Clinical Pharmacology of ARVs in the last 10 years: achievements and gaps.

David Back

University of Liverpool

January 2015

UNIVERSITY OF LIVERPOOL

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Outline

1. Achievements - Overview
2. Achievements – 6 Specific Areas
3. Gaps/Developments

1 Achievements - Overview

20 Approved Antiretroviral Agents in 2005

Approved Drugs With Intracellular Mechanisms of Action

NRTIs*	PIs	NNRTIs	Integrase Inhibitors
Abacavir	Amprenavir	Delavirdine	
Didanosine	Atazanavir	Efavirenz	
Emtricitabine	Fosamprenavir	Nevirapine	
Lamivudine	Indinavir		
Stavudine	Lopinavir/ritonavir		
Tenofovir	Nelfinavir		
Zalcitabine	Ritonavir		
Zidovudine	Saquinavir		

Approved Drugs With Extracellular Mechanisms of Action

Fusion Inhibitors
Enfuvirtide

28 Approved Antiretroviral Agents in 2015

Approved Drugs With Intracellular Mechanisms of Action				Approved Drugs With Extracellular Mechanisms of Action
NRTIs*	**PIs**	**NNRTIs**	**Integrase Inhibitors**	**Fusion Inhibitors**
Abacavir	Amprenavir	Delavirdine	Raltegravir	Enfuvirtide
Didanosine	Atazanavir	Efavirenz	Elvitegravir/c	Maraviroc
Emtricitabine	Darunavir	Etravirine	Dolutegravir	
Lamivudine	Fosamprenavir	Nevirapine		
Stavudine	Indinavir	Rilpivirine		
Tenofovir	Lopinavir/r			
Zalcitabine	Nelfinavir			
Zidovudine	Ritonavir			
	Saquinavir			
	Tipranavir			

Change in Recommendation for Initial Therapy

- NRTI: zidovudine (ZDV)
- NNRTI: nevirapine (NVP)*
- PI:
  - unboosted atazanavir (ATV)
  - fosamprenavir (FPV/r)
  - saquinavir (SQV/r)
- Other: maraviroc (MVC)*

** Alternative in EACS Guidelines*

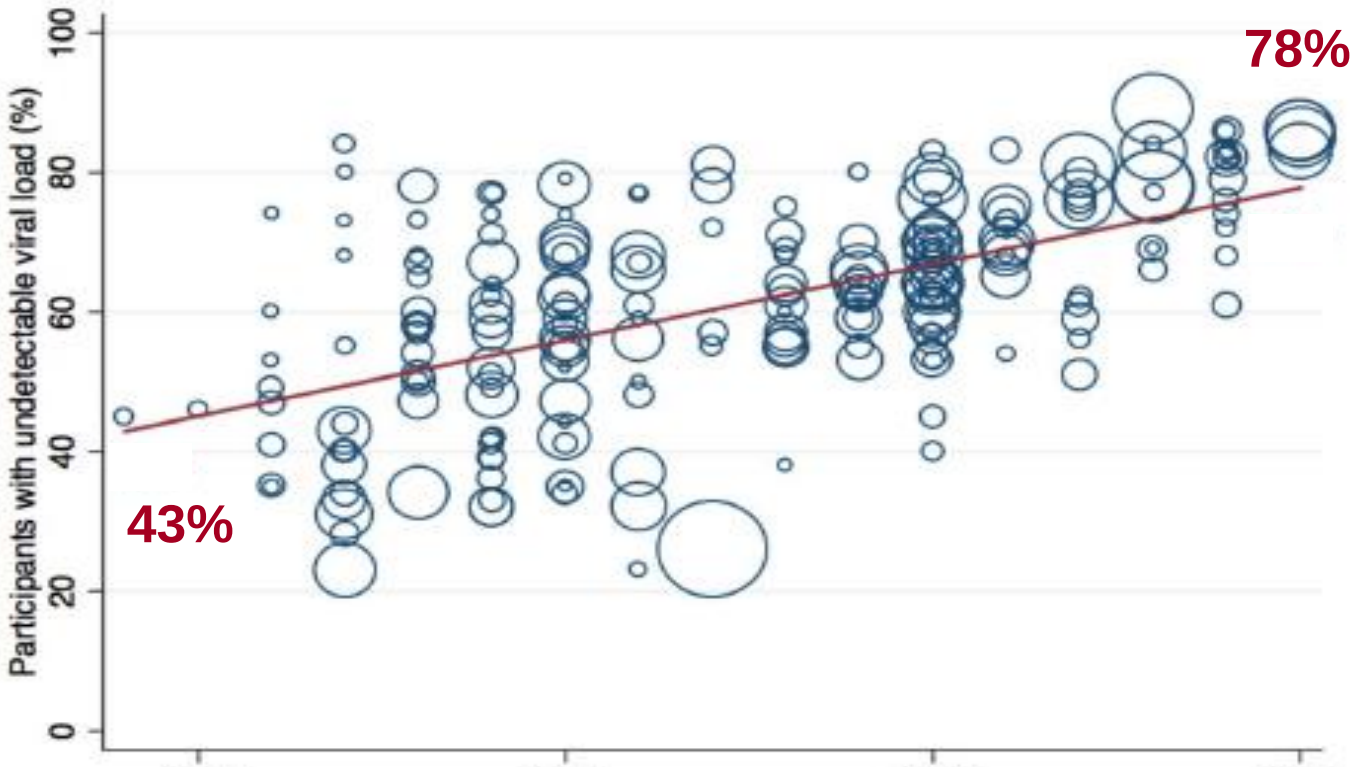
EACS Guidelines Version 7.1, Nov 2014; US DHHS 2014 www.aidsinfo.nih.gov

ART: Convenience - STR

2006 Atripla; 2011 Eviplera; 2012 Stribild; 2014 Triumeq

ART Trials: Virologic Responses

114 studies through 2012, up to 3 years of f/u: ITT analyses



Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Efficacy (SD)	47% (14)	52% (17)	64% (7.1)	74% (8.5)	82% (6.7)

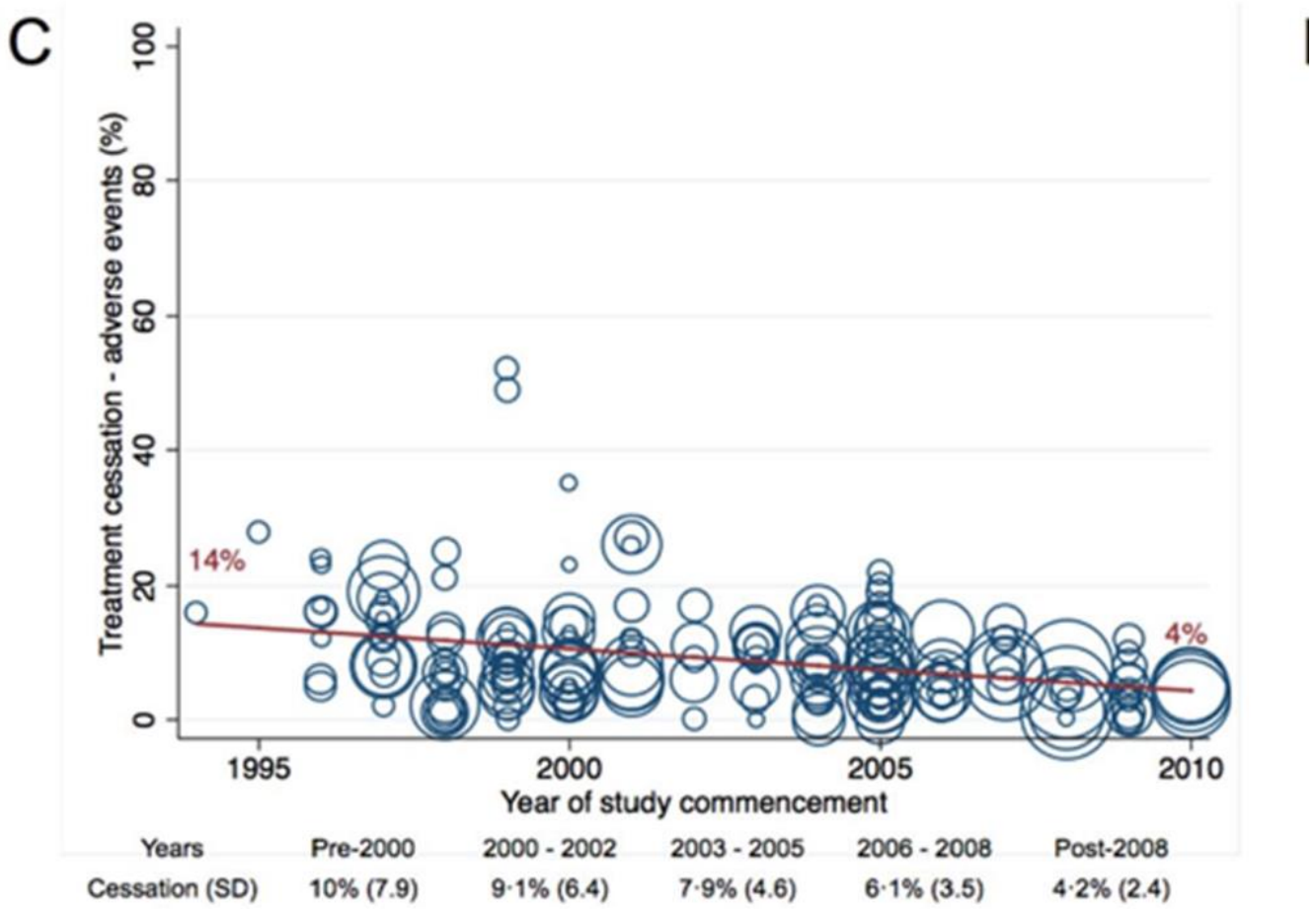
Lee FJ et al PLoS One 2014;9:e97482

Virologic Response Rates

Study (reference)	Study arm (N)	Regimen	HIV RNA <50 at 96 wks
ECHO/THRIVE *Cohen AIDS 2013*	**682**	**2 NRTI + EFV**	**78%**
	686	**2 NRTI + RPV**	**78%**
SPRING-2 *Raffi Lancet Infect Dis 2013*	**411**	**2 NRTI + DTG**	**81%**
GS–US–236–0103: *Rockstroh JAIDS 2013*	**353**	**TDF/FTC/EVG/c**	**83%**
ACTG 5257 *Lennox Ann Intern Med 2014*	**605**	**2 NRTI + ATV/r**	**88%**
	601	**2 NRTI + DRV/r**	**89%**
	603	**2 NRTI + RAL**	**94%**

ART Trials: Safety and Tolerability

114 studies, through 2012, up to 3 years of f/u: ITT analyses



Lee FJ et al PLoS One 2014;9:e97482

Safety/Tolerability Rates

Study (reference)	Study arm (N)	Regimen	% d/c for adverse events at 96 wks
ECHO/THRIVE ***Cohen AIDS 2013***	**682**	**2 NRTI + EFV**	**9%**
	686	**2 NRTI + RPV**	**4%**
SPRING-2 ***Raffi Lancet Infect Dis 2013***	**411**	**2 NRTI + DTG**	**2%**
GS–US–236–0103: *Rockstroh JAIDS 2013*	**353**	**TDF/FTC/EVG/c**	**4%**
ACTG 5257 ***Lennox Ann Intern Med 2014***	**605**	**2 NRTI + ATV/r**	**14%**
	601	**2 NRTI + DRV/r**	**5%**
	603	**2 NRTI + RAL**	**<1%**

Newer Approaches

- **Nucleos(t)ide-sparing regimens**
  - PI monotherapy: multiple studies
    - PROTEA *Antinori Glasgow 2014 #O423A*
  - PI/r + 3TC
    - GARDEL (LPV/r + 3TC): *Cahn Lancet Infect Dis 2014;14:572*
    - OLE (switch; LPV/r + 3TC or FTC): *Gatell IAS 2014 #LBPE17*
    - SALT (switch; ATV/r + 3TC): *Perez-Molina IAS 2014 #LBPE18*
  - PI/r + integrase inhibitor
    - Second-Line (LPV/r + RAL) *Boyd Lancet 2013;381:2091*
    - NEAT-001 (DRV/r + RAL) *Raffi Lancet 2014; 384: 1942-1951*
    - HARNESS (switch; ATV/r + RAL) *Van Lunzen IAS 2014 #LBPE19*

Newer Approaches

- **Lower doses:**
  - **ENCORE 1 (EFV 400 mg vs. 600 mg*):*** *Puls Lancet 2014;383:1474* and *Carey Glasgow 2014 #O421*
  - **PI/r + TDF**: *Hill Glasgow 2014 #P051*
- **New drugs**
  - **tenofovir alafenamide fumarate (TAF)**
    - Phase 2:
      - TAF/FTC/EVG/c vs. TDF/FTC/EVG/c *Sax JAIDS 2014*
      - TAF/FTC/DRV/c vs. TDF/FTC + DRV + cobi *Mills ICAAC 2014 #H-647c*
    - Phase 3: TAF/FTC/EVG/c vs. TDF/FTC/EVG/c
      - *Gilead Press Release 9/24/14*

2 Achievements – A Few Specific Areas

- ❑ Bioanalytical Pharmacology
- ❑ Pharmacogenetics
- ❑ Modelling Pharmacology
- ❑ Transporter Pharmacology
- ❑ Nano Pharmacology
- ❑ IT Pharmacology

Bioanalytical Pharmacology

JAIDS Journal of Acquired Immune Deficiency Syndromes
32:287–291 © 2003 Lippincott Williams & Wilkins, Inc., Philadelphia

Brief Report

Evaluation of Antiretroviral Drug Measurements by an Interlaboratory Quality Control Program

*Jacqueline A. H. Droste, *Rob E. Aarnoutse, †Peter P. Koopmans, *Yechiel A. Hekster, and *David M. Burger

*Departments of Clinical Pharmacy and †General Internal Medicine, University Medical Centre, Nijmegen, The Netherlands

- 30 Labs reported – all using HPLC

Poor Performance of Laboratories Assaying Newly Developed Antiretroviral Agents: Results for Darunavir, Etravirine, and Raltegravir From the International Quality Control Program for Therapeutic Drug Monitoring of Antiretroviral Drugs in Human Plasma/Serum

David Burger, PharmD, PhD, Stefanie Krens, PharmD,* Karen Robijns, PharmD,†
Rob Aarnoutse, PharmD, PhD,* Roger Brüggemann, PharmD, PhD,* and Daan Touw, PharmD, PhD†

(*Ther Drug Monit* 2014;36:824–827)

- 56% using LC-MS

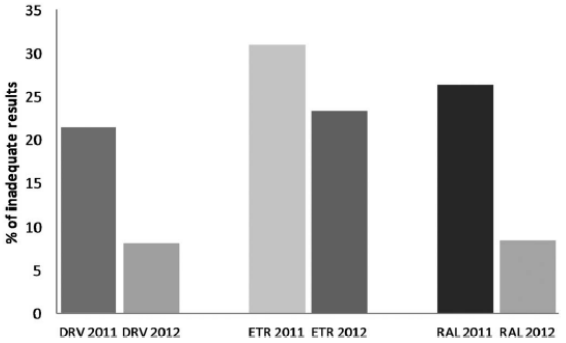


FIGURE 1. Proportion of samples with inaccurate result for darunavir (DRV), etravirine (ETR), and raltegravir (RAL) in 2011 and 2012.

- LC-MS did not perform better

Bioanalytical Pharmacology
Matrices

- *Plasma*
- *Peripheral Blood Mononuclear cells (PBMCs)*
- *Dried Blood Spots (DBS)*
- *CSF*
- *Semen*
- *Vaginal tissue*
- *Vaginal fluid*
- *Rectal tissue*
- *Rectal fluid*
- *GALT*
- *Fine needle aspirates (FNA) of liver.*

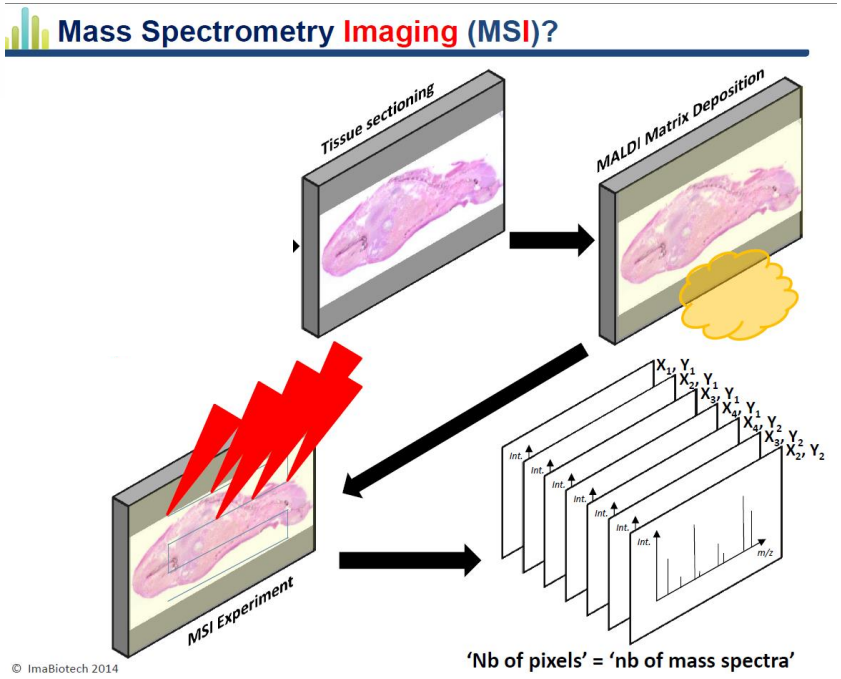
Bioanalytical Pharmacology

Anal Bioanal Chem
DOI 10.1007/s00216-014-8220-y

RESEARCH PAPER

Quantitative mass spectrometry imaging of emtricitabine in cervical tissue model using infrared matrix-assisted laser desorption electrospray ionization

Mark T. Bokhart · Elias Rosen · Corbin Thompson · Craig Sykes · Angela D. M. Kashuba · David C. Muddiman



Pharmacogenetics

Evidence Required to Demonstrate Clinical Utility of Pharmacogenetic Testing: The Debate Continues

NK Gillis[1] and F Innocenti[1,2]

Pharmacogenetics is an area of research that has potential to greatly benefit patients. However, the routine use of diagnostic pharmacogenetic testing to inform treatment decisions is limited. Here we discuss the determination of clinical utility of pharmacogenetic testing and the level of evidence required to support translation into clinical practice.

> Success stories of PGx tests, such as HLA-B*5701 testing and the antiretroviral agent abacavir as well as HER2 testing and trastuzumab, do meet the three criteria of statistical association, clinical utility, and cost-effectiveness. However, in these examples testing is directed at selected populations prior to prescribing, and at present these cases do not warrant preemptive testing for the population at large.

Janssens & Deverka 2014

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 96 NUMBER 6 | DECEMBER 2014

Pharmacogenetics

Review

EXPERT OPINION

Pharmacogenetics of antiretroviral therapy

Pablo Barreiro, José Vicente Fernández-Montero, Carmen de Mendoza, Pablo Labarga & Vincent Soriano†

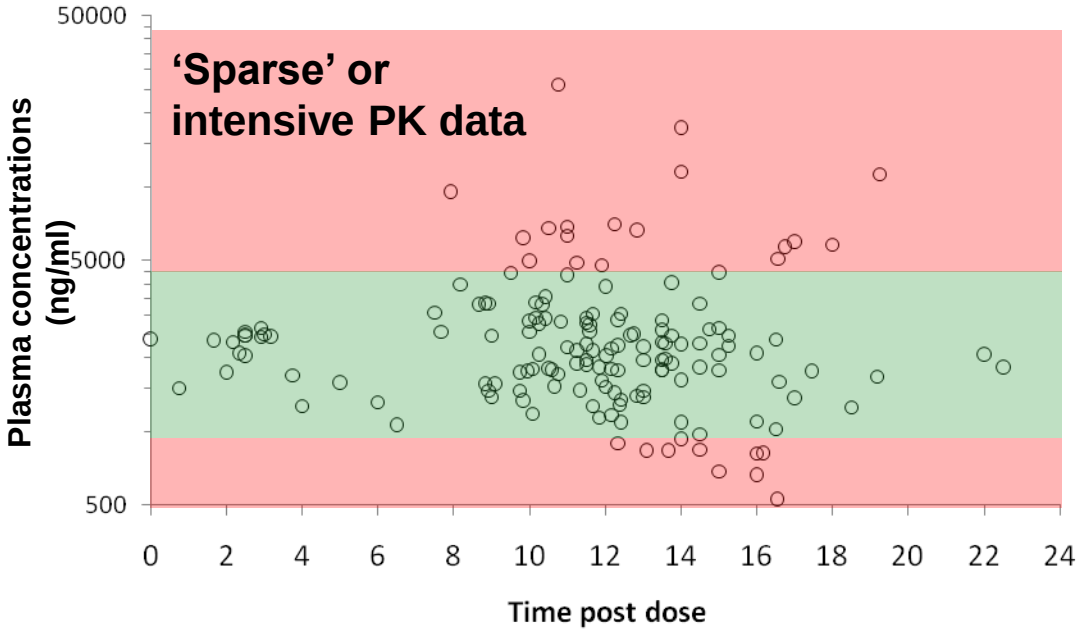
†*Hospital Carlos III, Department of Infectious Diseases, Madrid, Spain*

- Identification of SNPs at genes involved in ADME of ARVs has increased understanding of determinants of drug exposure and potentially drug response

- Genotyping prior to prescribing ARVs would allow
  - Maximising antiviral effect
  - Minimising ADRs
  - Managing DDIs

Barreiro P et al Expert Opinion Drug Metab Toxicol 2014; 10: 1119-1130

Modelling Pharmacology



TOP-DOWN

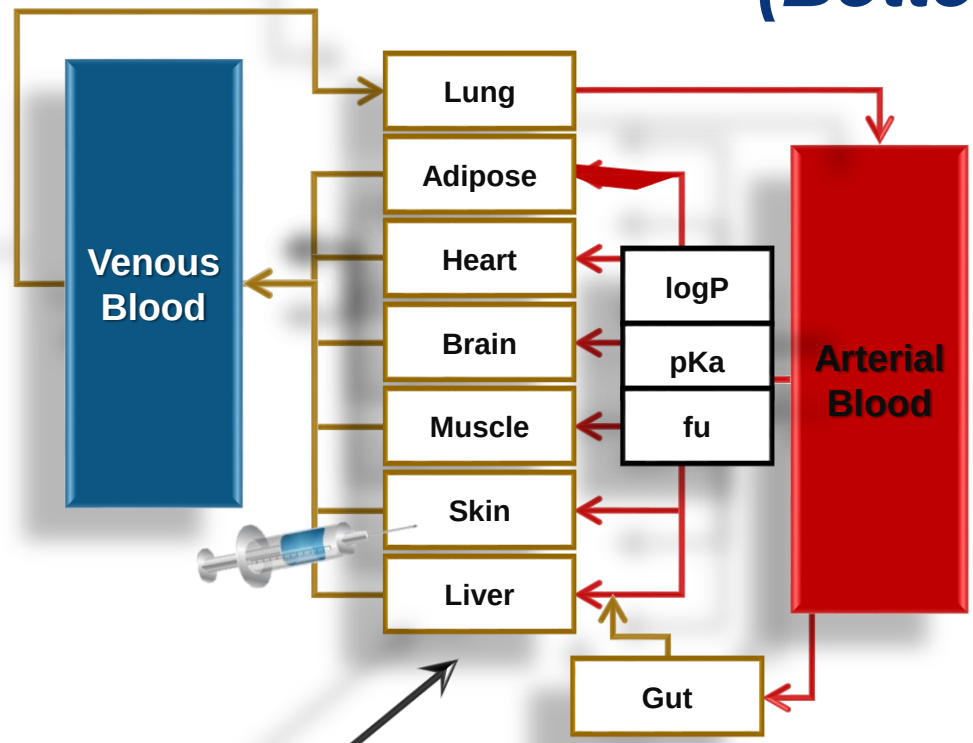
Analyse the data by POPULATION PK to help explain the variability by identifying factors such as:

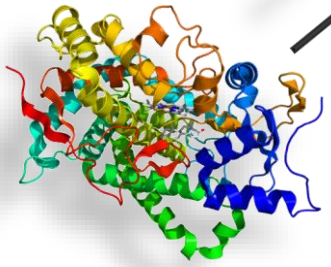
DEMOGRAPHICS **COMORBIDITIES**

DRUG DRUG INTERACTIONS **GENETICS**

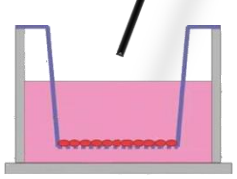
Modelling Pharmacology (PBPK)

(Bottom Up)





baculosomes

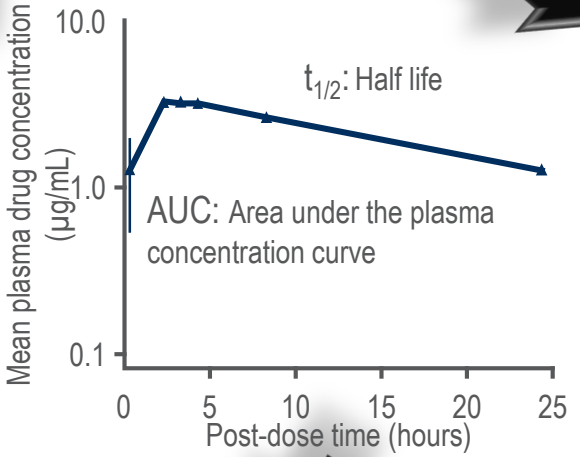


CACO-2 transwell

CLEARANCE

VOLUME OF DISTRIBUTION

BIOAVAILABILITY



DOSE REDUCTION

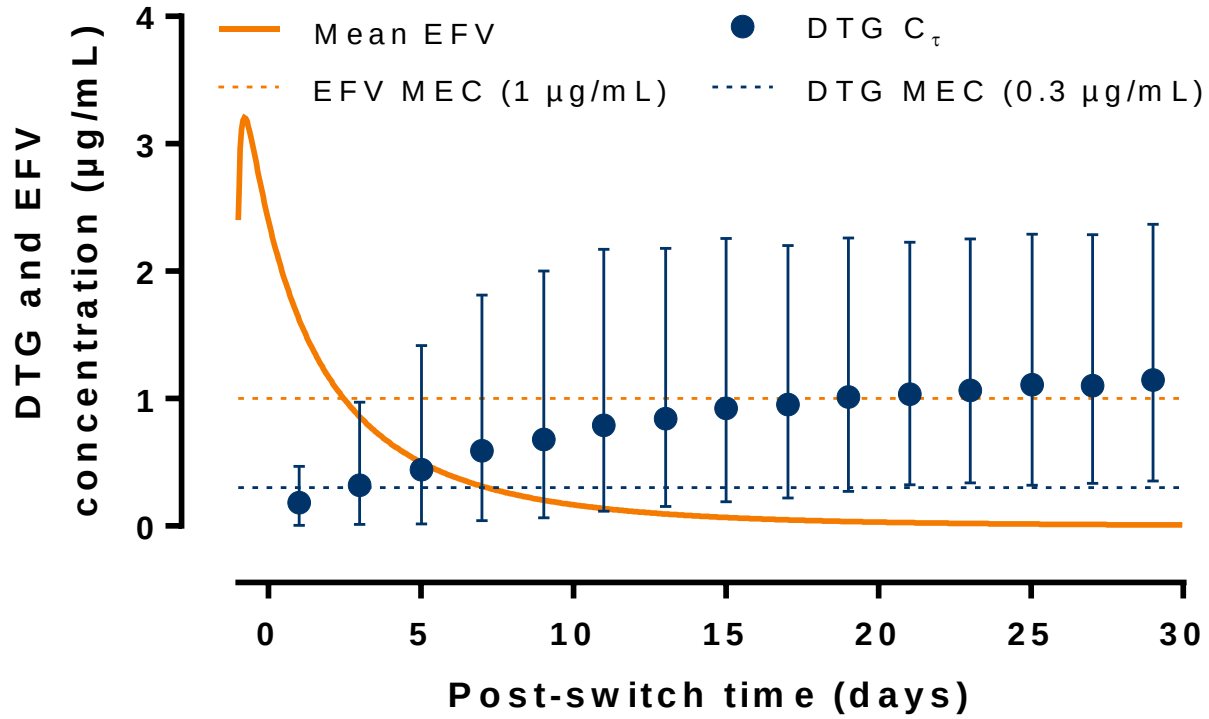
PK IN SPECIAL POPULATION

DRUG-DRUG INTERACTION

NOVEL FORMULATIONS

PHARMACOGENETICS

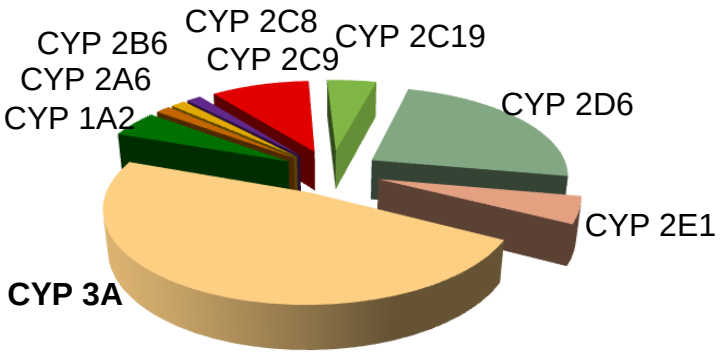
A mechanistic simulation evaluating dolutegravir and efavirenz PK following a switch from once-daily efavirenz to once-daily dolutegravir

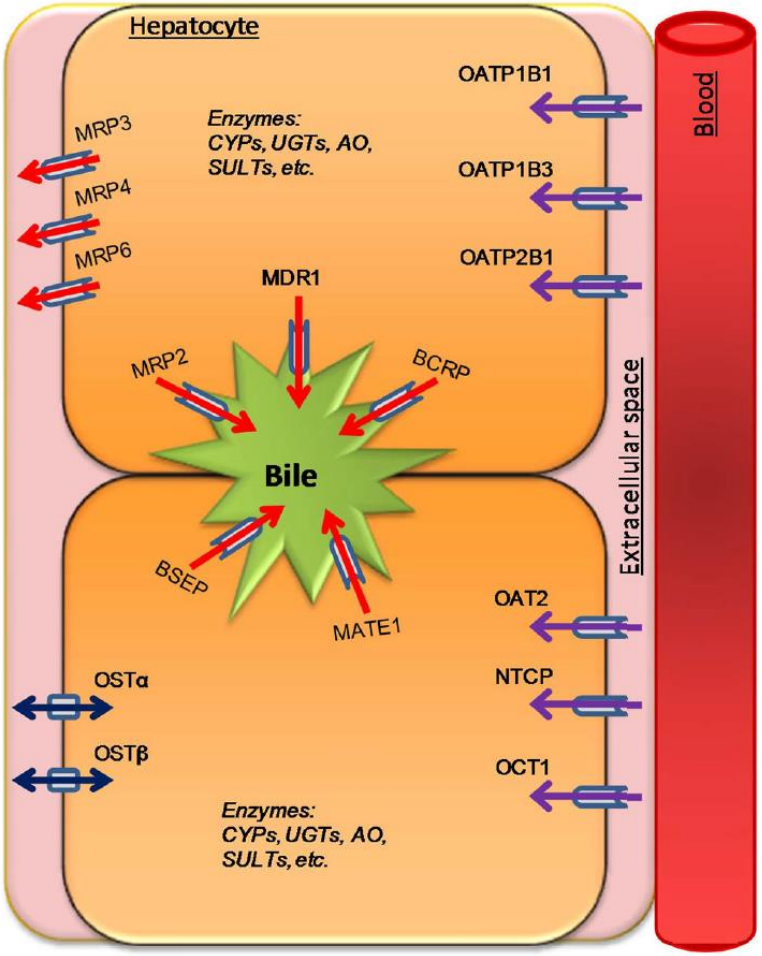


Generaux G et al. 15th Int Wkshp on Clin Pharm of HIV and Hep Tx. May 19-21, 2014; Washington, DC. P_36.

Transporter Pharmacology: Hepatic

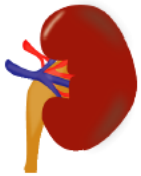
Proportion of drugs that are substrates for major CYP enzymes

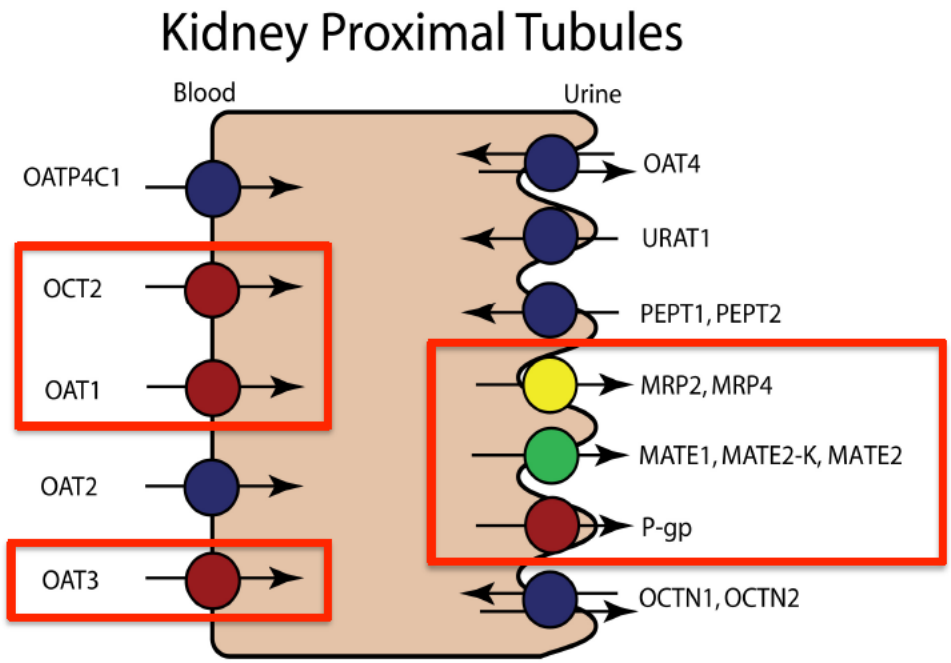




Li R et al Clin Pharmacokinetic 2014; 53: 659-678.

Transporter Pharmacology: Renal

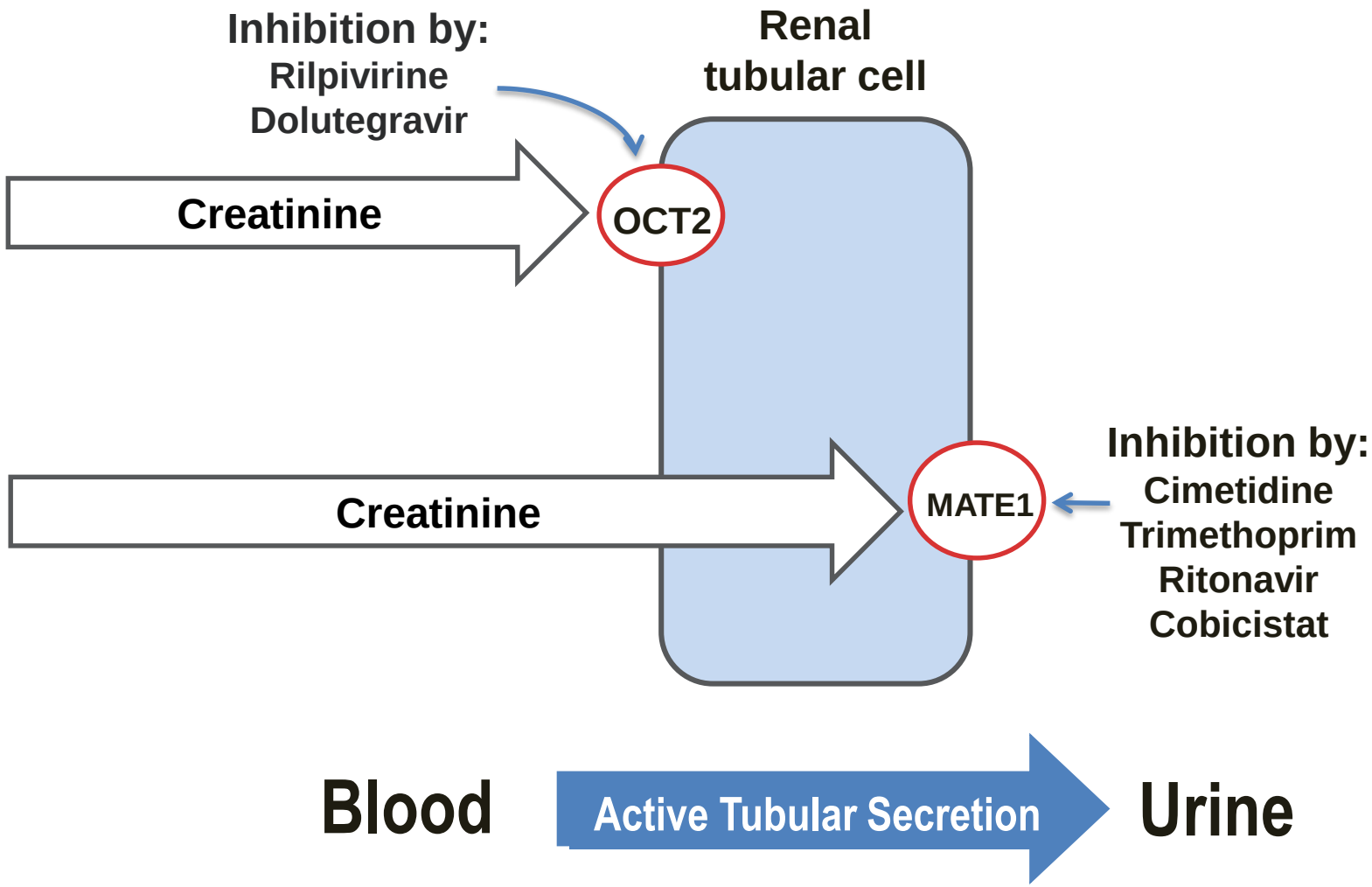




INTERNATIONAL TRANSPORTER CONSORTIUM

Giacomini KM, et al. Nat Rev Drug Discov. 2010 Mar;9(3):215-36.
Zamek-Gliszczynski et al., Clin Pharmacol Ther 92: 553-556, 2012.

Renal Transporters and Creatinine Clearance



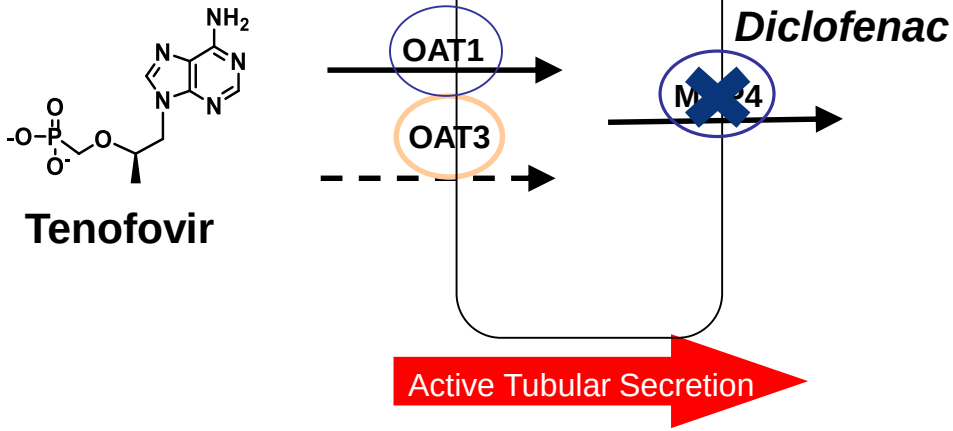
CR, creatinine

Adapted from Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724

Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration ‡

M Bickel,[1] P Khaykin,[1] C Stephan,[1] K Schmidt,[1] M Buettner,[2] K Amann,[2] T Lutz,[3] P Gute,[3] A Haberl,[1] H Geiger,[4] HR Brodt[1] and O Jung[4]

- Retrospective analysis of 89 patients with diclofenac prescriptions
- 68.5% treated with TDF regimen
- 31.5% treated with TDF-sparing regimen
- 13 patients (14.6%) developed AKI after initiating diclofenac. ALL were TDF-treated patients.



NSAID	IC50 MRP4 [uM]
Celecoxib	35
Diclofenac	**0.006**
Ibuprofen	26.3
Indomethacin	6.1
Naproxen	42.3
Piroxicam	216

Nanomedicine

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Are You New To Nanomedicine?

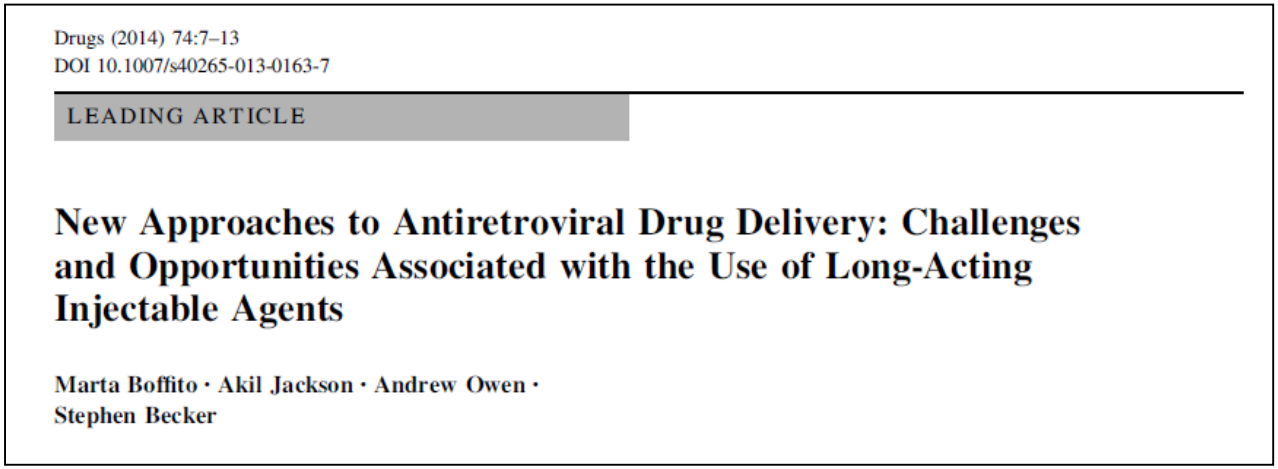
Information about nanomedicine for people without background knowledge in science is provided. Provides an introduction to nanomedicine, an overview of the nanomedicines currently in clinical use, a glossary of sciencitifc terms often used in nanomedicine and a section on frequently asked questions.

read more

An application of Nanomedicine: Long-acting formulations

- Used to improve adherence and prevent missed doses/treatment fatigue in several therapeutic areas
- Contraception: (Depo Provera)
- Schizophrenia: 6 long-acting antipsychotics available (e.g. risperidone, olanzapine, aripiprazole)
- Hypogonadism: (testosterone undecanoate)

Nanomedicine applied to antiviral drug delivery



Drugs (2014) 74:7–13
DOI 10.1007/s40265-013-0163-7

LEADING ARTICLE

New Approaches to Antiretroviral Drug Delivery: Challenges and Opportunities Associated with the Use of Long-Acting Injectable Agents

Marta Boffito · Akil Jackson · Andrew Owen · Stephen Becker

- Main focus on *prevention* but interest also in *treatment*
- 2 drugs in clinical trials (PK and PK-PD):
  - *Rilpivirine*
  - *Cabotegravir (GSK-1265744)*

Boffito M, et al. Drugs 2014;74:7–13

IT Pharmacology

ARV Drug Interaction Resources

- **hivinsite.ucsf.edu.**

  Updated drug interaction database and interactive tool to assess DDIs

- **www.aidsinfo.nih.gov**

  DHHS guidelines for use of ARVs with updated interaction tables

- **www.hivclinic.ca.**

  Updated drug interaction tables. Downloadable.

- **www.eacsociety.org**

  European guidelines including drug interaction tables.

- **www.hivmedicationguide.com**

  Updated interactive drug interaction database. Apps (iPhone; iPad)

- **Micromedex.com.**

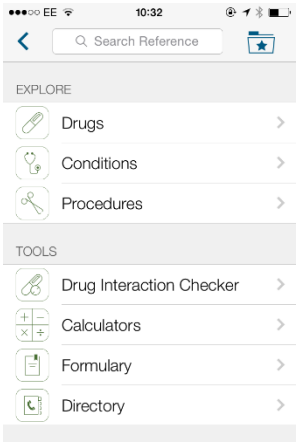
  Comprehensive database (subscription required)

- **www.lexi.com**

  Lexi-interact database (subscription required)

- **www.hiv-druginteraction.org;**
- **www.hep-druginteraction.org.**

Valuable Apps



Top 5 RED searches in 12 month period

Number of Searches	Interaction	
500	Atazanavir - Omeprazole	*v*
268	Darunavir – Quetiapine	*p*
237	Rilpivirine - Omeprazole	*v*
230	Darunavir - Rifampicin	*v*
186	Ritonavir - Quetiapine	*p*

PIs = 4; NNRTIs = 1;
v = victim; p = perpetrator

Top 10 AMBER searches in 12 month period

Number of Searches	Interaction	
642	Darunavir - Atorvastatin	*p*
587	Efavirenz - Atorvastatin	*p*
542	Darunavir - Tenofovir	*p*
461	FTC - Trimethoprim/Sulfamethoxazole	*v*
441	Tenofovir - Ibuprofen	*v*
426	Atazanavir - Ranitidine	*v*
393	Darunavir - Pravastatin	*p*
389	Rilpivirine - Ranitidine	*v*
378	Darunavir - Mirtazapine	*p*
368	Raltegravir – Rifampicin	*v*

PIs = 5; NNRTIs = 2; NRTIs = 2; InI = 1
Statins = 3; ARAs = 2

Antiretrovirals and Interaction Potential

Highest potential	Moderate Potential	Low Potential
Boosted PIs Perpetrators – enzyme and transporter Inhibition Victim - absorption (ATV); induction	**Rilpivirine** Victim of enzyme inhibition and induction. Also absorption.	**Raltegravir** Victim of few induction and absorption interactions
EVG/cobi Perpetrator – enzyme and transporter inhibition Victim - absorption; induction	**Maraviroc** Victim of enzyme inhibition and induction.	**Most NRTIs** Some transporter mediated
Efavirenz, nevirapine, etravirine Perpetrators – enzyme and transporter induction	**Dolutegravir** Victim of enzyme inhibition and absorption interactions	

www.hiv-druginteractions.org

3 Gaps/Developments

Newer Approaches

- Active against drug-resistant strains
  - **Doravirine (NNRTI)**
    - Active in vitro against viral strains with K103N, Y181C, G190A, E101K, E138K or K103N/Y181C *Lai AAC 2014;58:1652-1663*
    - Phase 2*: Morales-Ramirez CROI 2014 #92LB; Gatell Glasgow 2014 #O434*
  - **Fostemsavir (BMS-66308) – CD4 Attachment Inhibitor**
    - Phase 2: *Lalezari CROI 2014 #86; Lataillade Glasgow 2014 #O432A/B*
  - **Maturation inhibitors:**
    - BMS-955176 Phase 1: (clinicaltrials.gov: NCT01803074)
    - GSK2838232 Phase 1: (clinicaltrials.gov: NCT01802918)

Anticipated developments in the Integrase Inhibitor field

- EVG/cobi/TAF/FTC – single tablet regimen
  (NDA submitted to FDA – Nov 2014)
- DTG/RPV – single tablet regimen
- RAL/3TC – once daily co-formulation
- Cabotegravir (GSK 1265744)

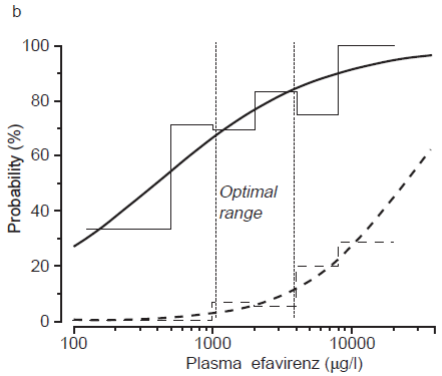
Challenges

- PK-PD in Pre-exposure prophylaxis
- Pharmacology of eradication
- Target concentrations for treatment and prevention

Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients

Catia Marzolini[a], Amalio Telenti[b], Laurent A. Decosterd[a], Gilbert Greub[b], Jérôme Biollaz[a] and Thierry Buclin[a]

AIDS 2001, **15**:71–75



- Post approval drug interaction studies
- Net effect of multiple concomitant interactions

Challenges

- Special populations (*Elderly, Paediatrics, Breast Feeding)*
- Generics –what are the questions?; what are the studies?
- If we are overdosing ARVs – what is the path to acceptance and implementation?

- ***Training of Clinical Scientists who will take forward this vital area.***

- ***Greater involvement of Pharmacists***

16TH INTERNATIONAL WORKSHOP ON

CLINICAL PHARMACOLOGY OF HIV & HEPATITIS THERAPY

HIV Hepatitis

WASHINGTON DC, USA • 26 - 28 MAY 2015

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University of Colorado, USA

Angela Kashuba, PharmD
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Juergen Rockstroh, MD
University of Bonn, Germany

Jonathan Schapiro, MD
Sheba Medical Centre, Israel

virology education

TENTATIVE PROGRAM

Tuesday 26 May

16.00h **Opening of the Workshop**
David Back & Jürgen Rockstroh

16.15h **Opening Lecture: The Ebola Crisis – Prospects for Antiviral Treatment**
Sina Bavari, PhD - *U.S. Army Medical Research Institute of Infectious Diseases, USA*

Session 1: Hepatitis B

16.45h **Invited lecture: HBV – What's in the Pipeline?**
Shyamasundaran Kottilil, MBBS, PhD (t.b.c.)

17.15h Oral Abstract Presentations

18.15h Discussion

18.30h End of Plenary Session

Poster Viewing & Drinks

Wednesday 27 May

Session 2: Novel Formulations

08.30h **Nanoformulations – Enhancing Drug Exposure in Cells**
Rodney J Ho, PhD - *University of Washington, Seattle, USA*

09.00h **Nanoformulations – an Update from Janssen**
Herta Crauwels, PhD - *Janssen Infectious Diseases, Belgium*

09.20h **Nanoformulations – an Update from GlaxoSmithKline**
William Spreen, PharmD - *GlaxoSmithKline, USA*

09.40h Discussion

10.00h Oral abstract presentations

10.30h Coffee break + Poster viewing

Session 3: Abstract-driven presentations

11.30h Oral Abstract Presentations

12.30h **Case Presentation: Recreational Drug Use**
Marta Boffito, MD, PhD - *Chelsea and Westminster Hospital, United Kingdom*

13.00h Lunch

Session 4: Roundtable Discussion: Methodology for Determining Drug in Reservoirs/Tissue

14.00h **Quantitative Imaging**
Angela Kashuba, PharmD - *University of North Carolina, Chapel Hill, USA*

14.30h **Determining drug in Liver**
Andrew Talal, MD, MPH - *University of Buffalo, New York, USA*

15.00h **Determining drug in Lymph nodes**
Courtney Fletcher, PharmD - *University of Nebraska Medical Center, USA*

15.30h Discussion

16.00h Coffee break

Session 5:

16.30h **Case presentation: Patient with Renal Failure**
Cristina Wyatt, MD, BA, MS - *Mount Sinai Hospital, New York, USA*

17.00h **Oral abstract presentations**

17.45h **Pharmacogenetics of CYP3A5**
Namandje Bumpus, PhD - *Johns Hopkins University, Baltimore, USA*

18.15h End of Plenary session

Workshop Dinner

Thursday 28 May

Session 6: Hepatitis C

08.30h **The Clinical Pharmacology of HCV Drugs in Severe Liver Disease**
Jennifer Kiser, PharmD – *University of Colorado Skaggs, Denver, USA*

08.50h **Company updates on the Clinical Pharmacology and DDI profile of HCV drugs:**

Abbvie
Rajeev Menon, PhD - *Abbvie, USA*

Merck
Wendy Yeh, PhD - *Merck, USA*

Gilead
T.b.c.

BMS
T.b.c.

10.00h Oral abstract presentations

10.30h Coffee break & Poster viewing

Session 7: Debate: 'Are we overdosing Antivirals?'

11.30h **Yes-standpoint**
David Ripin, BS, PhD - *Clinton Health Access Initiative (CHAI), Boston, USA*

No-standpoint
Richard Elion, MD - *Whitman-Walker Health, Washington, USA*

FDA perspective
Jeffrey Murray, MD - *US Food and Drug Administration, USA (t.b.c.)*

13.00h Lunch

Session 8: Abstract-driven presentations

14.00h Oral abstract presentations

15.00h Best of posters / Clinical case presentations

15.30h Closure of the workshop

10TH RESIDENTIAL COURSE ON CLINICAL PHARMACOLOGY OF ANTIRETROVIRALS

2005
2006
2007
2009
2010
2011
2012
2013
2014

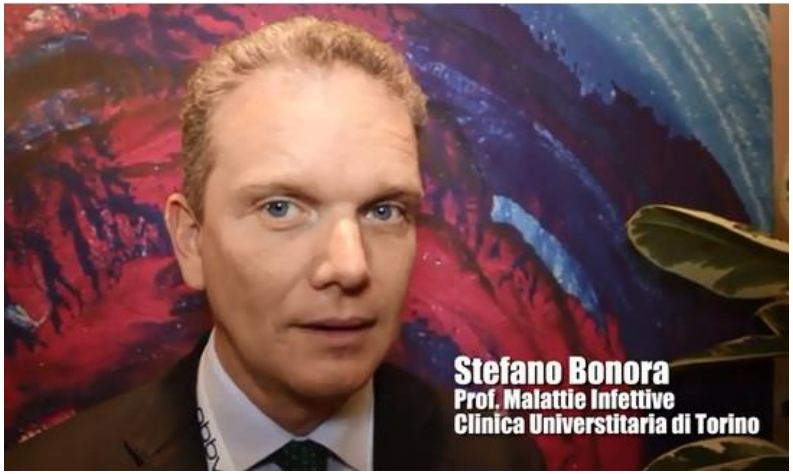
21-22-23 January 2015

Starhotels Majestic

corso Vittorio Emanuele II 54 - **TURIN**

10TH ANNIVERSARY

Grateful Thanks



Pos	Team	P	GD	Pts
1 —	Juventus	19	33	46
2 —	Roma	19	18	41
3 ▲	Napoli	19	10	33
4 ▲	Sampdoria	19	8	33
5 ▼	Lazio	19	11	31
6 —	Fiorentina	19	9	30
7 —	Genoa	19	4	28
8 —	Milan	19	5	26
9 —	Inter Milan	19	4	26
10 —	Palermo	19	0	26
11 —	Sassuolo	19	-3	25
12 —	Udinese	19	-3	24
13 ▲	Torino	19	-5	22
14 ▼	Verona	19	-11	21
15 ▲	Atalanta	19	-9	20
16 ▼	Empoli	19	-6	19
17 ▼	Chievo	19	-8	18
18 —	Cagliari	19	-12	16
19 ▲	Cesena	19	-22	9
20 ▼	Parma	19	-23	9

Pos	Team	P	GD	Pts
1 —	Chelsea	22	32	52
2 —	Man City	22	23	47
3 —	Southampton	22	21	42
4 —	Man Utd	22	15	40
5 —	Arsenal	22	14	39
6 —	Tottenham	22	2	37
7 —	West Ham	22	10	36
8 —	Liverpool	22	4	35
9 —	Swansea	22	-4	30
10 —	Stoke	22	-4	29
11 —	Newcastle	22	-9	27
12 —	Crystal Palace	22	-8	23
13 —	Everton	21	-4	22
14 —	Aston Villa	22	-14	22
15 —	West Brom	21	-9	21
16 —	Sunderland	22	-14	20
17 —	Burnley	22	-15	20
18 —	Hull	22	-10	19
19 —	QPR	22	-16	19
20 —	Leicester	22	-14	17