Plasma measurement of antivirals in the clinical setting: which role in 2020?

15th Residential Course on Clinical Pharmacology of Antiretrovirals, Torino, January 15-17, 2020

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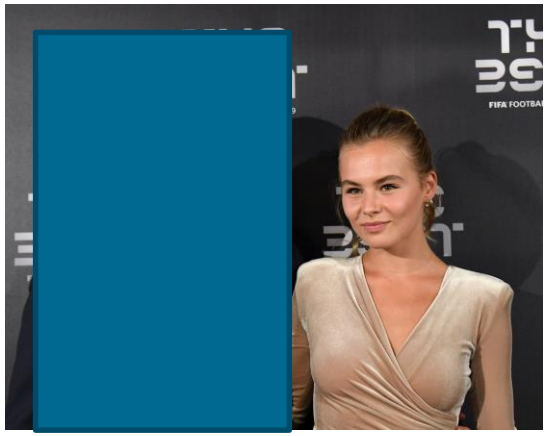
David Burger's famous soccer quiz:

Who is also scoring outside the soccer pitch?



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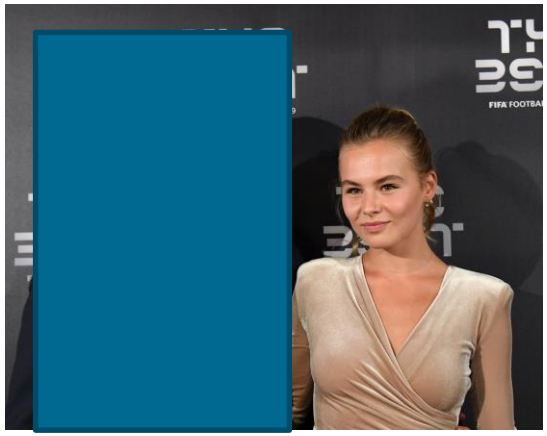

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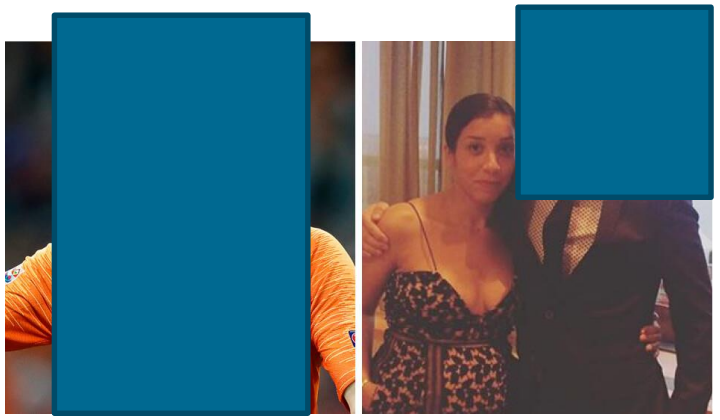

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David Burger's famous soccer quiz:

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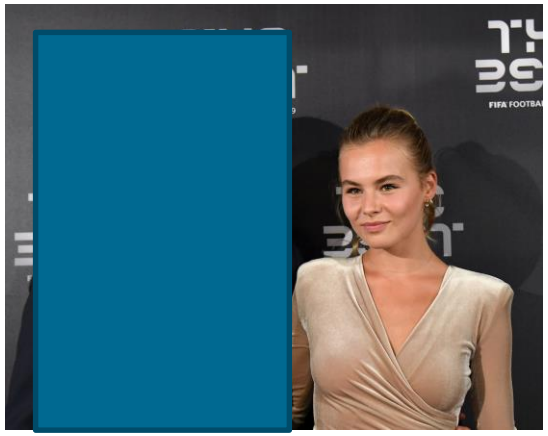

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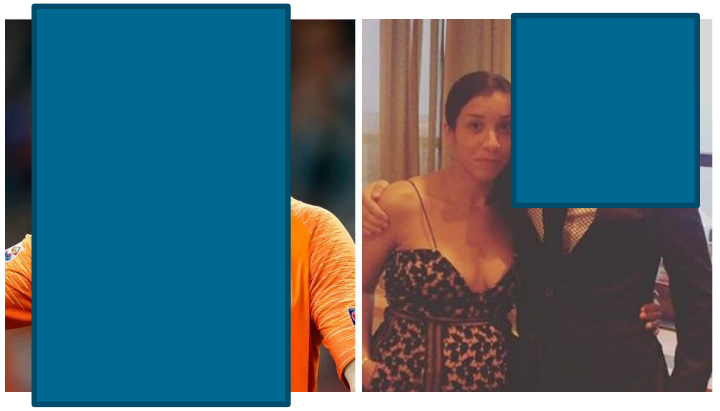

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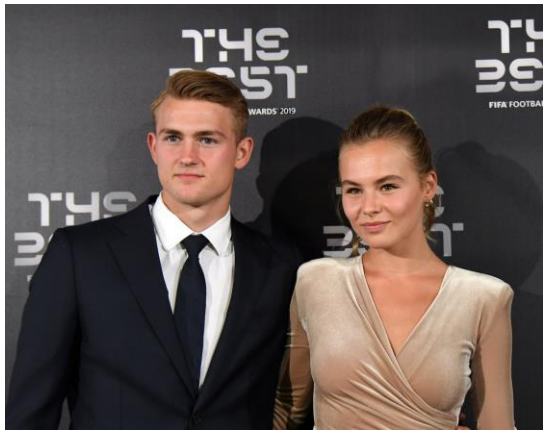

Matthijs de Ligt

Marten de Roon

Stefan de Vrij

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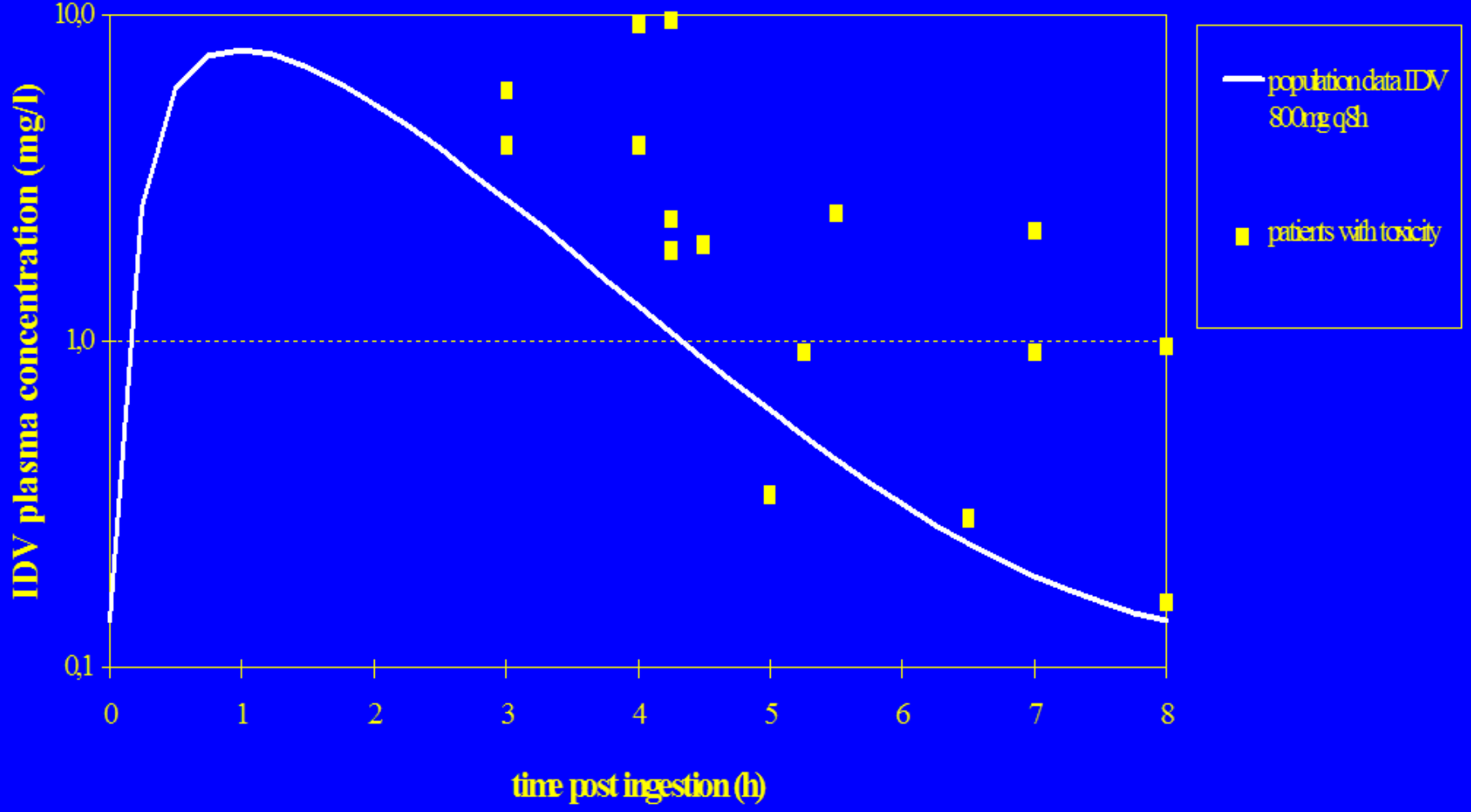
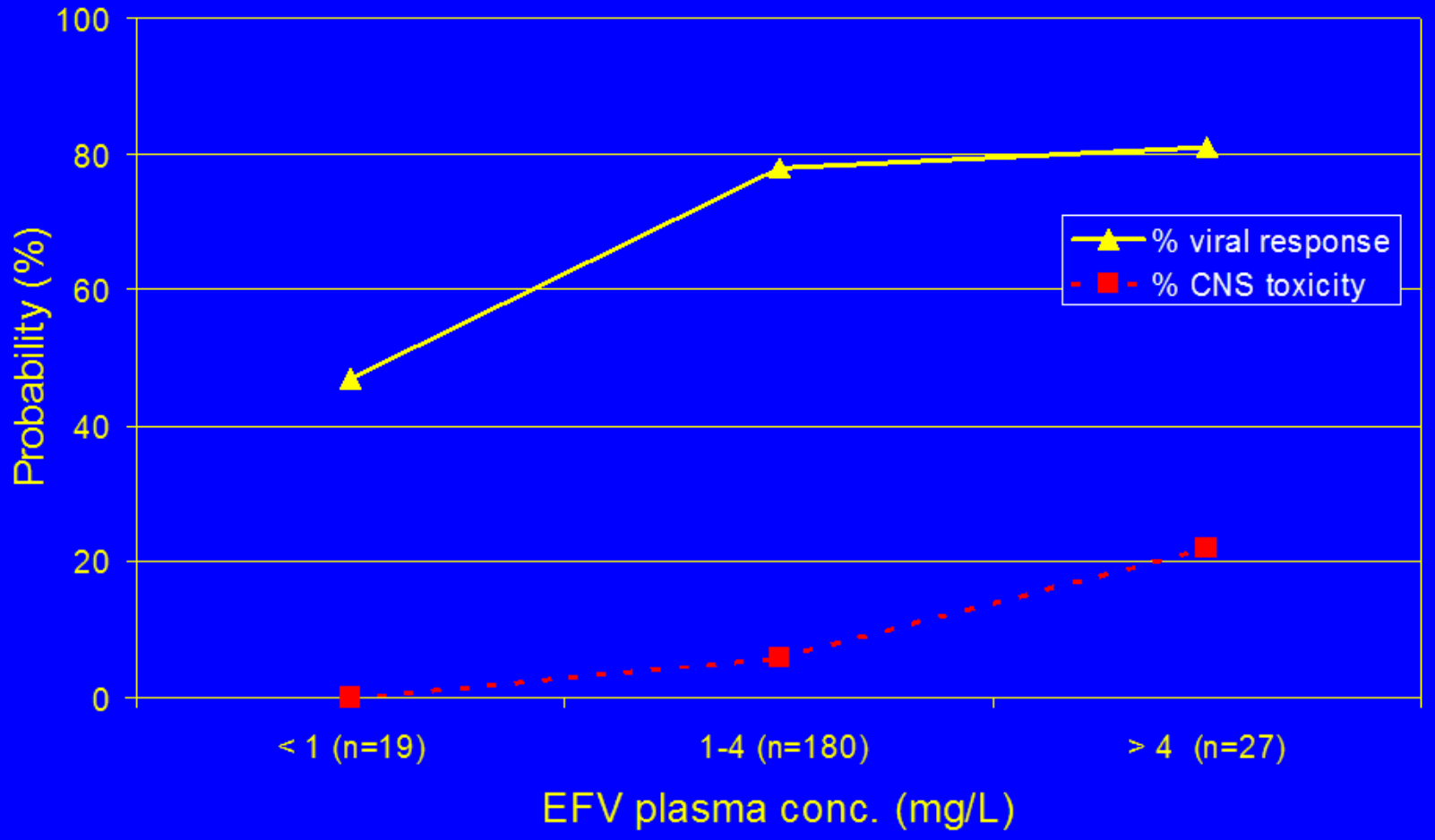
Nephrotoxicity and IDV concentrations



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

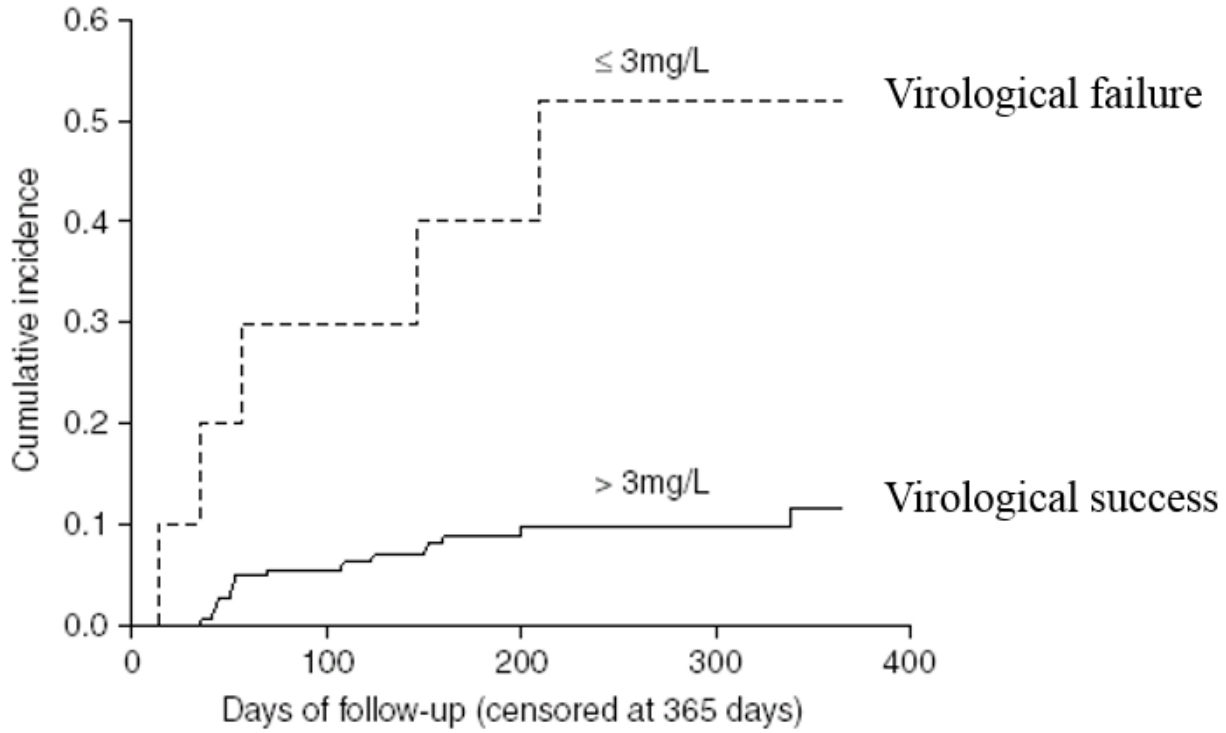
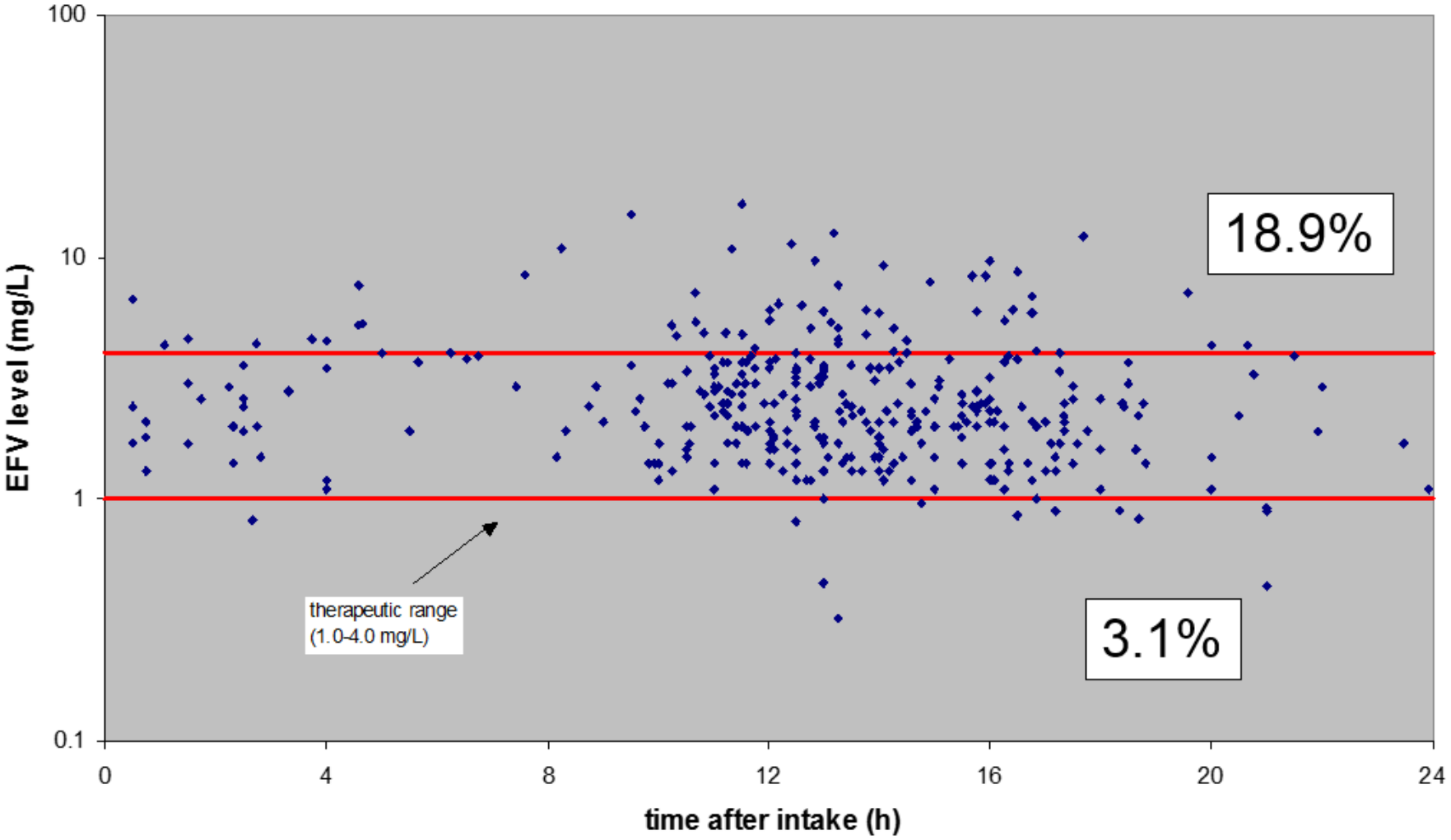


Fig. 2. Cumulative incidence of virological failure according to nevirapine plasma concentration measured at the start of follow-up.

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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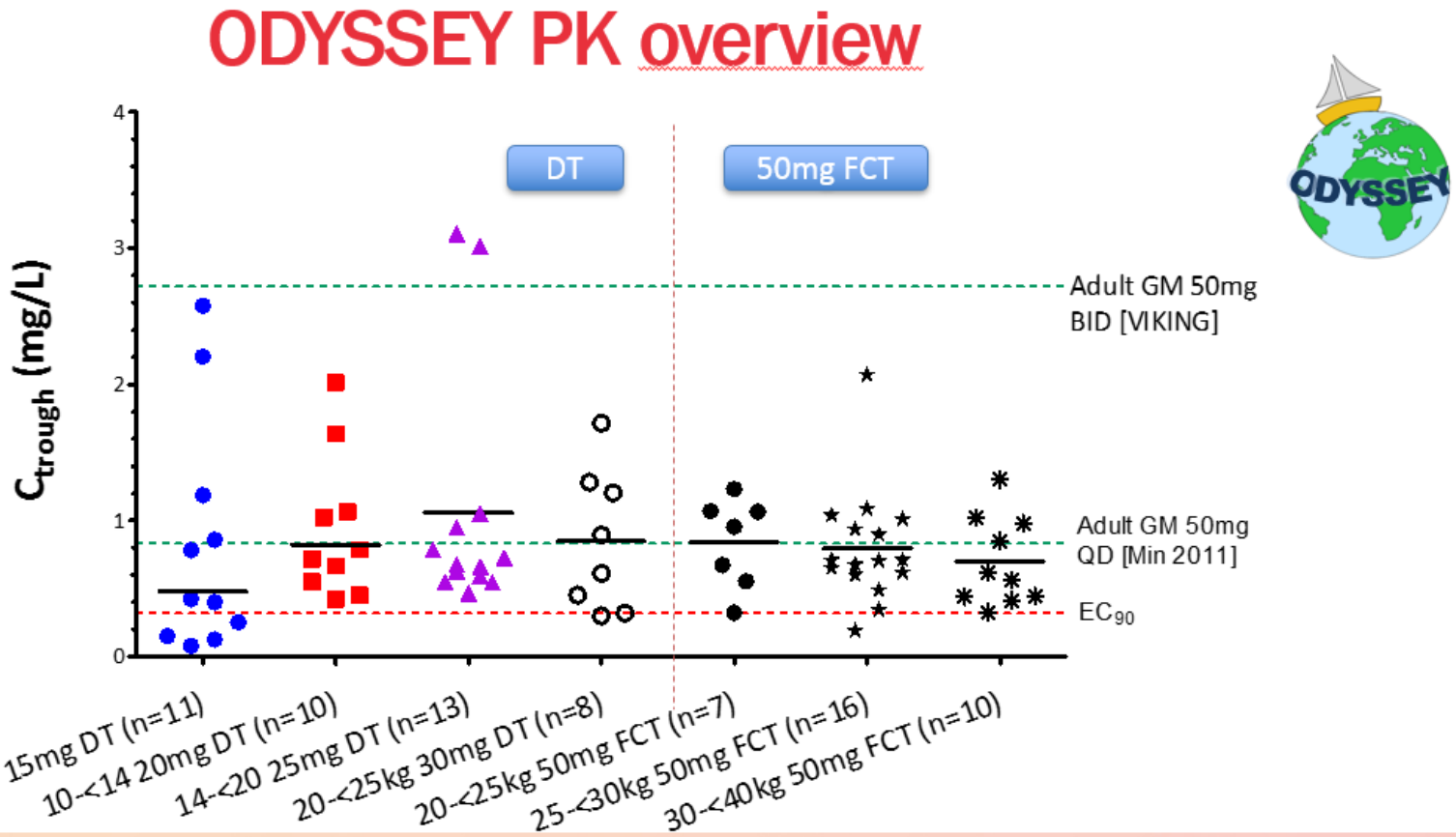
TDM had to reinvent itself (3)



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TDM of ARVs anno 2020 (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)

TDM of ARVs anno 2020 (2)

Virological Failure

Definition	**INCOMPLETE SUPPRESSION**: HIV-VL > 200 copies/mL at 6 months[i] 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[ii]
	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/2019_guidelines-10.0_final.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

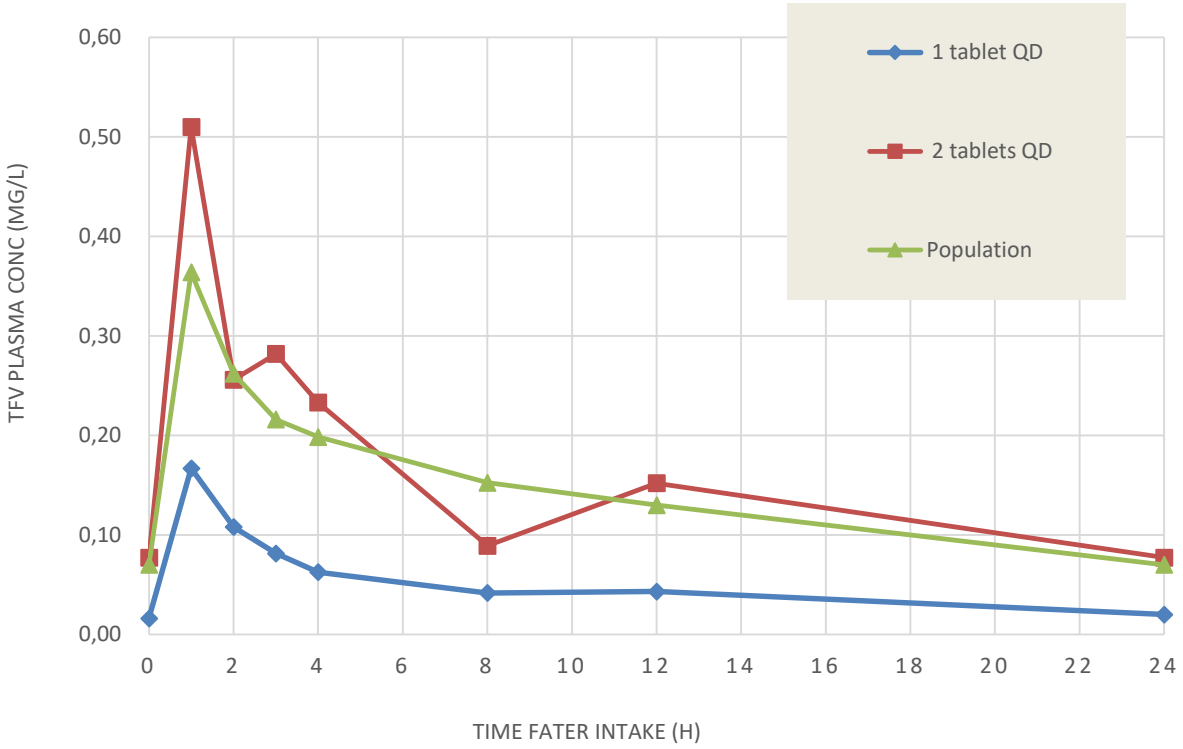
Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid

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



TDM of ARVs anno 2020 (5)

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 (5)

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 $AUC_{0\text{-}24h}$ (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

PK substudy 2: Valganciclovir PK/PD

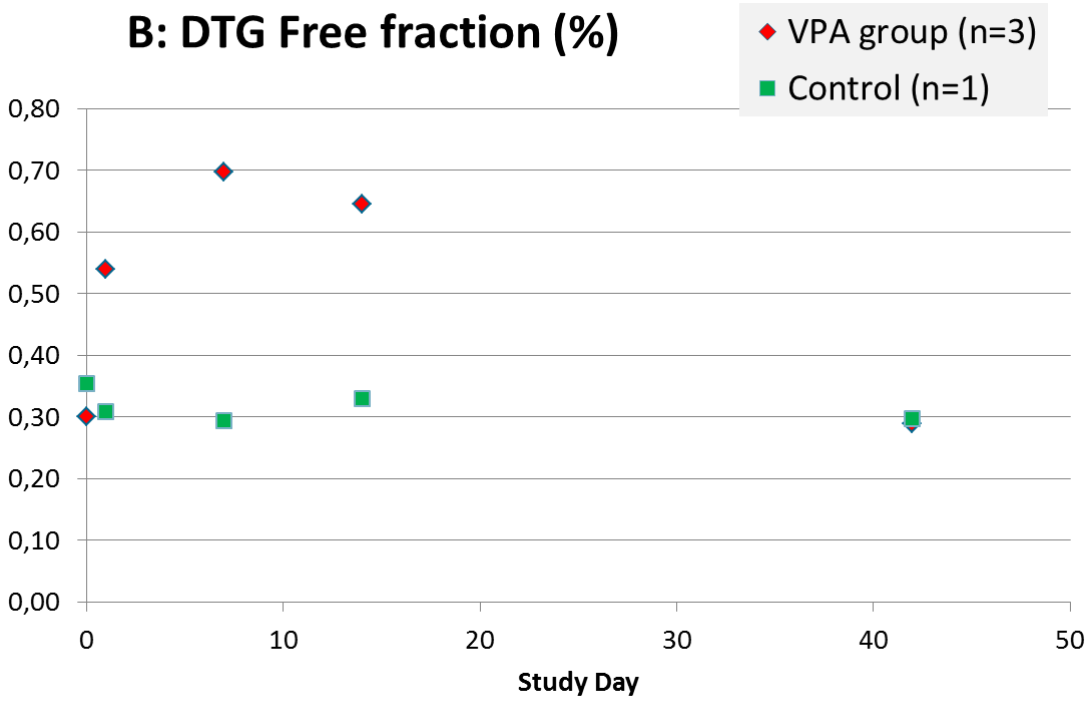
Proposal:

A PK/PD study on ValGCV dosing in EMPIRICAL

- Sampling at Day 3; T=2 and 5h post dosing
- $AUC_{0\text{-}12h} = 2.7 + ((C_{2h} + C_{5h})/2) + 6$ (Villeneuve et al. Ped Transpl 2012)
- 1 mL/sample
- Uganda/Zimbabwe: 200 children; 50% will receive ValGCV; total number of samples 200
- Data can be used to analyze interactions with ART (non-naives vs. naives)
- Data can be used to understand rates of efficacy and toxicity

- EMPIRICAL is a strategic study which (heavily) depends on appropriate dosing

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



Bollen et al. 20th PK Workshop, Noordwijk, 2019

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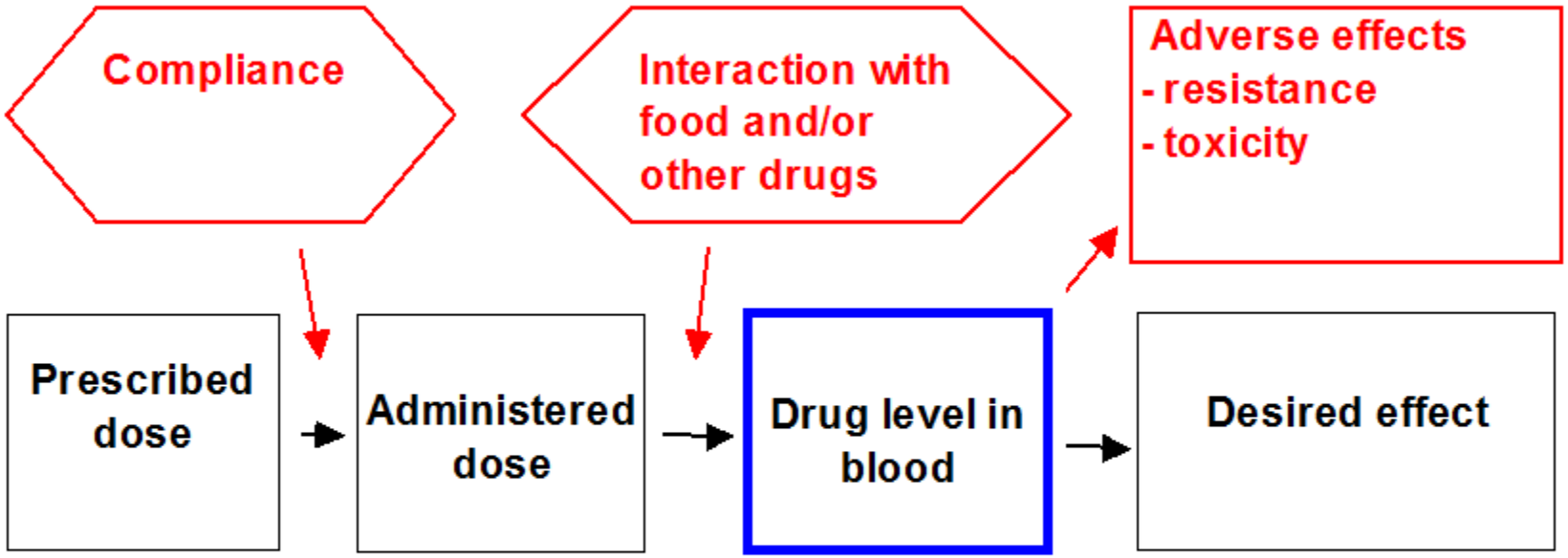
A bright future for TDM!

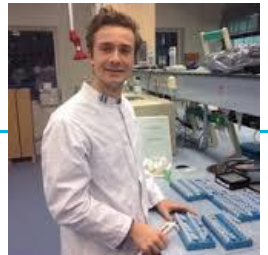


R.E. Aarnoutse, thesis 2003

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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