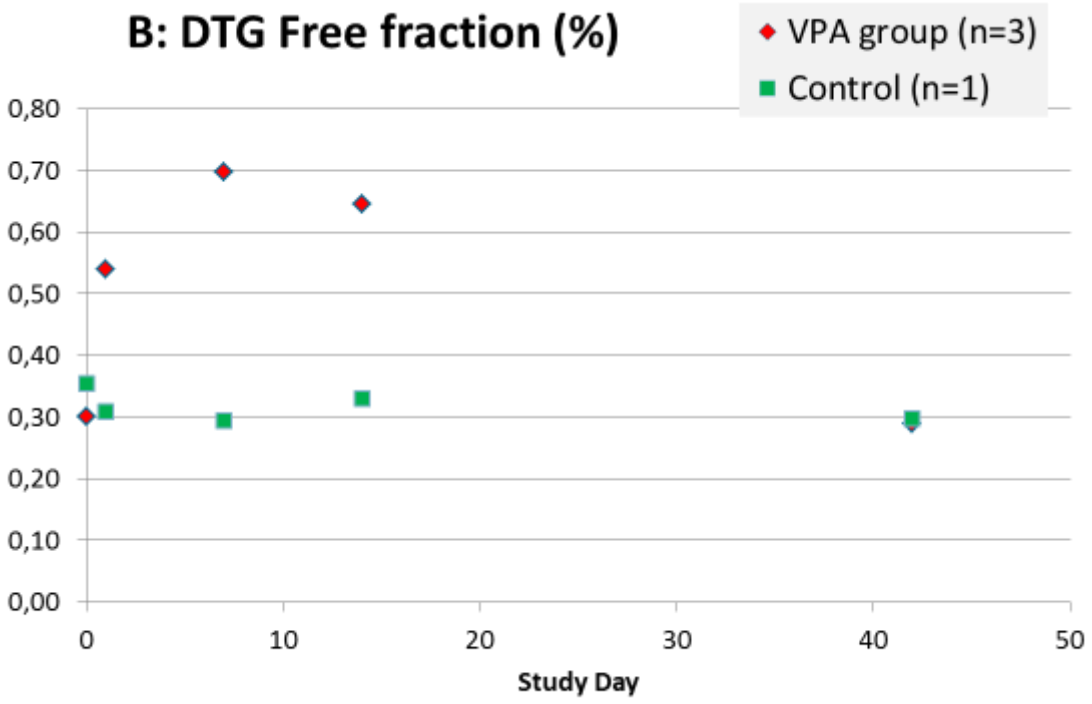
TDM beyond total drug concentrations: The valproic acid – DTG case



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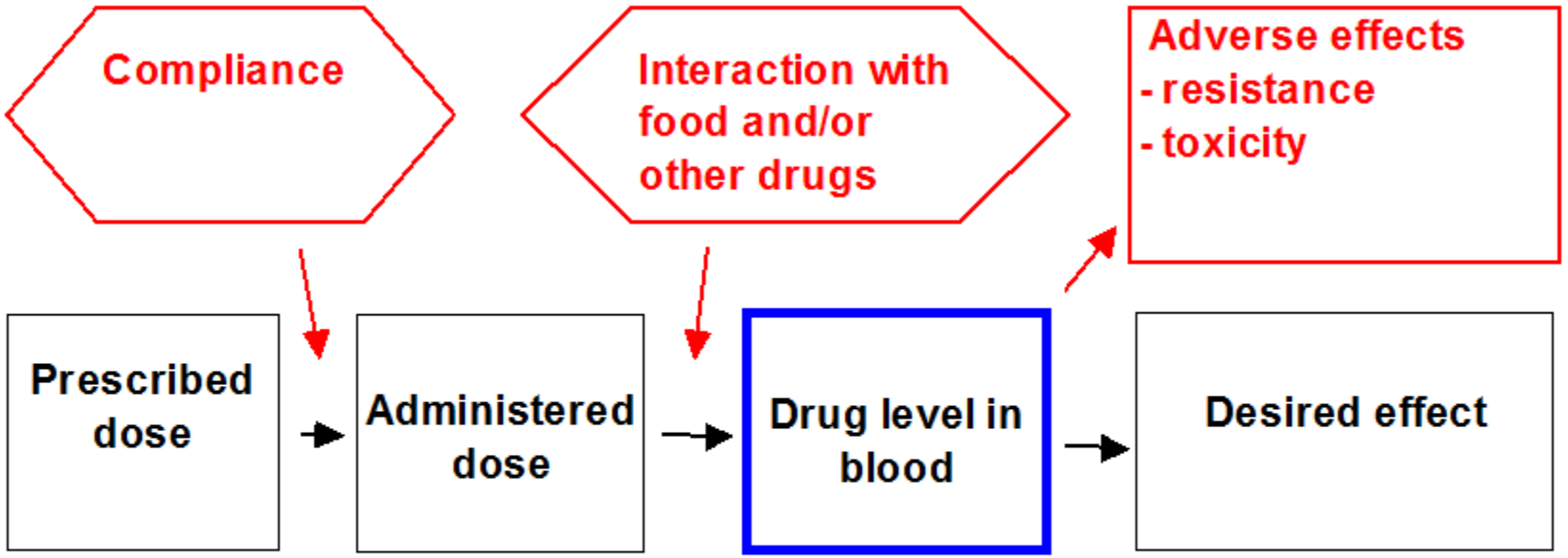
A bright future for TDM!



R.E. Aarnoutse, thesis 2003

A bright future for TDM!

- From now and into the future: fewer TDM requests, but more interesting
- “TDM-ologists” should define the patient cases where optimal response is not a guarantee
- Think beyond borders: other antivirals, free drug concentration, etc.

Thank you for your attention & and greetings from Nijmegen!

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