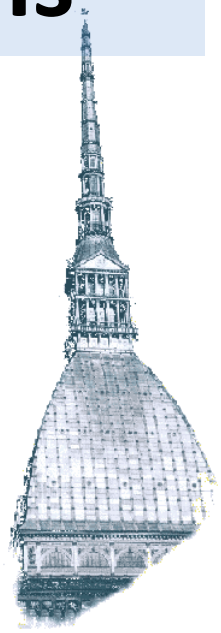
14th Residential Course on Clinical Pharmacology of Antiretrovirals

Turin, 16-18 January 2019

Why Clinicians should know the Clinical Pharmacology of Antivirals

Gianni Di Perri

Clinica di Malattie Infettive
Università degli Studi di Torino
Ospedale Amedeo di Savoia



Ospedale Amedeo di Savoia

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- Abbvie
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- GS
- MSD
- Janssen
- ViiV
- Pfizer
- Novartis
- Astellas
- Basilea

BJCP British Journal of Clinical Pharmacology 2010

A manifesto for clinical pharmacology from principles to practice

Jeffrey K. Aronson

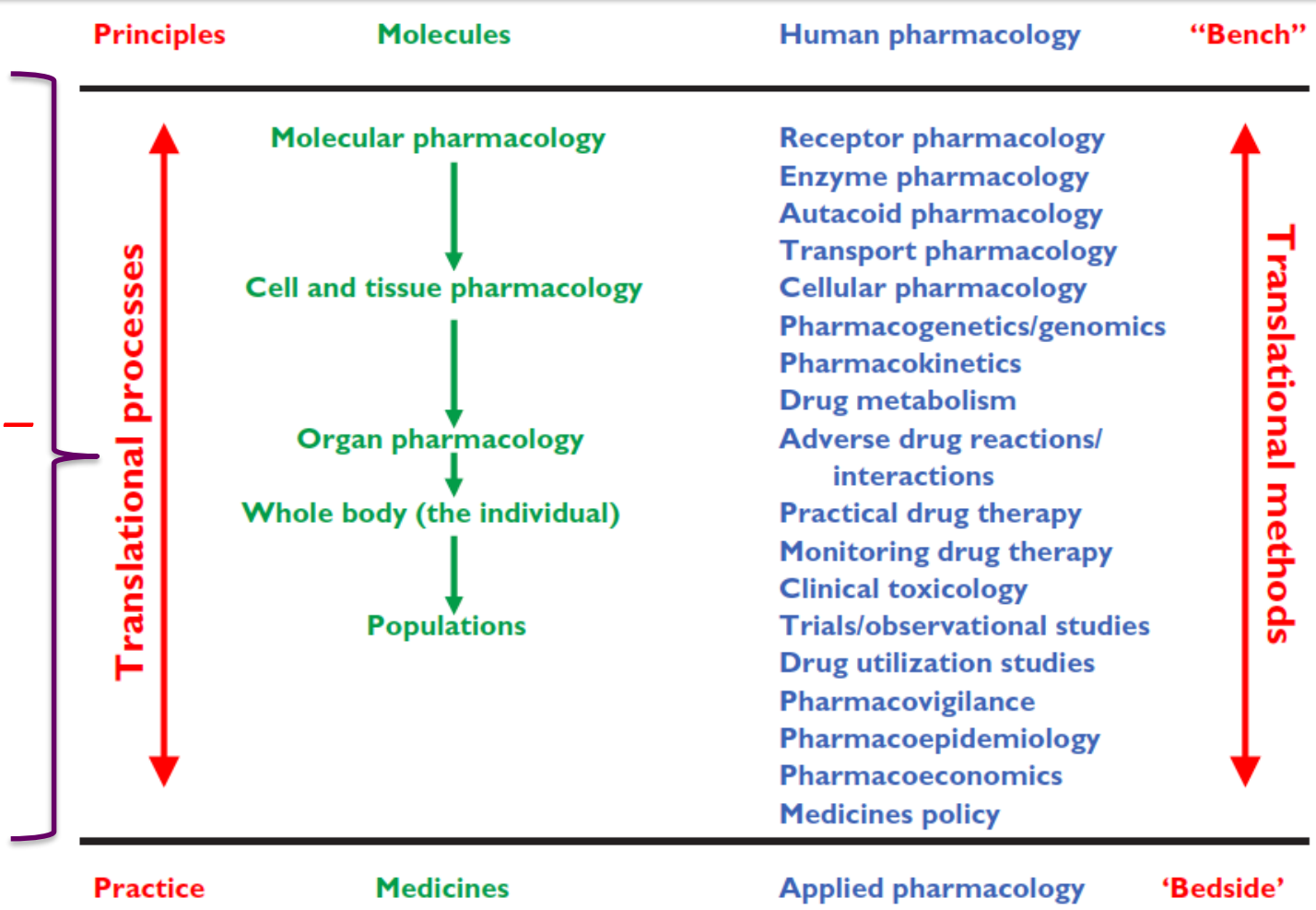
University Department of Primary Health Care, Rosemary Rue Building, Old Road Campus, Headington, Oxford OX3 7LF, UK

Br J Clin Pharmacol / **70**:1 / 3–13

The essence of clinical pharmacology – an intensional definition

Clinical pharmacology, intensionally defined, is all aspects of the study and use of drugs in humans.

The scope of clinical pharmacology – an extensional definition



A definition of a clinical pharmacologist

I define a clinical pharmacologist as 'a medically qualified practitioner who teaches, does research, frames policy, and gives information and advice about the actions and proper uses of medicines in humans and implements that knowledge in clinical practice.'

Medically qualified practitioner In the UK and elsewhere there are academic practitioners who are regarded as clinical pharmacologists but who are not clinically qualified. I am reluctant to exclude them from my definition, because I recognize and value the contributions that they make.

In Italy few MD work on clinical pharmacology and most pharmacologist do not work on applied clinical pharmacology

The clinical pharmacology of integrase inhibitors

Giovanni Di Perri, Andrea Calcagno, Alice Trentalange, Stefano Bonora

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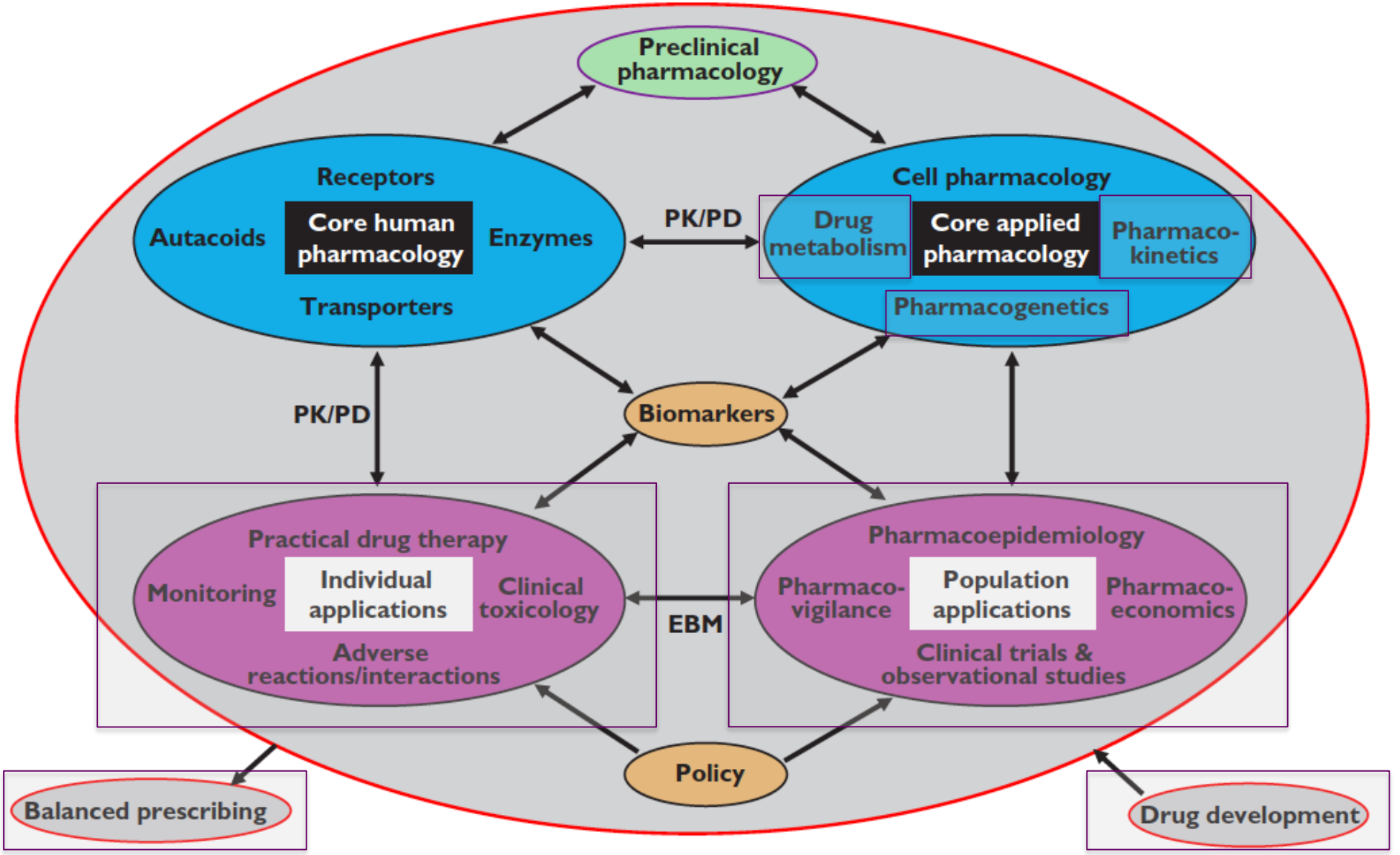
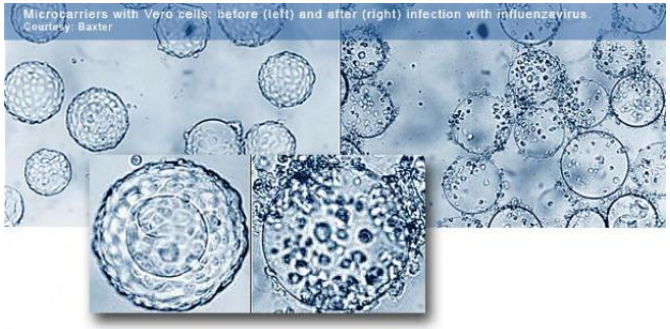
…Although many different definitions might apply for clinical pharmacology, (mainly depending on the side we look at the issue - from a pharmacologist' or clinician viewpoint), it usually stands for the study of those pharmacologic features of a given drug or regimen that may impact on the treatment outcome and should drive the therapeutic process…..


Preclinical pharmacology
Receptors
Autacoids
Core human pharmacology
Enzymes
Transporters
PK/PD
Cell pharmacology
Drug metabolism
Core applied pharmacology
Pharmaco-kinetics
Pharmacogenetics
PK/PD
Biomarkers
Practical drug therapy
Monitoring
Individual applications
Clinical toxicology
Adverse reactions/interactions
EBM
Pharmacoepidemiology
Pharmaco-vigilance
Population applications
Pharmaco-economics
Clinical trials & observational studies
Policy
Balanced prescribing
Drug development

POINT n. 1

As compared to other branches of medical therapy, here we fight against multiplying entities, whose sensitivity to drugs is first established in “in vitro” studies on cells, in animals and then in humans.



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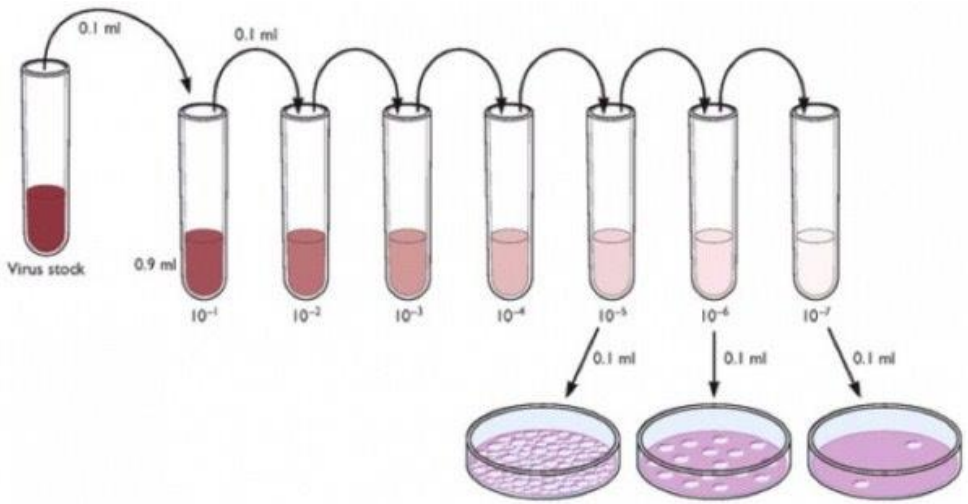
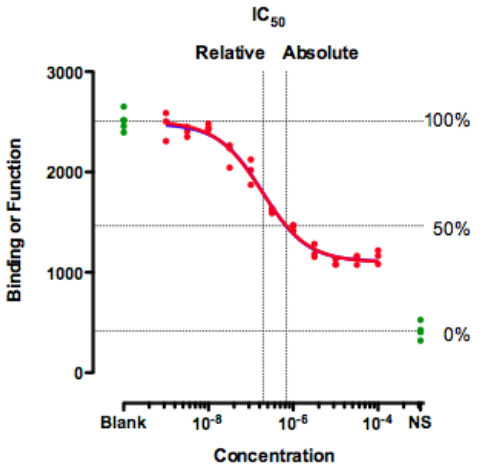
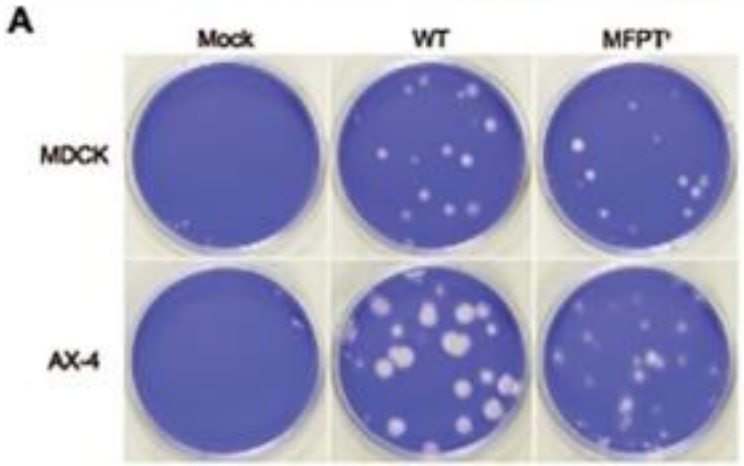
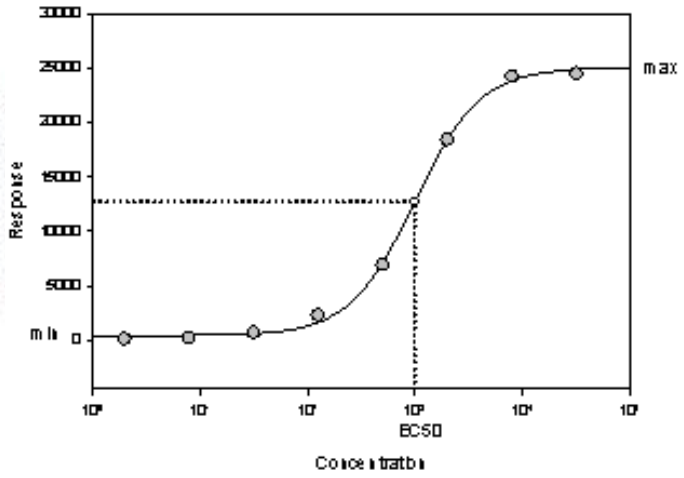




$IC_{50, 90...}$



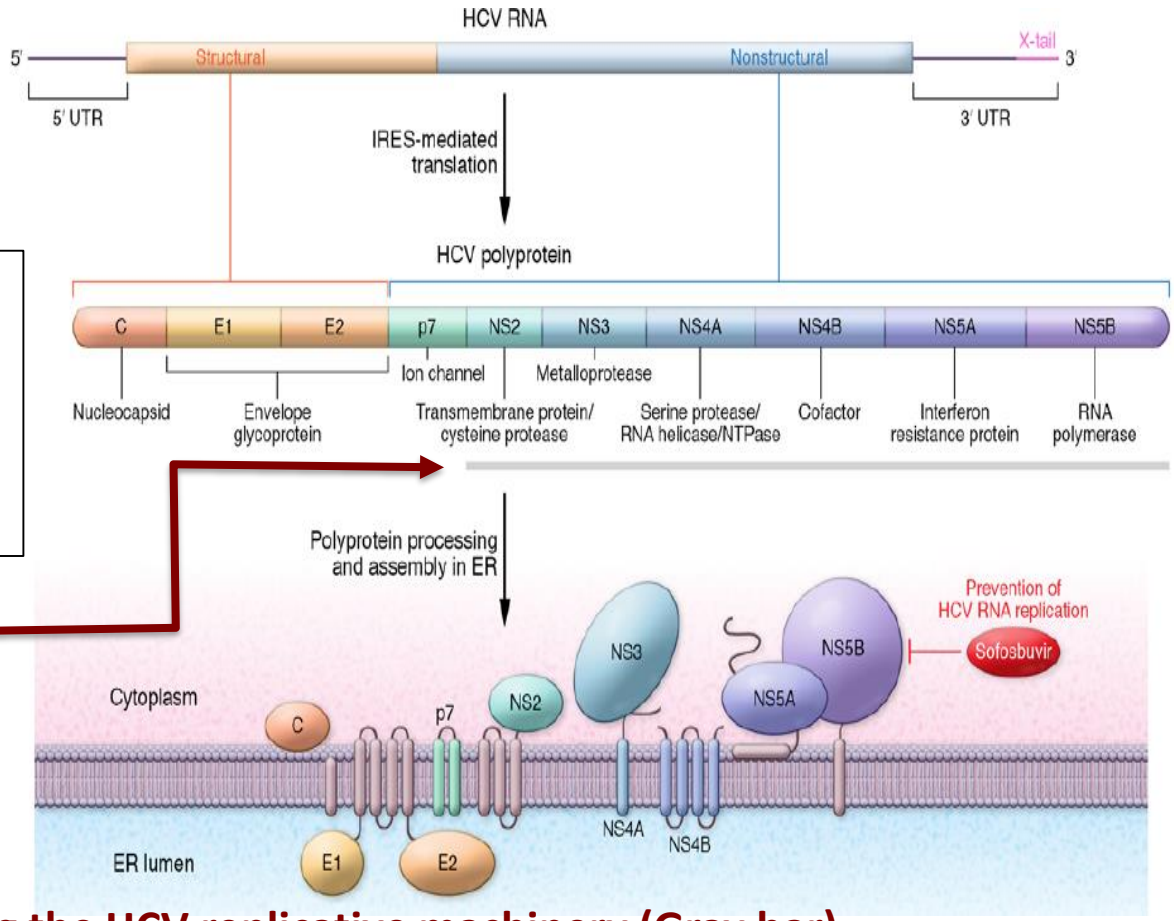


$EC_{50, 90...}$

Ralf Bartenschlager, Charles Rice, and Michael Sofia are honored with the 2016 Lasker~DeBakey Clinical Medical Research Award

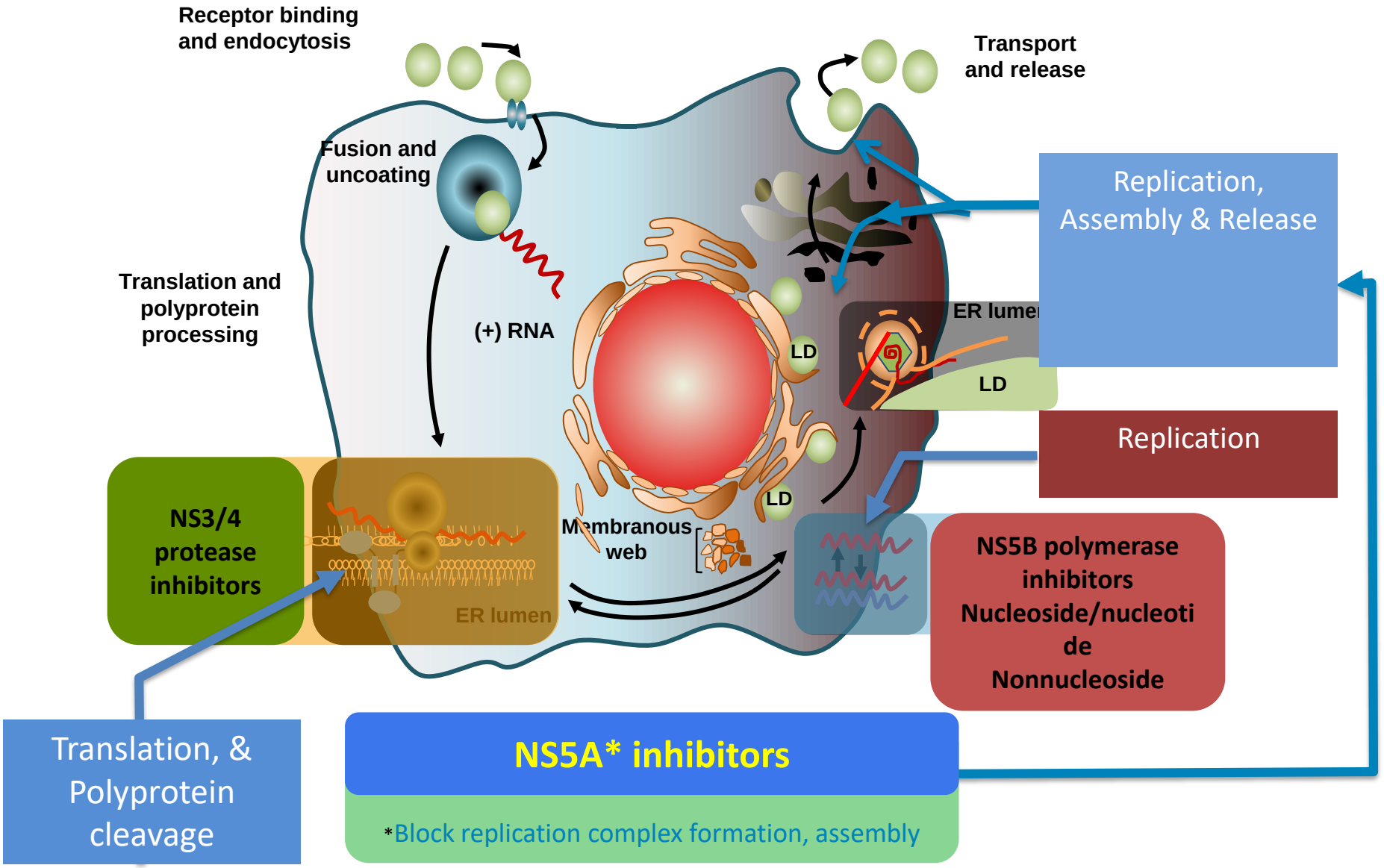
jci.org Volume 126 Number 10 October 2016

Lohmann V, Korner F, Koch J, Herian U, Theilmann I, Bartenschlager R.
Replication of subgenomic hapatitis virus RNAs in a hepatoma cell line.
Science 1999; 285: 110-113.



Subgenomic replicons containing the HCV replicative machinery (Gray bar) have been invaluable for studies of the HCV replication

Mechanisms of Action



Antiviral Activity Across HCV GT1–6 *In Vitro* of NS3/4AInhibitors

Compound	Replicon cell line EC_{50} (nM)						
	1a	1b	2a	3a	4a	5a	6a
Glecaprevir[1]	0.85	0.94	2.7	1.6	2.8	0.12	0.86
Paritaprevir[2]	1.0	0.21	5.3	19	0.09	0.42	0.68
Grazoprevir[3,4]	0.4	0.5	1.2	35	1.2	0.9	0.89
Simeprevir[5]	13	9.4	15	472		36	
Asunaprevir[6]	4	1.2	230	1162		52	
Voxilaprevir[7]	3.9	3.3	3.7	6.1	2.9	1.9	1.5

1. Ng T, et al. Hepatology 2014; 60(suppl):1142A (poster presentation);
2. AbbVie data on file;
3. Lahser F, et al. Hepatology 2014; 60 (suppl):1168A (poster presentation);
4. Chase R, et al. IVHD 2013: OA25 (oral presentation);
5. Olysio US Prescribing Information (accessed August 2015);
6. McPhee F, et al. Antimicrob Agents Chemother 2012;56:5387–96;
7. Taylor JG, et al. J Hepatol 2015; 62(suppl):S681 (poster presentation).

Activity Across HCV GT1–6 *In Vitro* of NS5A Inhibitors

Potency compared to GT1a:

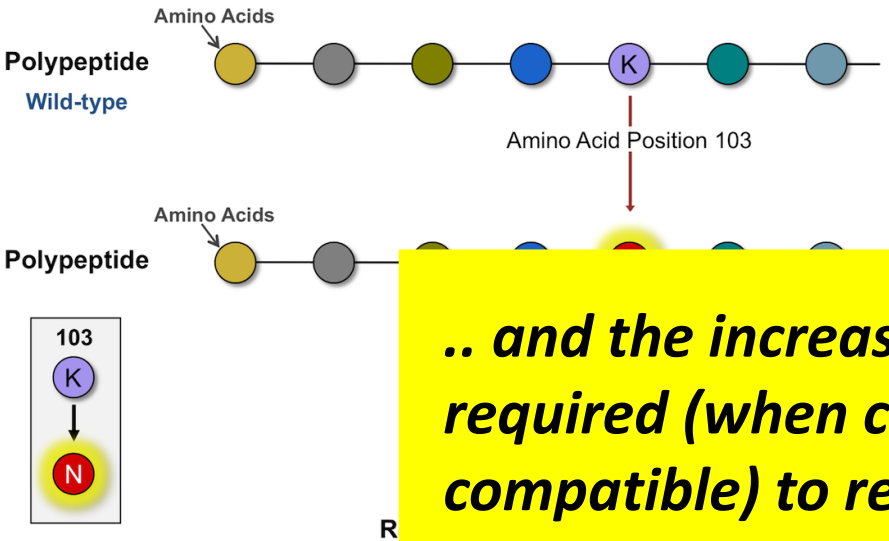
No loss | <10-fold loss | 10- to 100-fold loss | >100-fold loss | Data not available

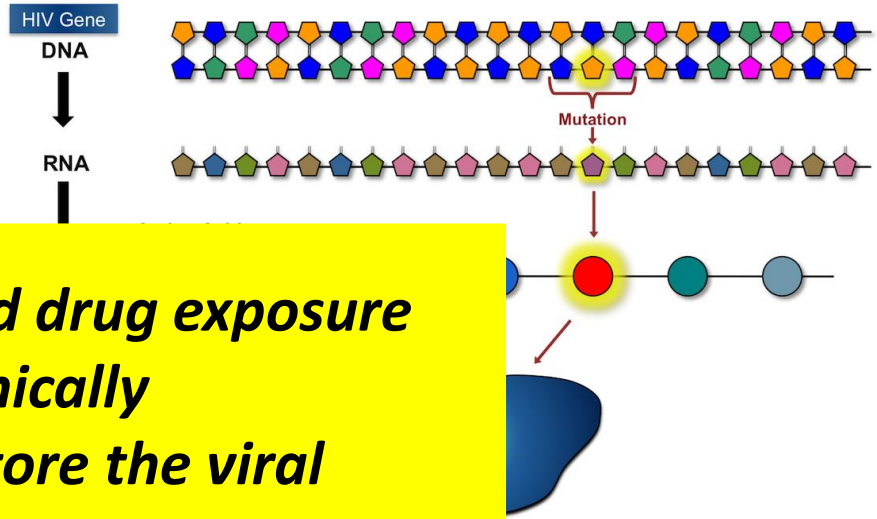
Compound	Replicon cell line EC_{50} (pM)							
	1a	1b	2a	2b	3a	4a	5a	6a
Pibrentasvir[1]	2	4	2	2	2	2	1	3
Ombitasvir[1]	14	5	12	4	19	2	3	366
Daclatasvir[2]	22	3	13,000		530	13	5	74
Ledipasvir[3]	31	4	21,000	16,000	168,000	390	150	1,100
Elbasvir[4]	4	3	3	3,000	20	3		
Velpatasvir[5]	12	15	9	8	12	9	75	6
Odalasvir[6]	14	12		~150				
Samatasvir								

It is reassuring to note that the differences among DAAs in terms of replicon-established antiviral activity are fully concordant with clinical trial results.

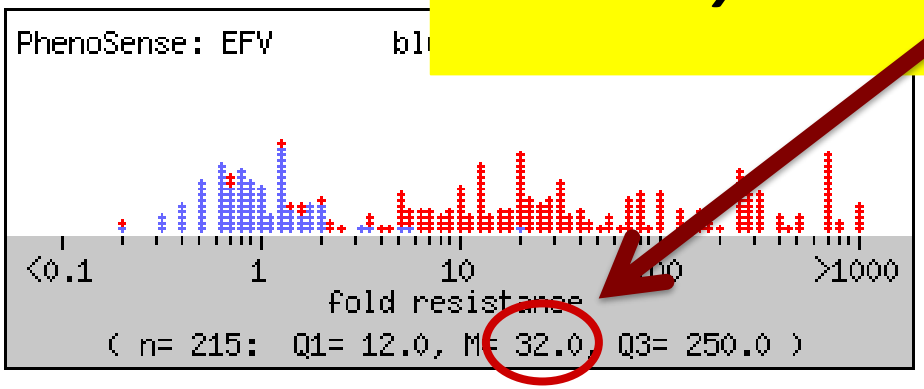
1. Ng T, *et al. Hepa*
2. Wang C, *et al. A*
3. Harvoni US Pres
4. Lui R, *et al. J He*
5. Cheng G, *et al.*
6. Zhao Y, *et al. J H*
7. Dousson C, *et al.* (poster presentation).

Molecular reading of Viral sensitivity to drugs

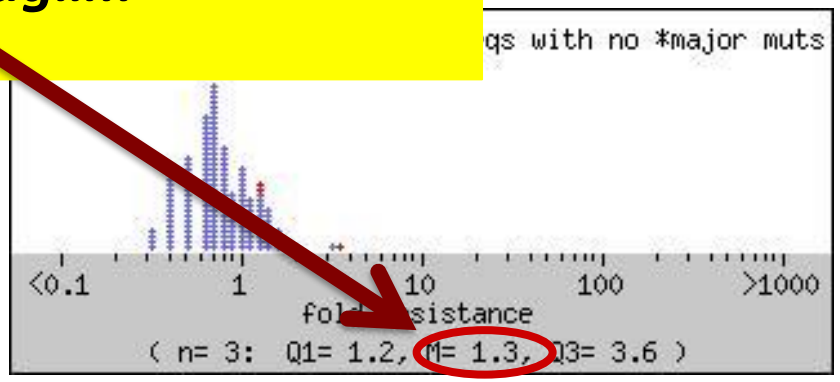




.. and the increased drug exposure required (when clinically compatible) to restore the viral sensitivity to the drug…..



EFV with Mutation K103N



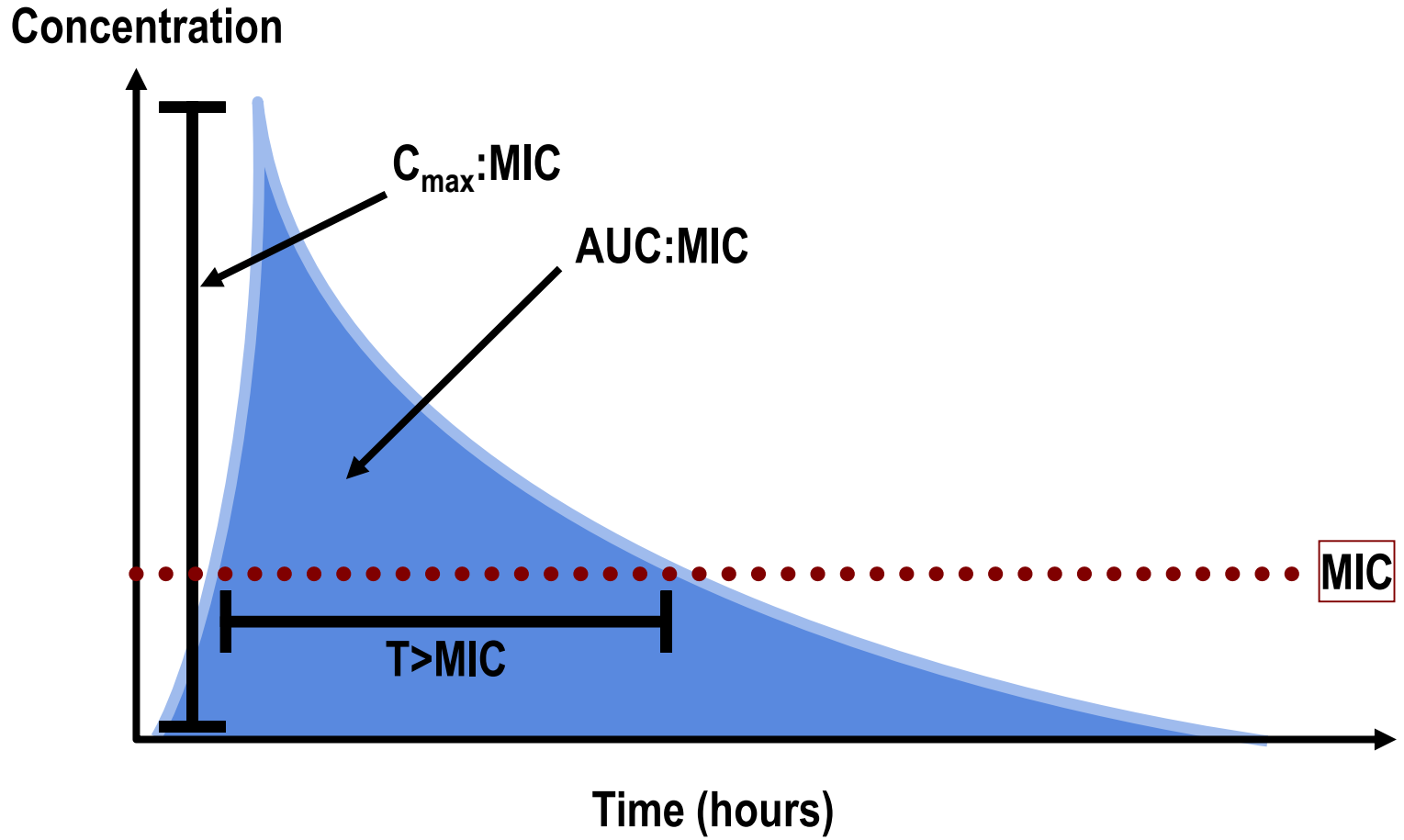
Increased Fold Change to DRV with Mutation I84V

Stanford Resistance Database, Dec 2010

POINT n. 2

How to optimize Viral exposure to drugs

Pharmacodynamic parameters (*in vivo* potency)



AUC = Area under the concentration–time curve

C_{max} = Maximum plasma concentration

JAMA®
The Journal of the American Medical Association

The inhibitory quotient. A method for interpreting minimum inhibitory concentration data. P. D. Ellner and H. C. Neu

1981; 246: 1575-78

THE INHIBITORY QUOTIENT*

HAROLD C. NEU, M.D.
Chief, Division of Infectious Diseases

PAUL D. ELLNER, Ph.D.
Director, Clinical Microbiology Services

Columbia University College of Physicians and Surgeons
New York, New York

THE past few years have seen many improvements in methods to determine the susceptibility of microorganisms to different antibacterial agents. Although most physicians continue to speak of bacteria as susceptible or resistant to an antibiotic, the use of minimal inhibitory concentrations (MICs) has become increasingly common when dealing with nosocomial pathogens which often resist older penicillins and cephalosporins. This paper will evaluate the meaning of inhibitory concentrations and peak serum concentrations as they relate to the use of antimicrobial agents in outpatient settings.[1]

THE INHIBITORY CONCENTRATION

What is an inhibitory concentration? The minimum inhibitory concentration (MIC) of an antibiotic is that amount of antimicrobial agent which will inhibit the visible growth of a microorganism, as measured by the eyes or by a machine using light scattering. The MIC is determined with generally agreed-upon numbers of bacteria, 10^4 or 10^5 colony-forming units (CFU), using a standard broth or agar medium which contains antibiotic in twofold differing concentrations. The minimal bactericidal concentration (MBC) is the lowest concentration of drug that kills 99.9% of the organisms. This is determined by removing clear fluid from tubes or wells in a plate and placing the fluid onto agar plates. Bacteria which were inhibited but not killed will grow. Although many factors, such as size of inoculum, type of medium, cation content, osmolality, and aerobic

*Presented as part of a *Symposium on Recent Developments in Oral Antibiotic Therapy: Bacampicillin Update* held by the Section on Pediatrics and the Section on Medicine of the New York Academy of Medicine December 19, 1982. This symposium was supported by a grant from Roerig, division of Pfizer Pharmaceuticals.

Address for reprint requests: Harold C. Neu, M.D., Department of Medicine, Columbia-Presbyterian Medical Center, 630 West 168th Street, New York, N.Y. 10032

$$\text{Inhibitory quotient (IQ)} = \frac{\text{Average peak level achievable in target tissue or fluid*}}{\text{Minimum inhibitory concentration (MIC) of pathogen}}$$

Fig. 1. Calculating the inhibitory quotient.

concentration data that we called the inhibitory quotient (IQ).[3] Calculated as shown in Figure 1, the IQ is a number that indicates the multiple of the MIC expected with the lowest dosage of an antimicrobial agent. Examples of typical MIC data are shown in Table I and typical blood levels in Table II.

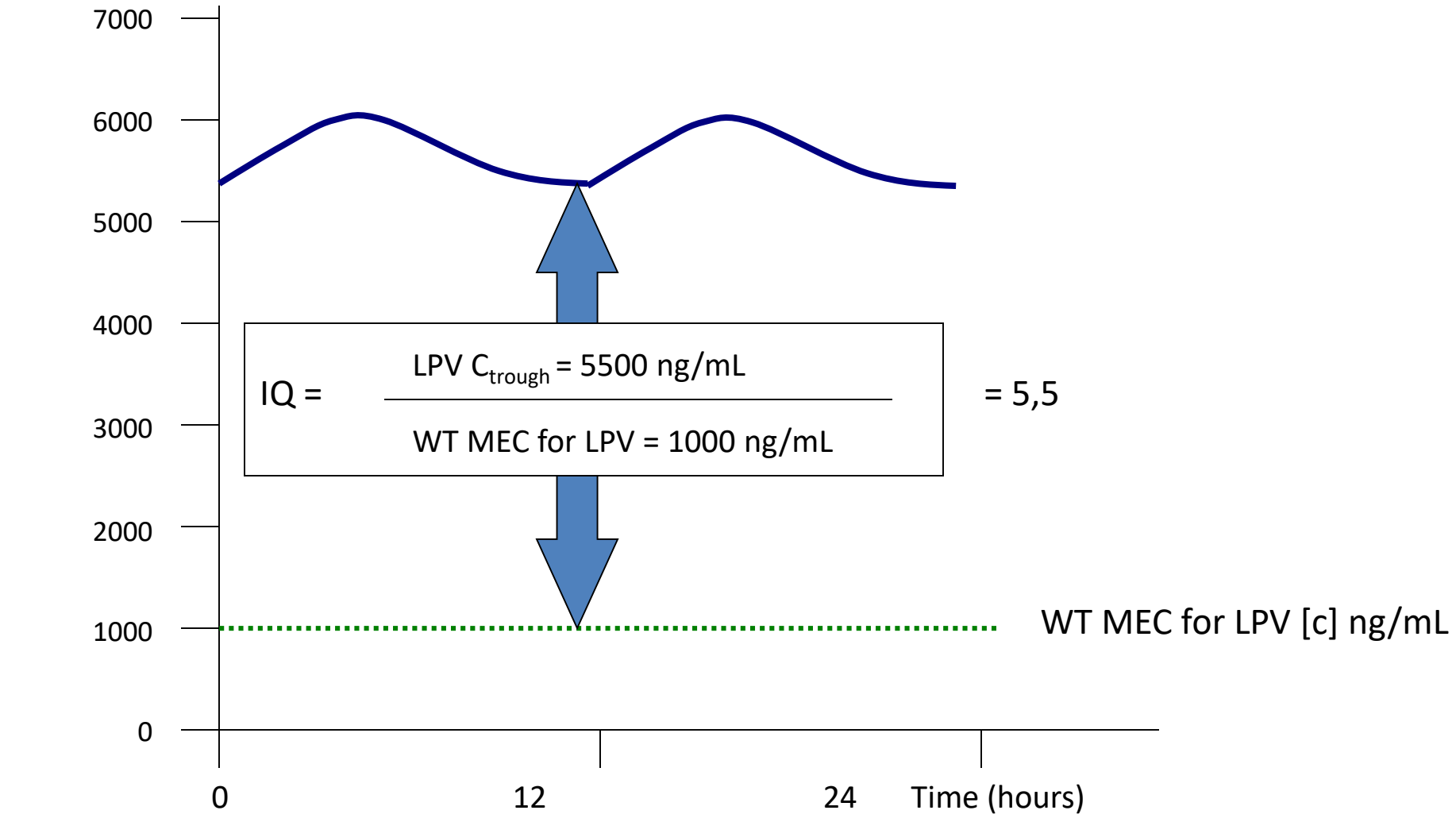
We initially applied the IQ system to parenteral therapy, but it also lends itself to use with oral agents. This method permits determination of MICs of bacterial isolates using either commercially frozen microdilution plates or such optical devices as the Autobac®. Antimicrobial agents selected for testing are those which would be used against the organisms. Concentrations used in testing are based upon those necessary to separate isolates which would be inhibited or killed from those which would survive.

In our institution, values for average peak serum levels of antibiotics are stored in a computer. Antibiotic blood levels chosen for intravenous use are those that would reflect the level achieved at the end of 20 to 30 minute infusions, while oral levels are based on the peaks known from studies in normal individuals, and may reflect a level at one hour or two hours, depending upon absorption kinetics of the particular antibiotic. Urine concentrations chosen are those found in the urine during the first several hours after administration of the drug. Certainly urine concentrations of some agents may be markedly depressed if the individual has impaired renal function with a glomerular filtration rate below 30 ml/mm and the agent in question is cleared primarily by glomerular filtration. Levels in cerebrospinal fluid, which of course apply only to parenteral therapy, are based on the much higher doses used to treat meningitis and on the presence of meningeal inflammation.

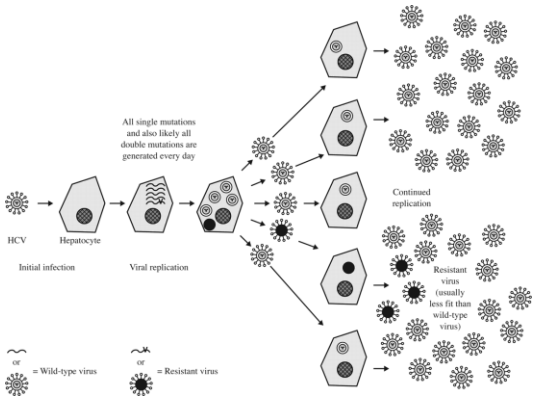
In each instance, inhibitory quotients reported to a physician are those appropriate to the body site of the specimen, such as serum, urine, bile, or

*Lung is considered part of the central body compartment due to its high blood flow and hence the serum level is used.

…the only IQ we can reliably measure as a true concentration ratio is that for the WT virus…..



Mutant Preventing Concentration (MPC)



[c]

Not only **effective** but also high enough to **prevent selection of resistant mutants**

MPC

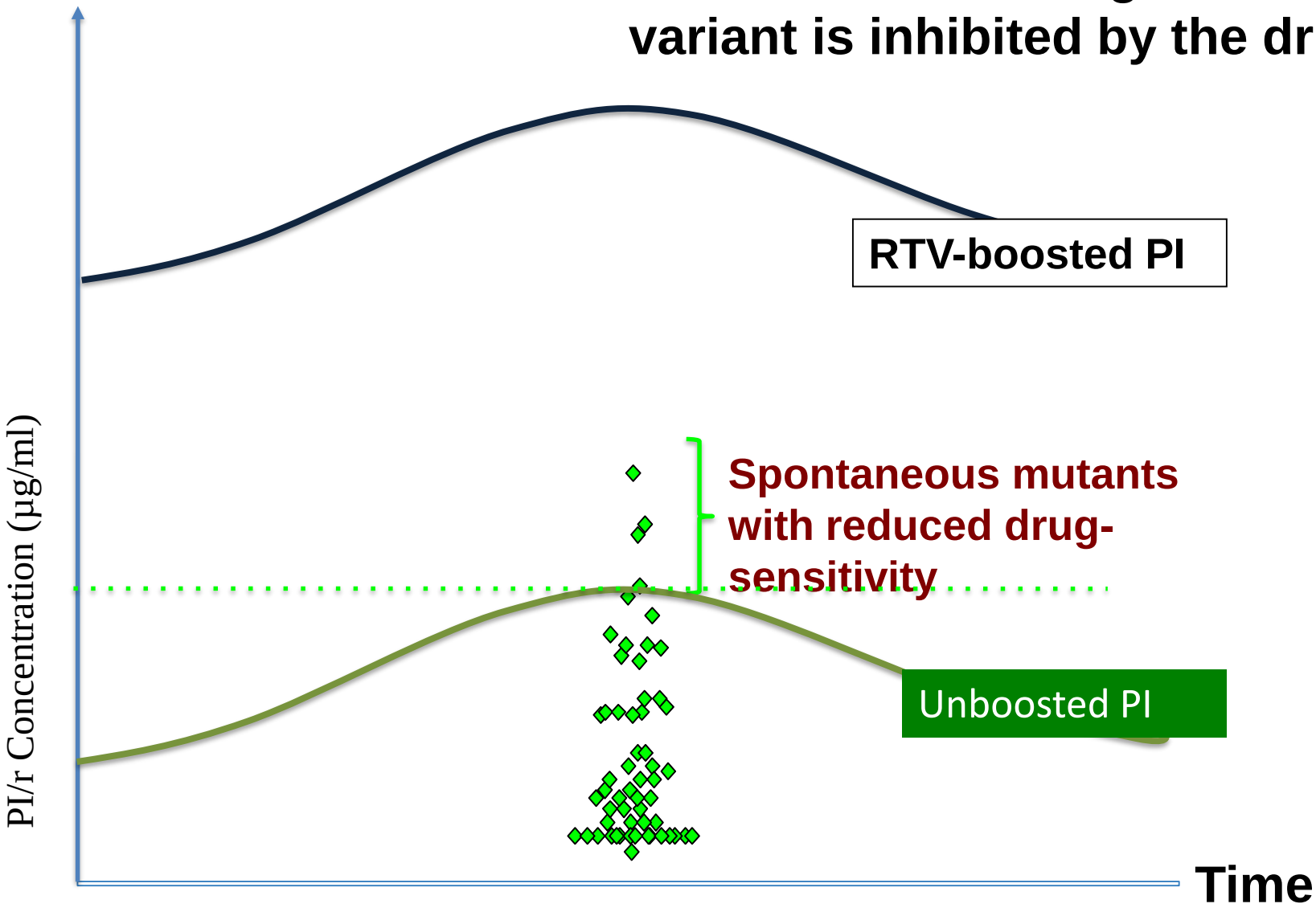
EFFECTIVE

MIC (or IC90 or EC90)

MSW = Mutant Selection Window

In antibacterial therapy could be irrelevant, unless neutropenic or diabetic or…….

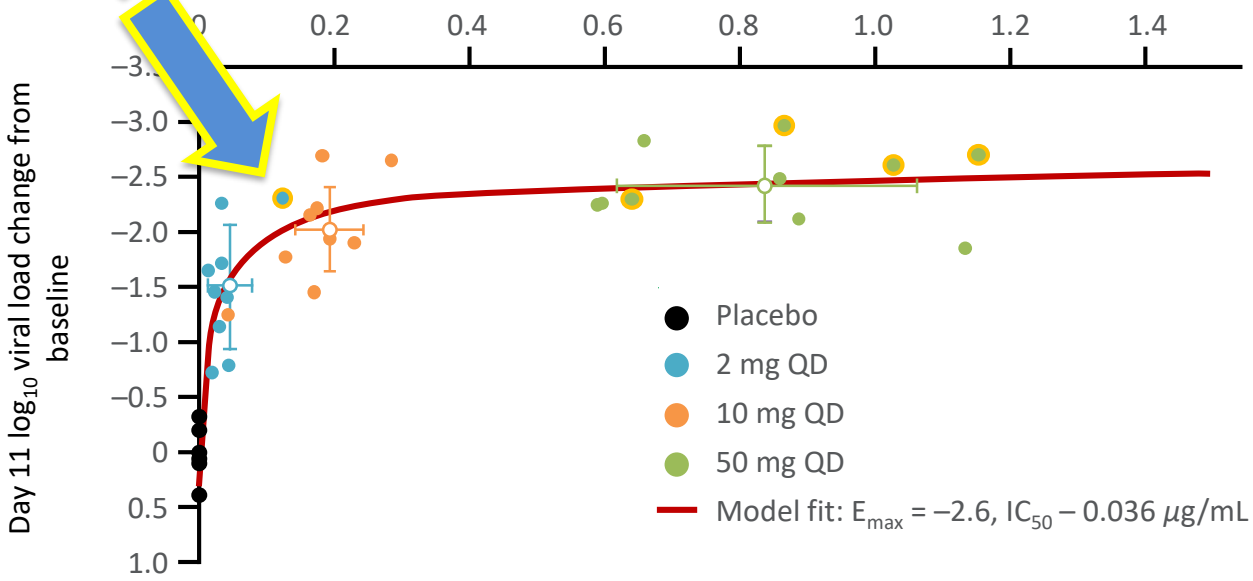
In case of a WT HIV viral population Pk exposure of boosted-PIs is such that even the least drug-sensitive variant is inhibited by the drug



RELATIONSHIP BETWEEN DTG TROUGH CONCENTRATION AND VIRAL LOAD REDUCTION

A patient taking the 2 mg dose underwent virologic suppression in 10 days !!!

Phase IIa, d led, 10-day monotherapy study



Subjects with HIV-1 RNA <50 c/mL are represented by orange-bordered circles

Open circles with lines denote mean standard deviation

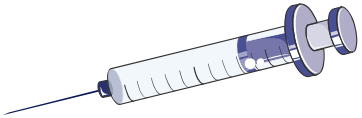
DTG is associated with a well characterised, predictable exposure-response relationship

c/mL, copies/mL; E_{max}, maximum effect; RNA, ribonucleic acid

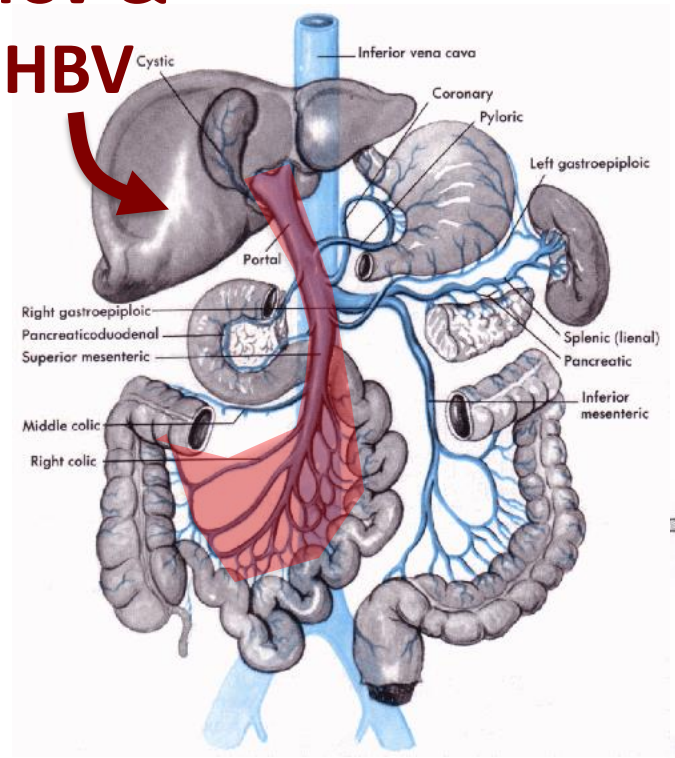
Adapted from Min S, et al. AIDS 2011; 25:1737–45

Plasma exposure of drugs administered for the treatment of chronic viral hepatitis might not be representative of the viral exposure into hepatocytes

First pass metabolism

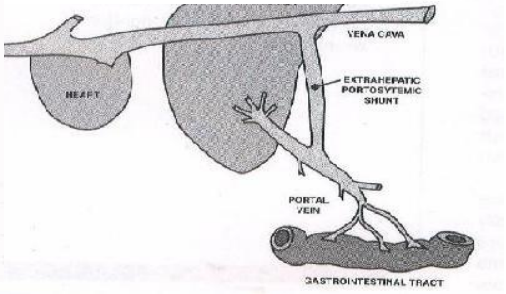


HCV & HBV

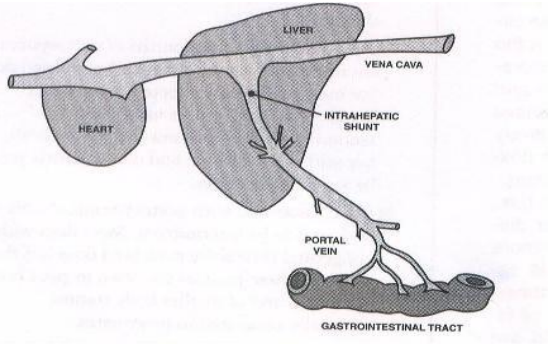


The decreased liver drug uptake in case of decompensated cirrhosis (shunts, sinusoid capillarization, transporters activation, etc..), especially for drugs characterized by a high extraction ratio (NS3/4A inhibitors) , is thought to be co-responsible for the lower response rate.

The extrahepatic shunt



The architecture of intrahepatic shunt



POINT n. 3

Consider the immunovirological and human variables

ANTIVIRAL EFFICACY

HIV: baseline HIV/RNA, nadir CD4+ T-cell count, WT vs RAM, age, comorbidities, lifestyle, adherence

PERMANENT TREATMENT REQUIRED

HCV: liver fibrosis status, adherence, genotype

DEFINED TREATMENT DURATION

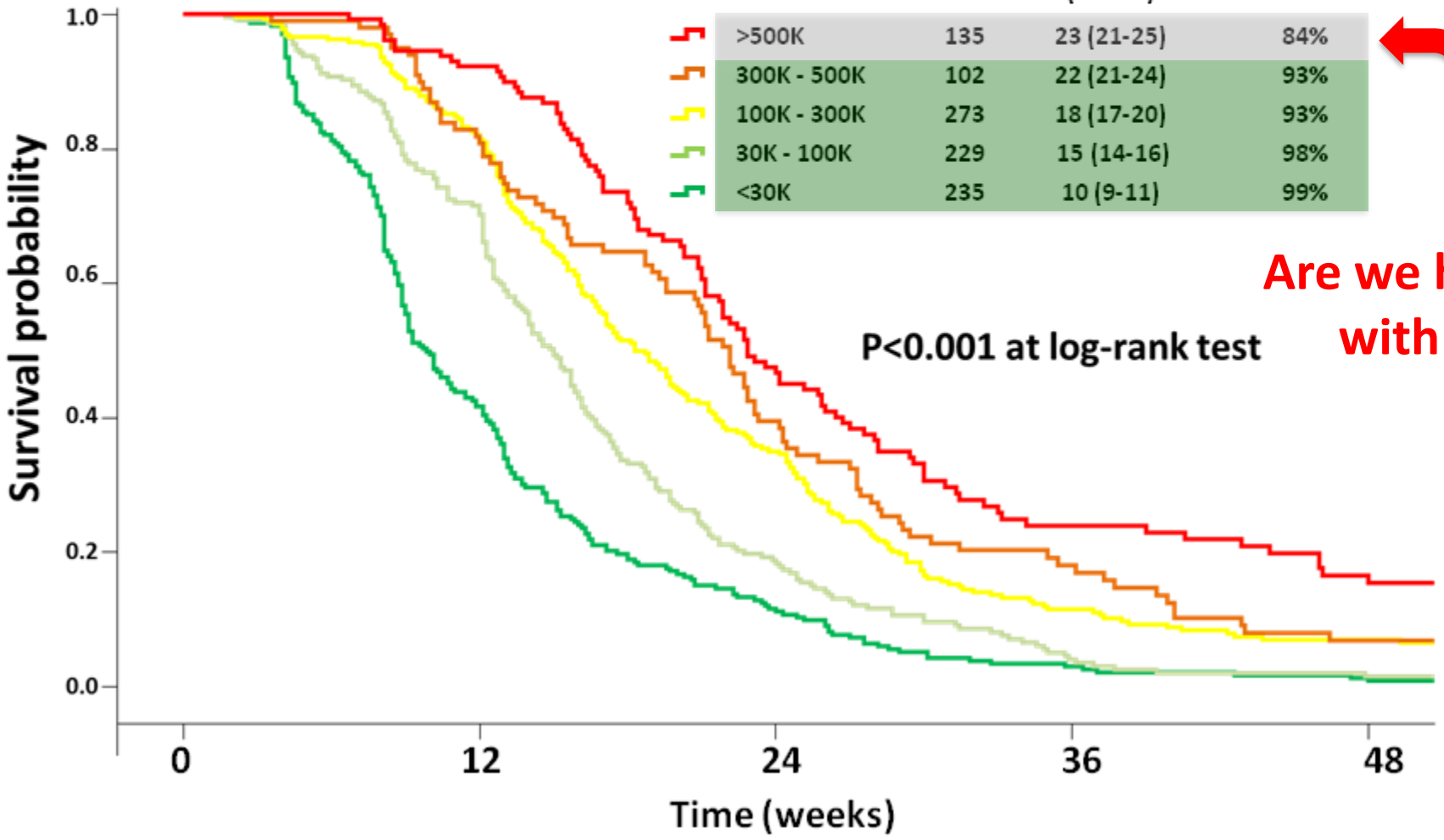
HBV: liver fibrosis status, baseline HBV/DNA, HBeAg +/-, adherence, genotype A>D & B>D (IFN), HBsAg decline on treatment

UNDEFINED TREATMENT DURATION

(in nearly 50% of cases: PERMANENT TREATMENT REQUIRED)

The time to achieve virological undectability and the rate of success at 48 weeks are pre-HAART viremia dependent

Pre-HAART viremia ranges (copies/mL)	No.	Median Time (95% CI) to achieve VS (weeks)	Probability of VS at 48 weeks
>500K	135	23 (21-25)	84%
300K - 500K	102	22 (21-24)	93%
100K - 300K	273	18 (17-20)	93%
30K - 100K	229	15 (14-16)	98%
<30K	235	10 (9-11)	99%



Are we happy with this ?

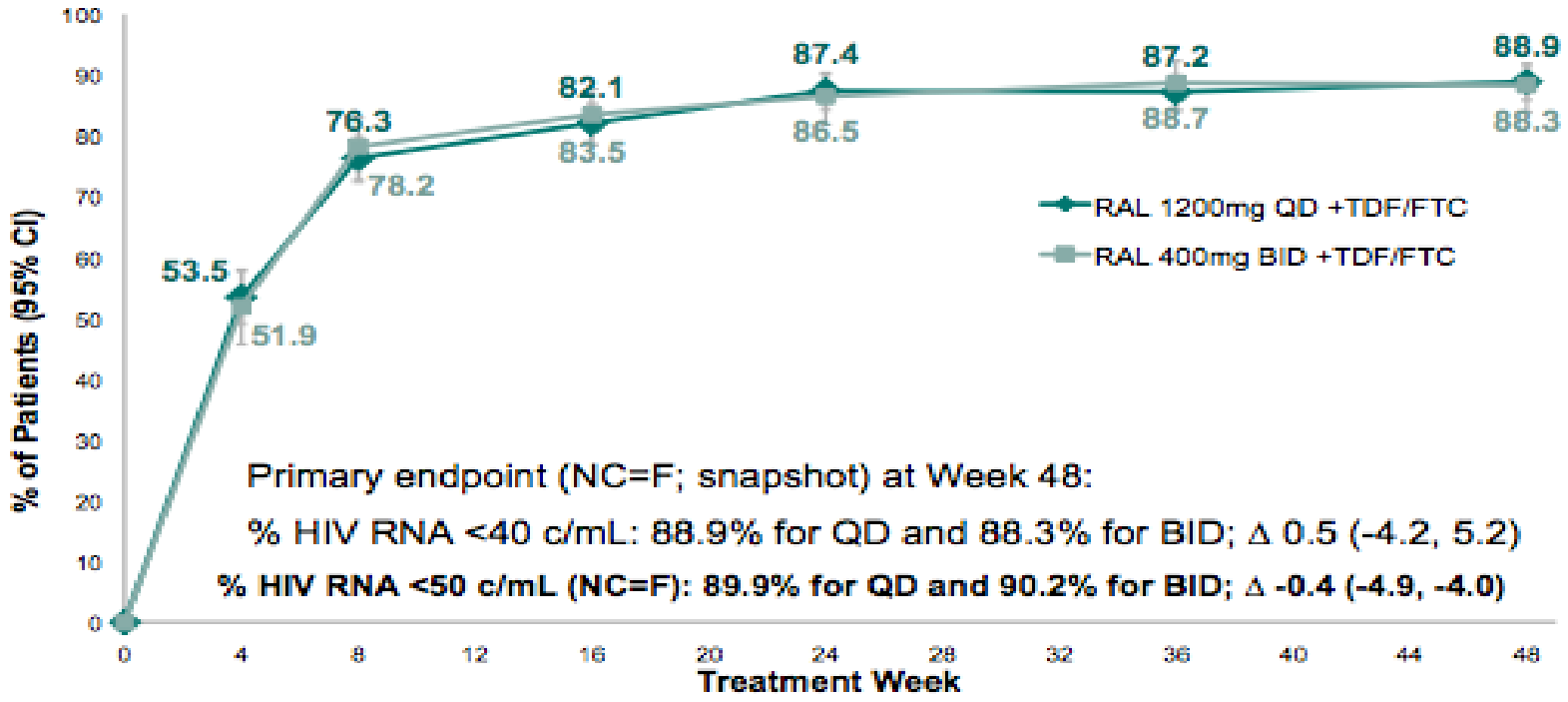
Santoro et al., Antivir ther 2013

ONCEMRK

- 802 pts randomized (2:1)
  - RAL 1200 mg QD + TDF/FTC
  - RAL 400 mg BID + TDF/FTC

- RAL QD non-inferior to RAL BID
  VL <40: 88.9% vs. 88.3%

Wk 48 VL<40 (Snapshot)



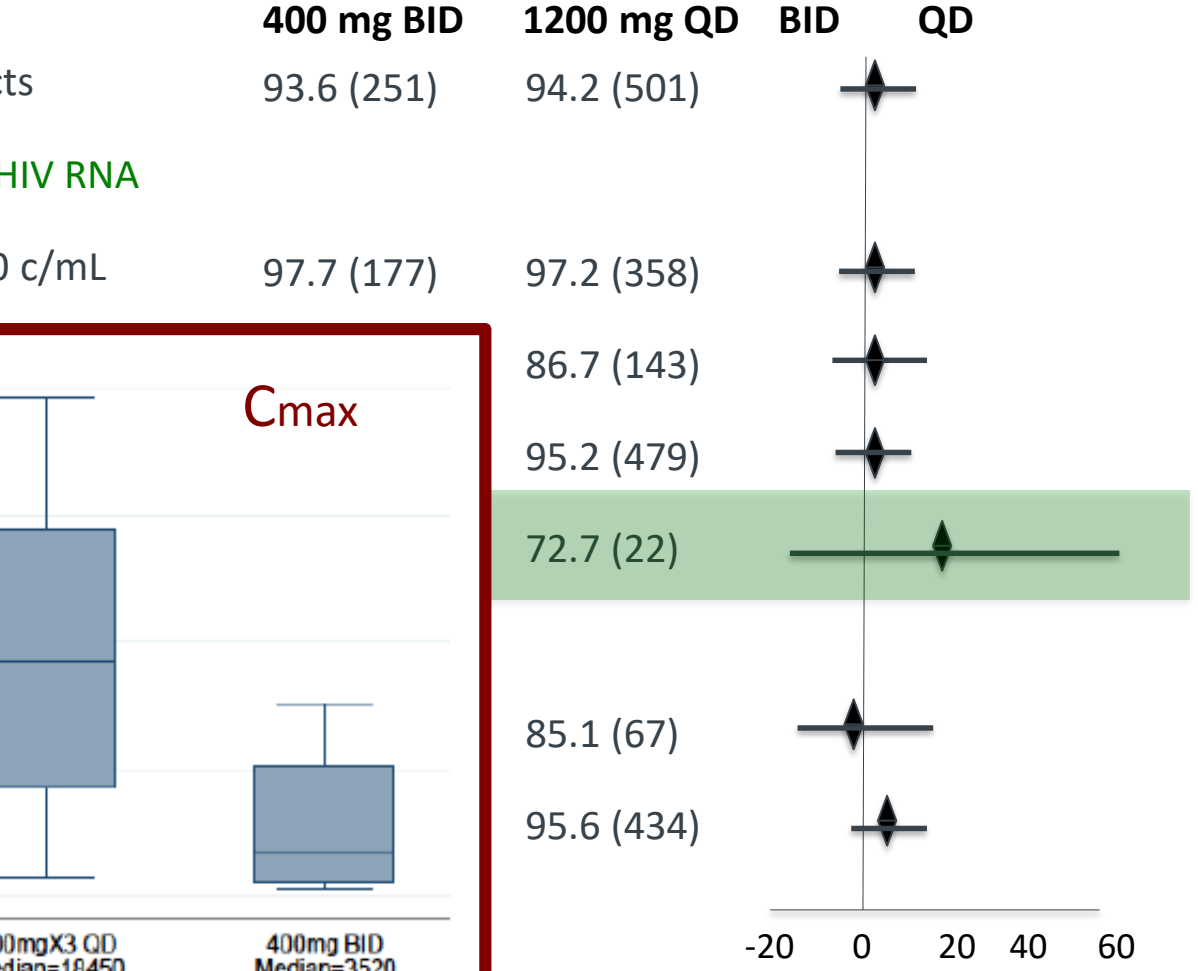
- **For subgroup with BL HIV RNA >100,000 c/mL:**
  % HIV RNA <40 c/mL (OF): 86.7% for QD and 83.8% for BID; Δ 2.9 (-6.5, 14.1)
- CD4 (cells/mm^3) increase (OF): 232 for QD and 234 for BID; Δ -2 (-31, 27)

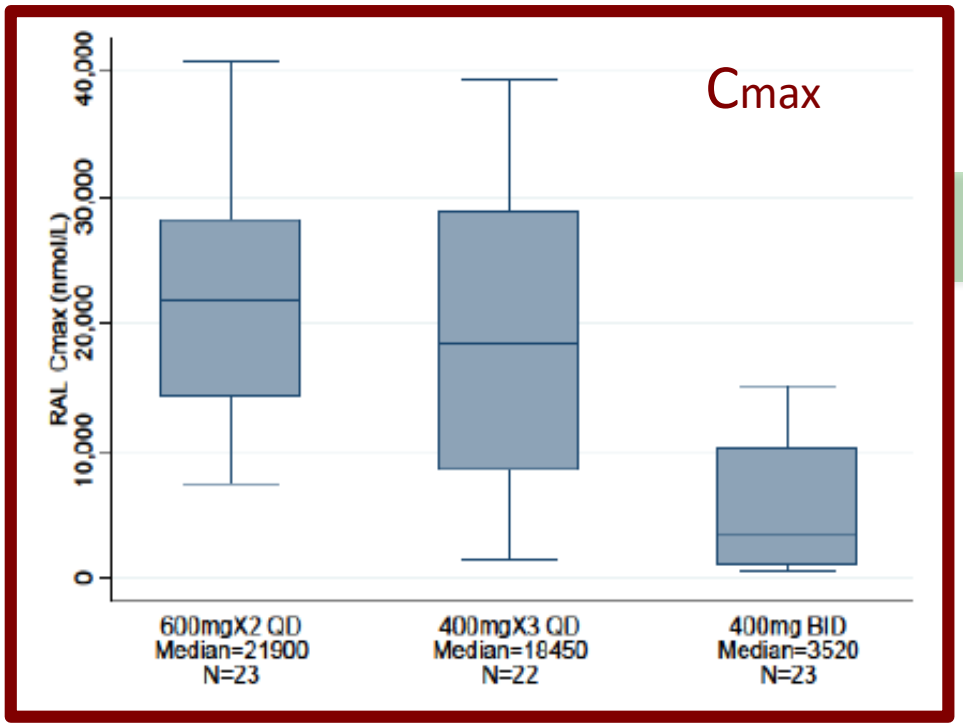
Cahn P et al, International AIDS Conference, 18-22 July 2016, Durban, South Africa. Abstract FRAB0103LB

Subgroup Analyses from ONCEMRK, a Phase 3 Study of Raltegravir 1200 mg Once Daily vs RAL 400 mg Twice Daily, in Combination with Tenofovir/Emtricitabine, in Treatment-Naïve HIV-1 Infected Subjects: Results

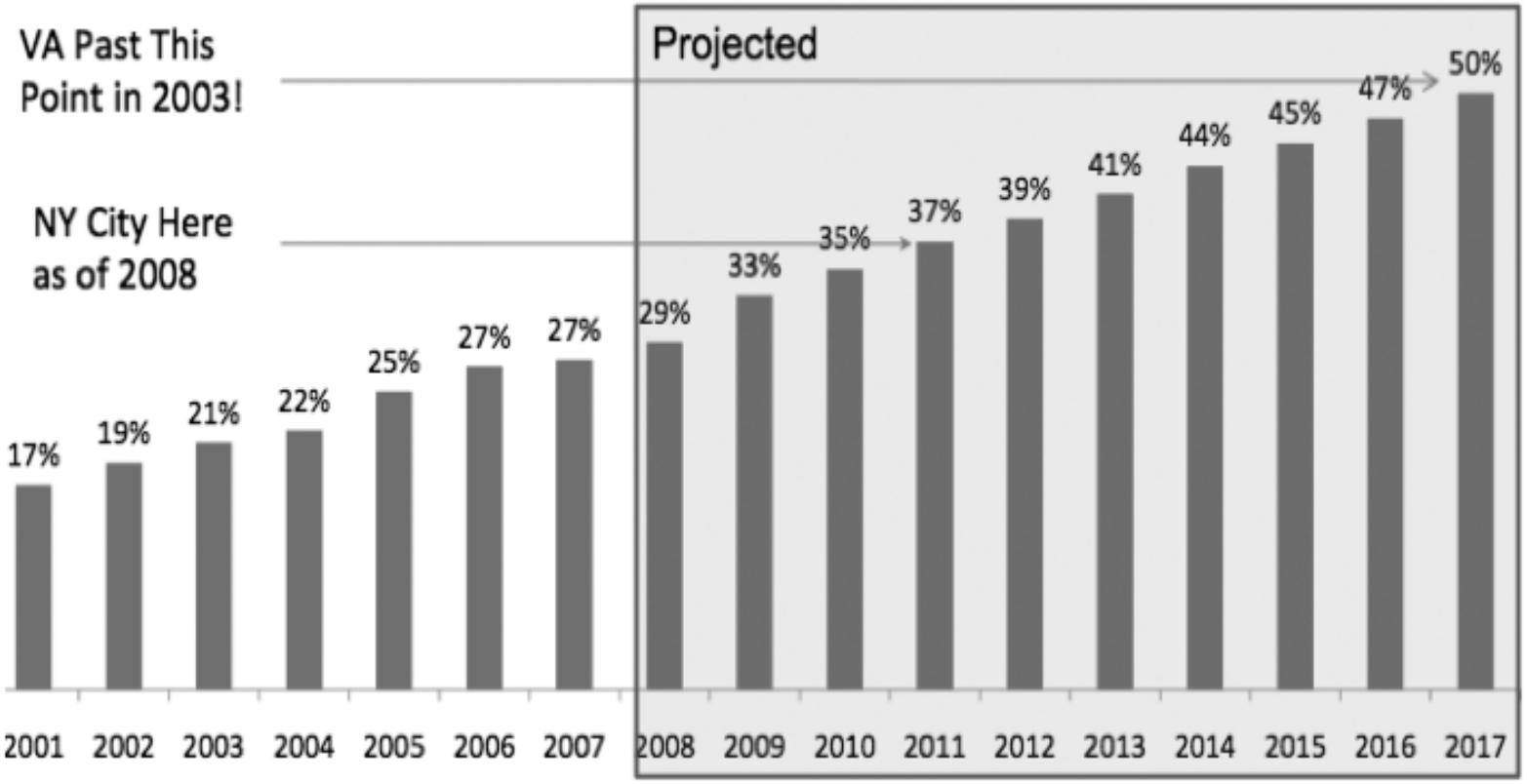
HIV RNA < 40 c./mL

	% of Subjects (N)	
	400 mg BID	1200 mg QD
All subjects	93.6 (251)	94.2 (501)
Baseline HIV RNA		
≤ 100.000 c/mL	97.7 (177)	97.2 (358)
	86.7 (143)	
	95.2 (479)	
	72.7 (22)	
	85.1 (67)	
	95.6 (434)	



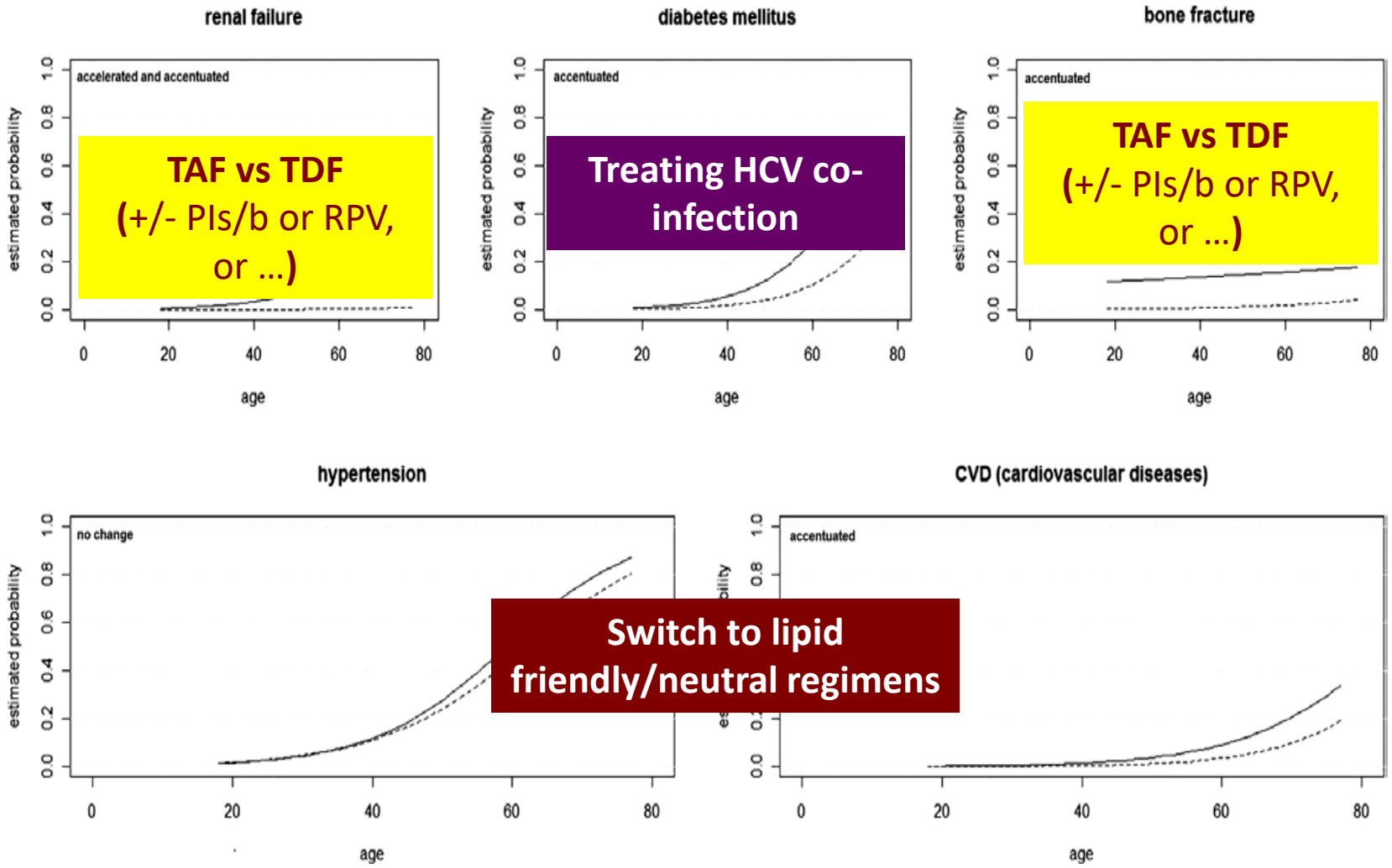


HIV+ Aging Population in the United States (people over 50 years of age)



LGBTQ Policy Journal at the Harvard Kennedy School: 2011 Edition
HIV and Aging: Emerging Issues in the HAART Era

Accelerated Aging During HIV Infection



Pathai et al, J of Gerontology 2013

POINT n. 4

Why Clinicians should know the Clinical Pharmacology of Antivirals

Consider the variables associated to different steps of the conventional pharmacological processes

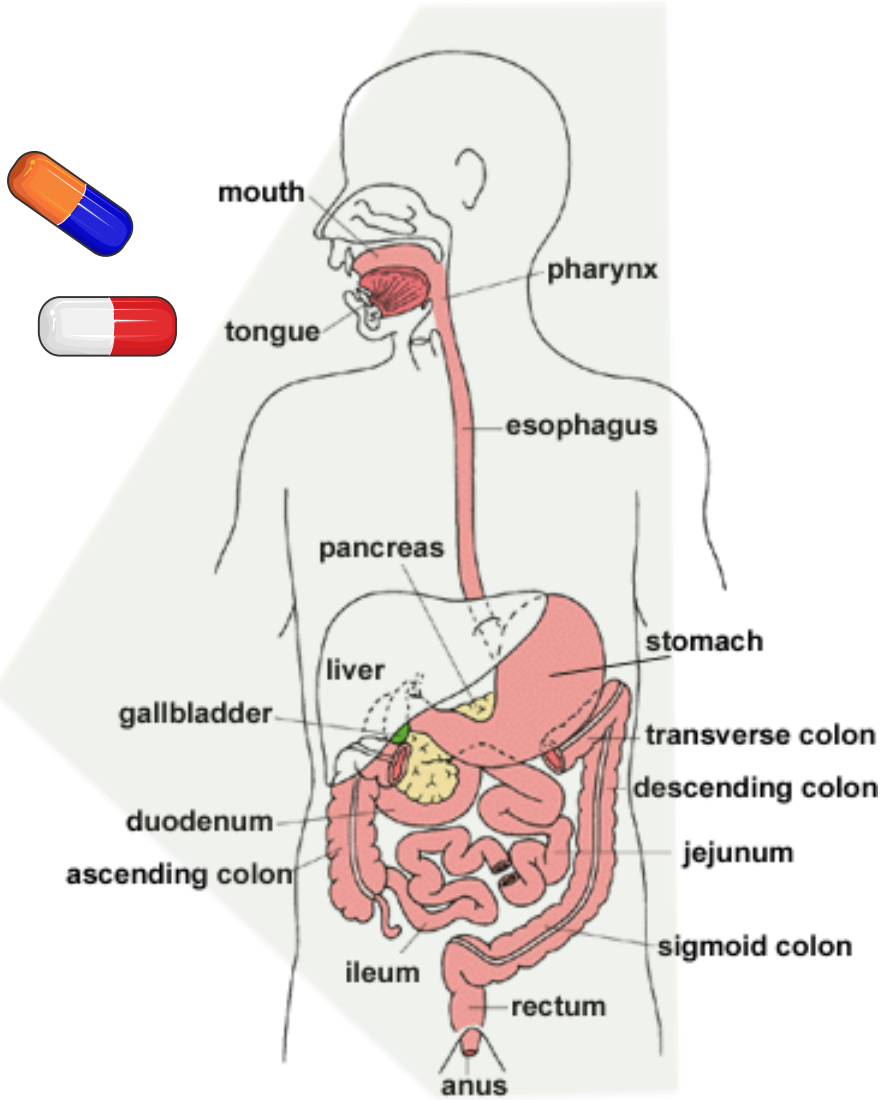
A → **Absorption**

D → **Distribution**

M → **Metabolism**

E → **Elimination**

PK



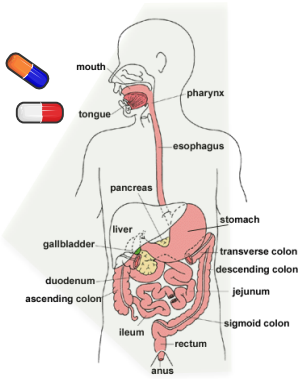
A → **Absorption**

D → Distribution

M → Metabolism

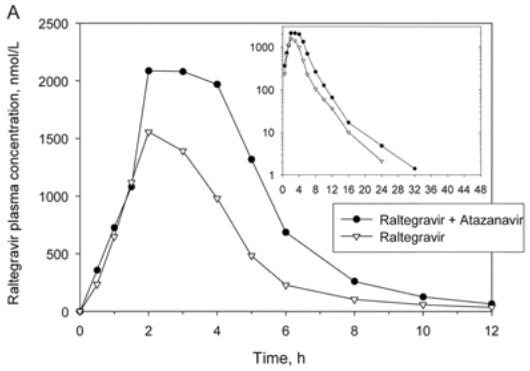
E → Elimination

PK

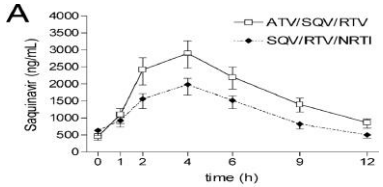


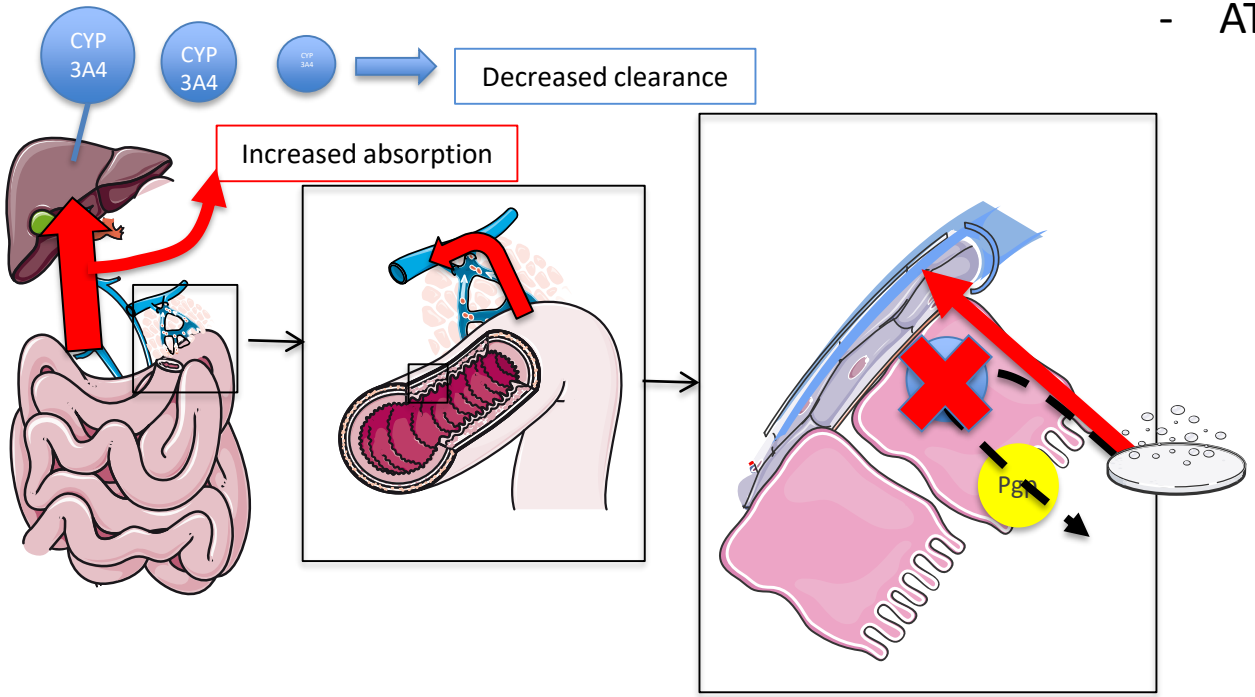
+ UGT1a1 inhibition:

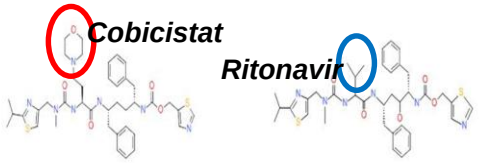
- ATV on INSTIs



- ATV on PIs







A → **Absorption**

D → Distribution

M → Metabolism

E → Elimination

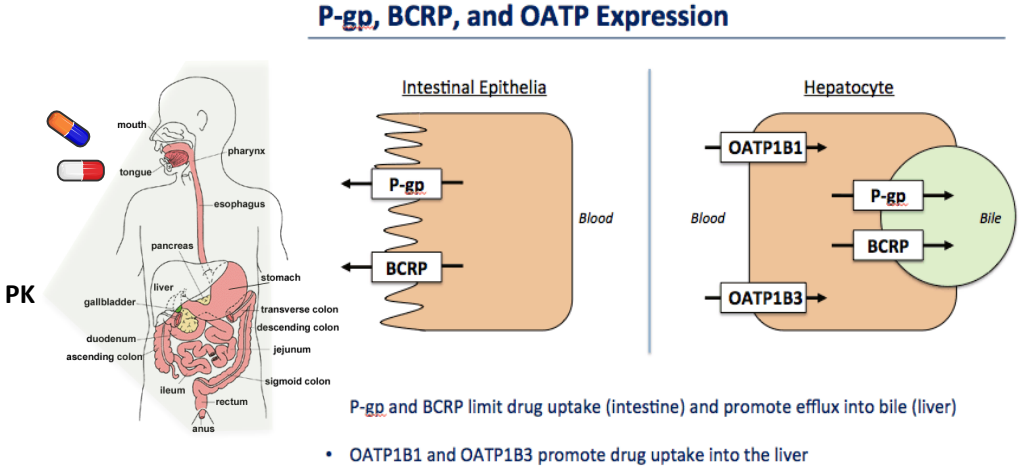
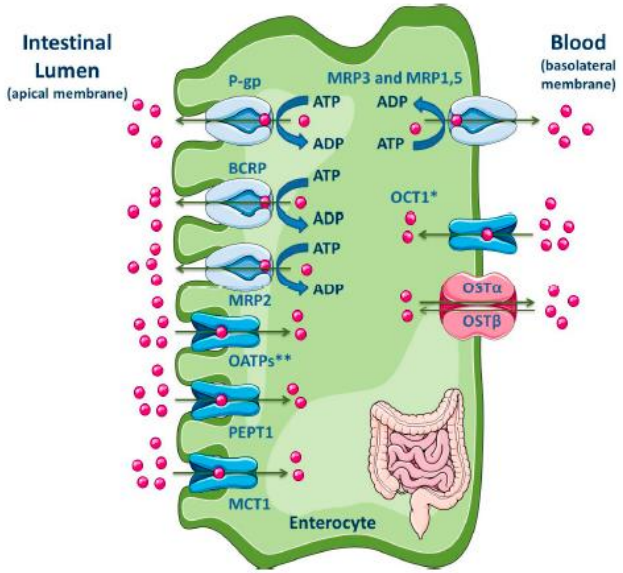
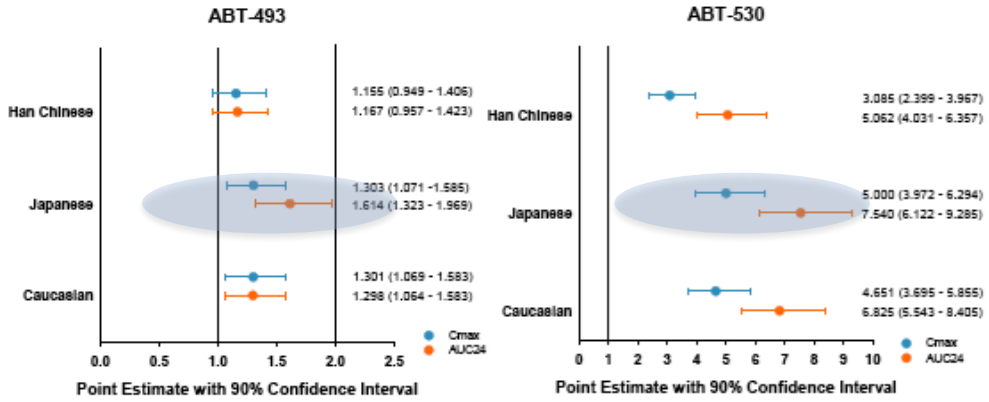


Figure 4. Interactions Between ABT-493 and ABT-530 Were Comparable Among Japanese, Han Chinese, and Caucasian





- Steady-state AUC_{24} central value of ABT-493 was increased by 17% to 61% and C_{max} central value of ABT-493 was increased by 16% to 30% in presence of steady state ABT-530
- Steady state AUC_{24} central value of ABT-530 was increased to 5.1- to 7.5-fold and C_{max} central value of ABT-530 was increased to 3.1- to 5.0-fold in presence of steady-state ABT-493

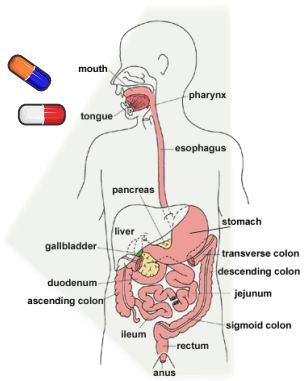
A → **Absorption**

D → Distribution

M → Metabolism

E → Elimination

PK

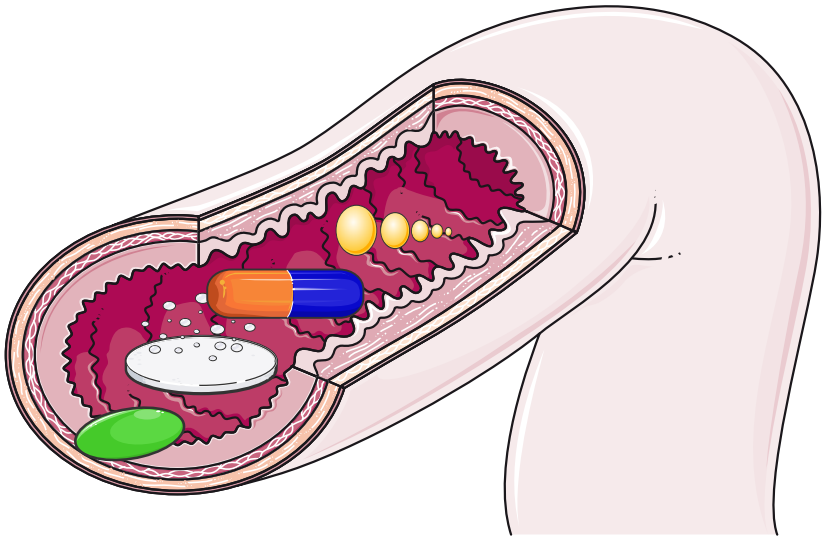


e.g. INSTIs, RPV, ATV

Intestinal Ph (e.g. Pka > or < Ph)

Drug chelation (polyvalent cations, e.g. Ca++, Mg++)

Food (e.g. Ph +/-, adsorption)

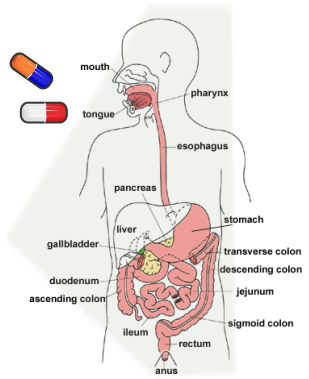


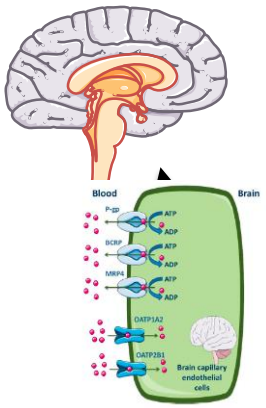
A → Absorption

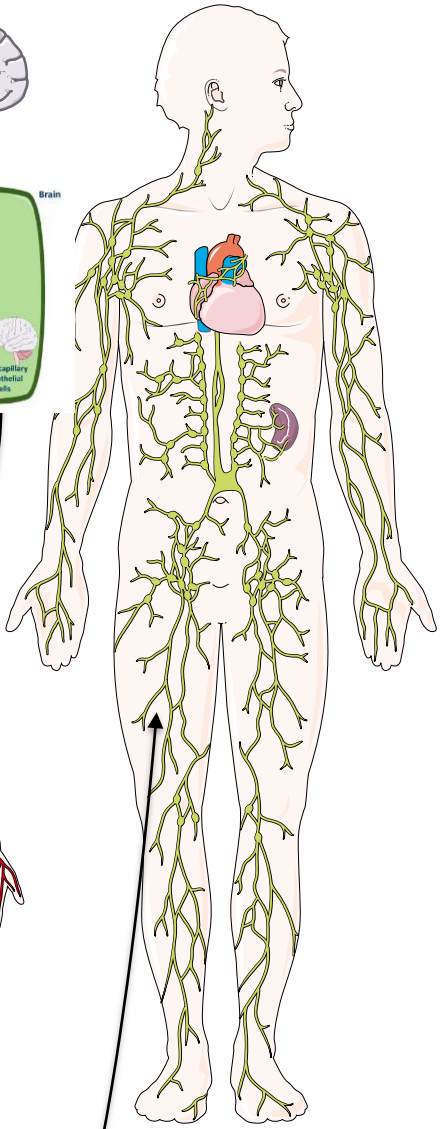
D → Distribution

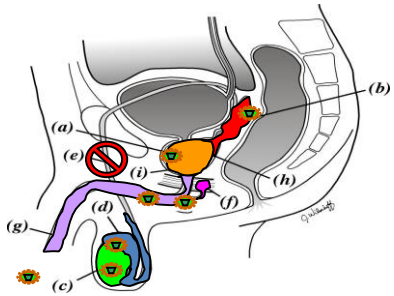
M → Metabolism

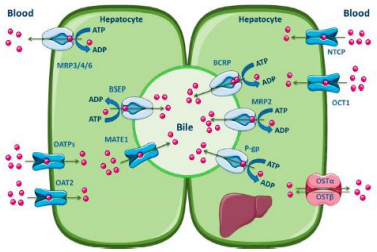
E → Elimination

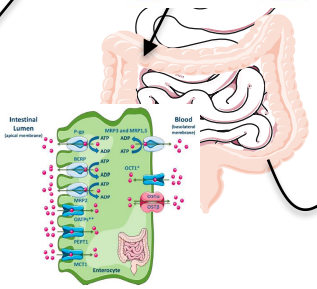


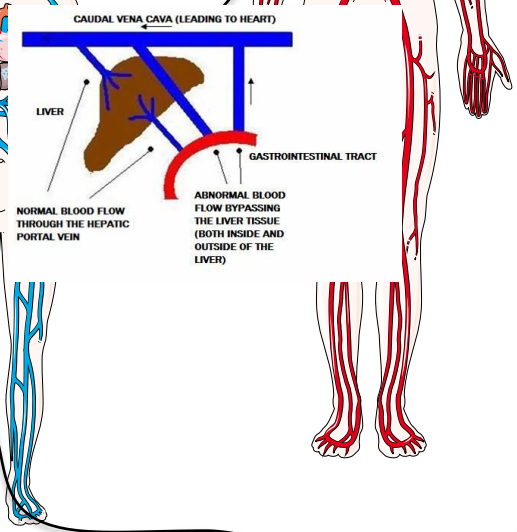


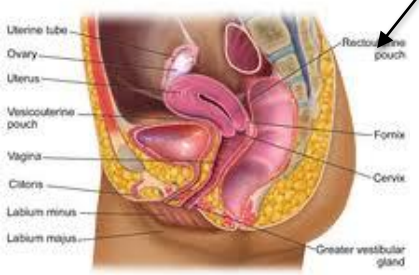












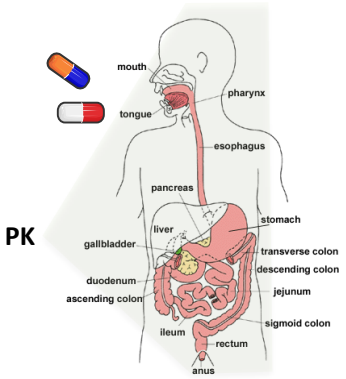
The Female Reproductive System

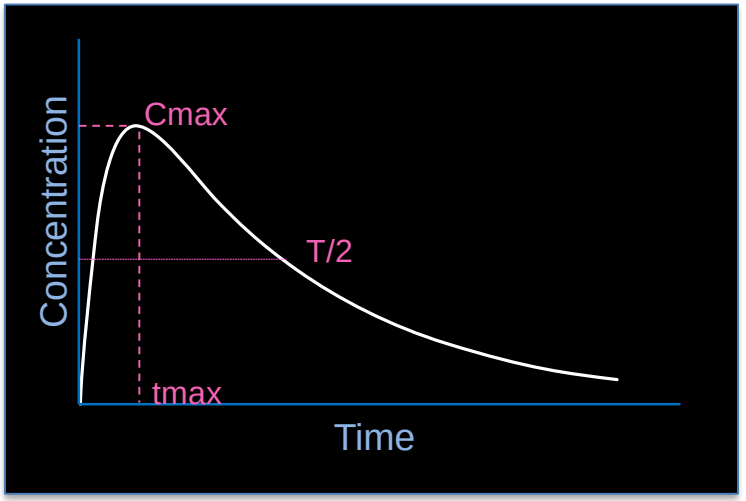
A → Absorption

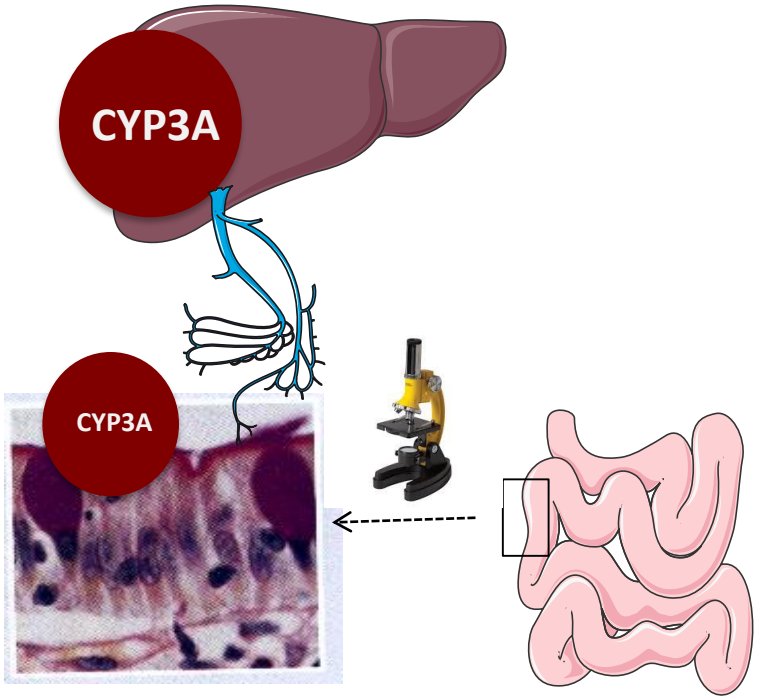
D → Distribution

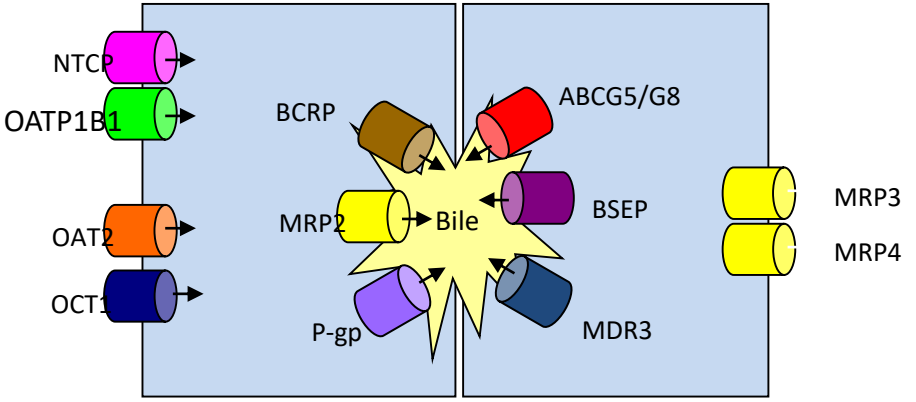
M → Metabolism

E → Elimination

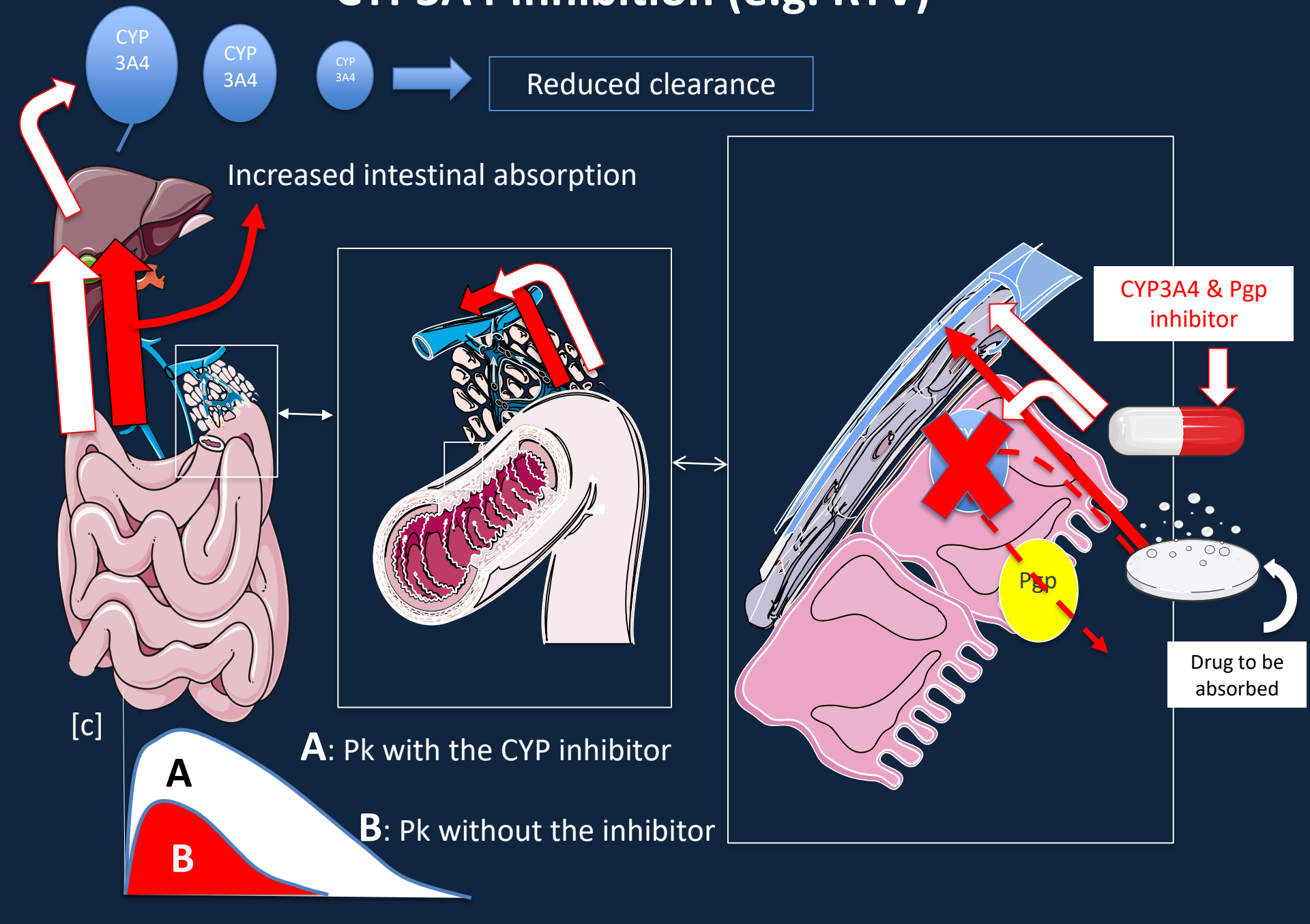




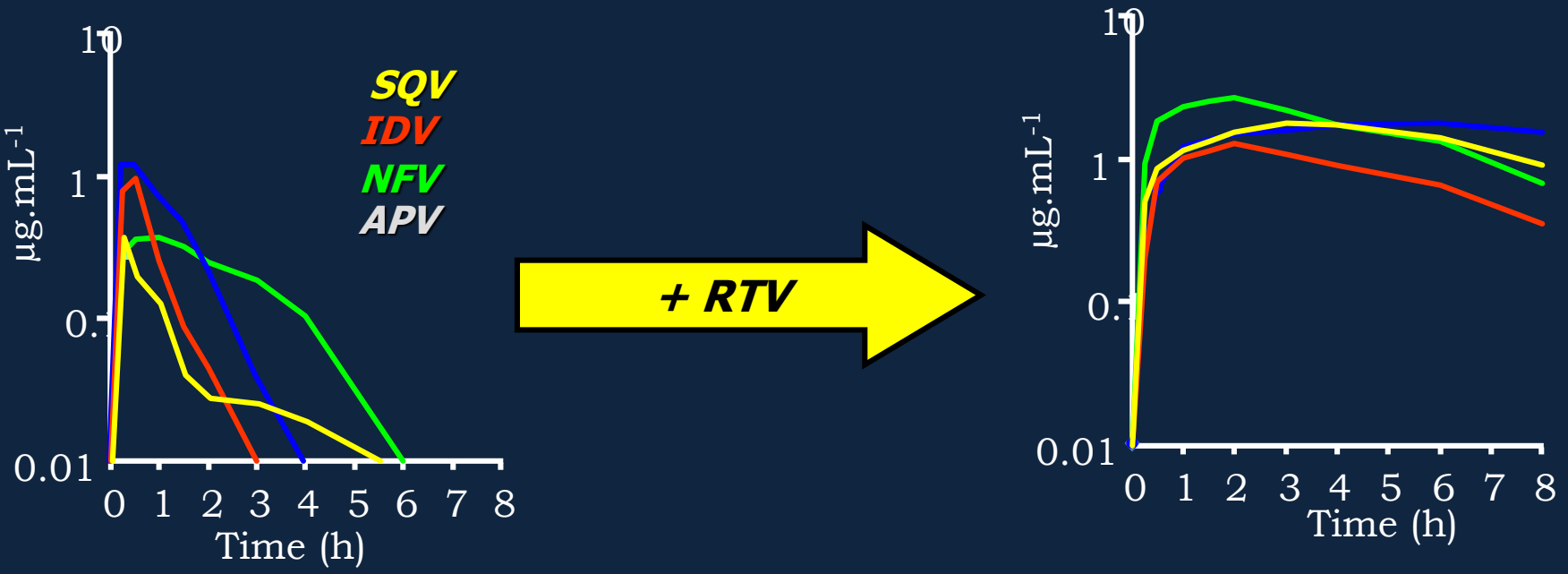




CYP3A4 Inhibition (e.g. RTV)



PK BOOSTING OF PIs



- ↑ *Antiviral potency / durability*
- ↑ *Effect on resistant strains*
- ↓ *Pill count / number of doses*
- *Liberalize the regimen*
- ↓ *Cost*

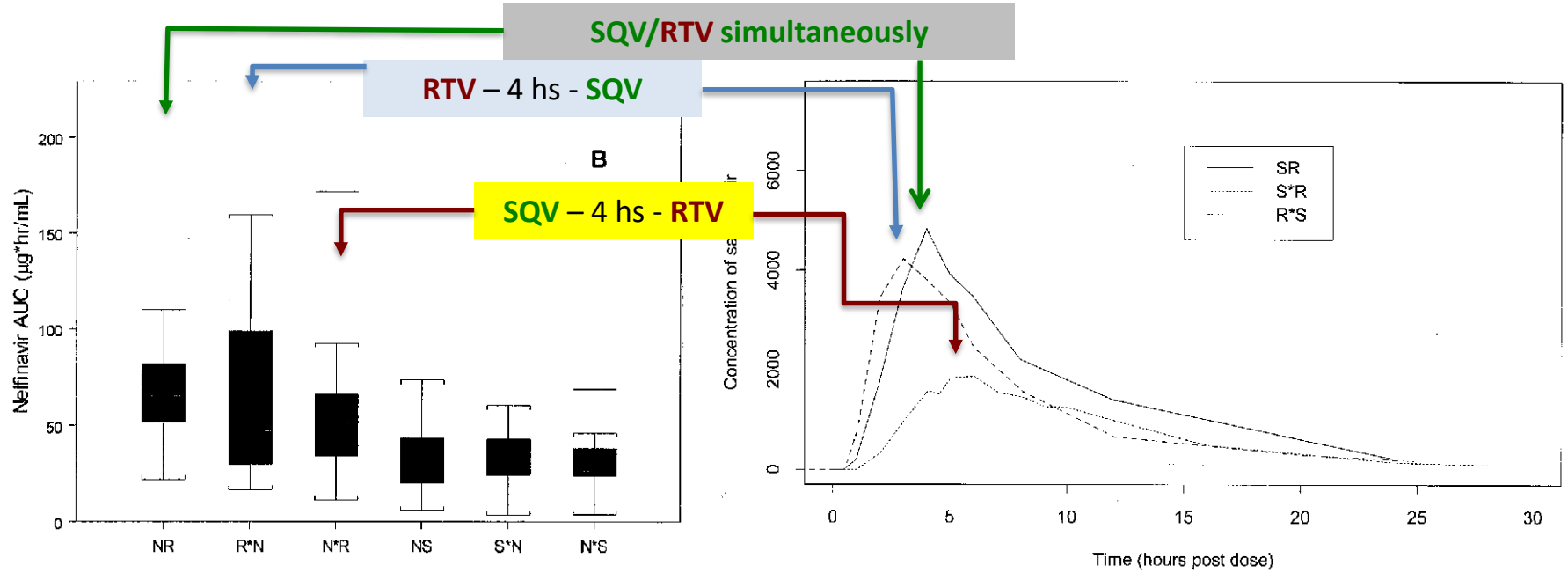
Kempf et al. 1997

Effect of simultaneous versus staggered dosing on pharmacokinetic interactions of protease inhibitors (Clin Pharmacol Ther 2003;73:406-16.)

Carla B. Washington, PhD, Charles Flexner, MD, Lewis B. Sheiner, MD, Susan L. Rosenkranz, PhD, Yoninah Segal, MS, Judith A. Aberg, MD, Terrence F. Blaschke, MD, and the AIDS Clinical Trials Group Protocol 378 (ACTG 378) Study Team,
Stanford and San Francisco, Calif, Baltimore, Md, and Boston, Mass

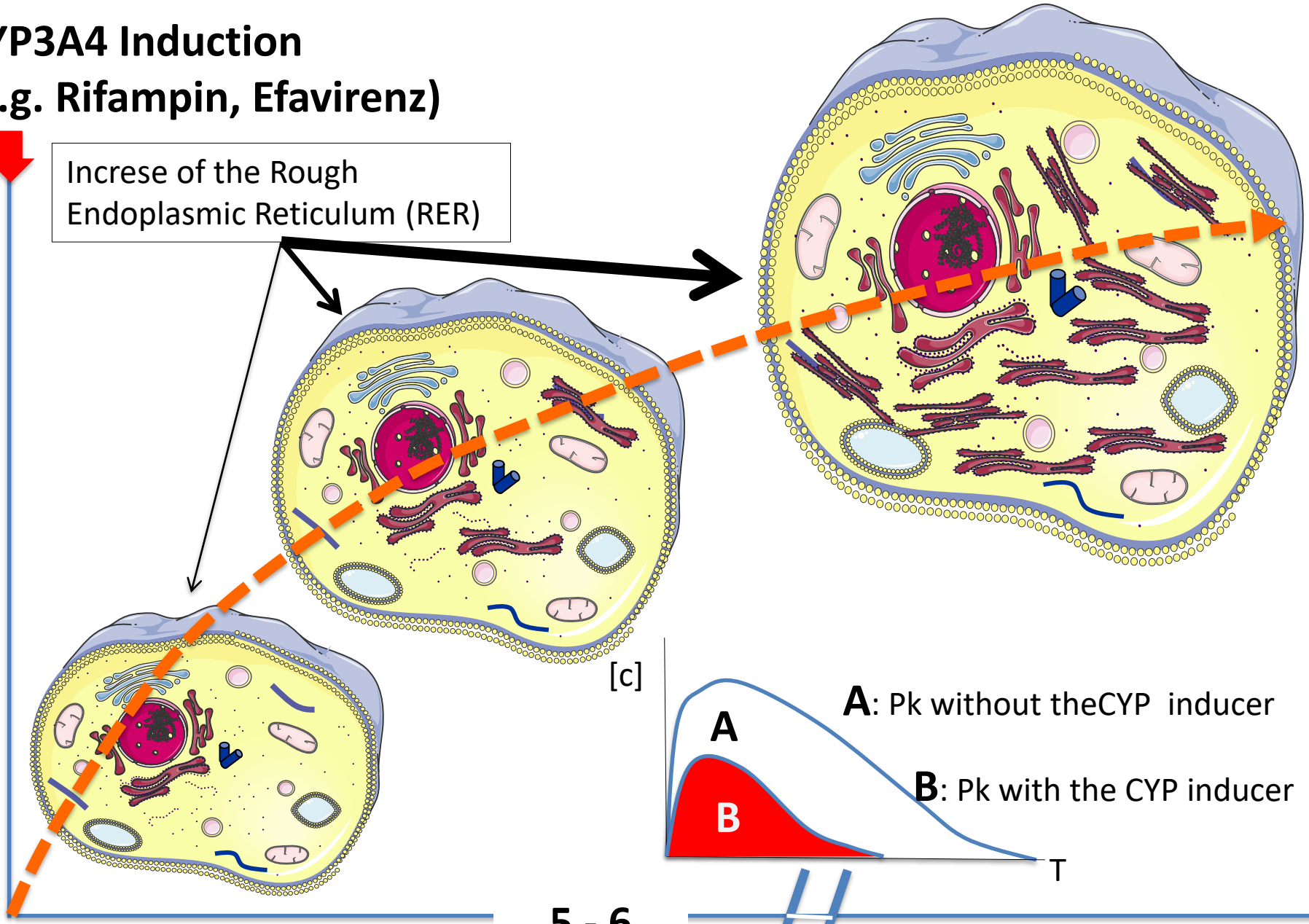
Objective: **The aim of this study was to determine whether pharmacokinetic interactions between the protease inhibitors saquinavir soft gel, nelfinavir, and ritonavir are affected by the timing of administration.**

Study design: **We used an open-label, 6-period, incomplete Latin square crossover study in 18 human immunodeficiency virus–negative subjects. Each received single oral doses of 2 of the 3 protease inhibitors during each of 6 periods. Single doses were given either simultaneously or separated by 4 hours.**



CYP3A4 Induction
(e.g. Rifampin, Efavirenz)

Increse of the Rough Endoplasmic Reticulum (RER)

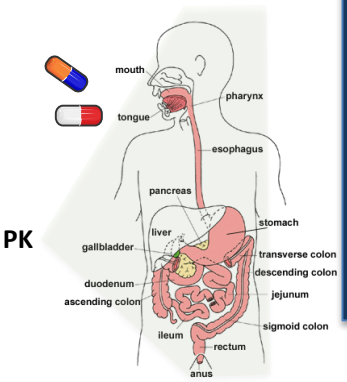


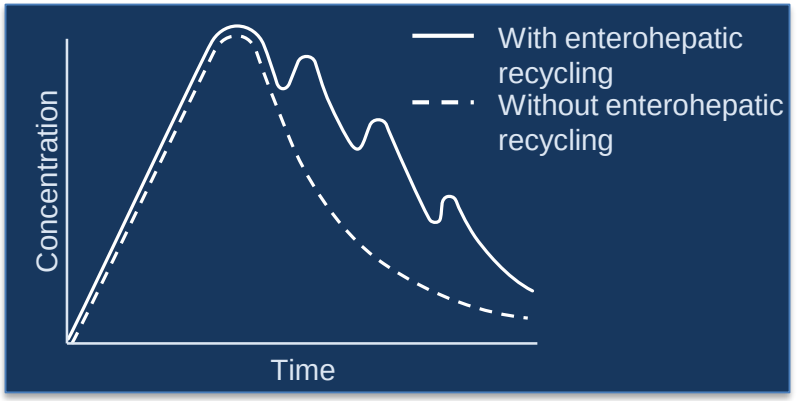
A → Absorption

D → Distribution

M → Metabolism

E → **Elimination**





Systemic circulation

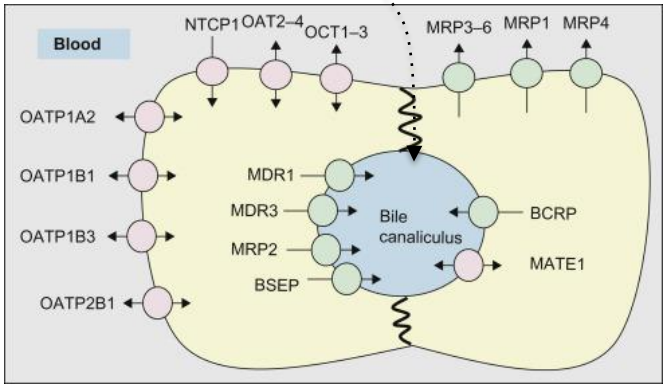
Systemic circulation

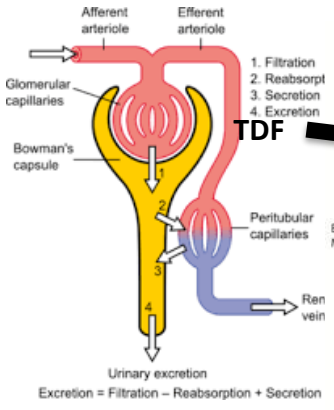
Portal Vein

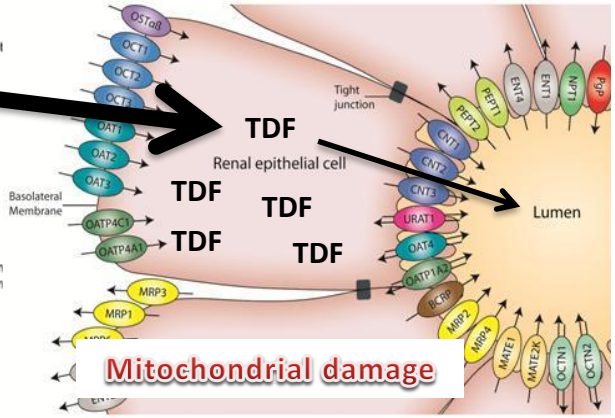
Polar species

Non polar species

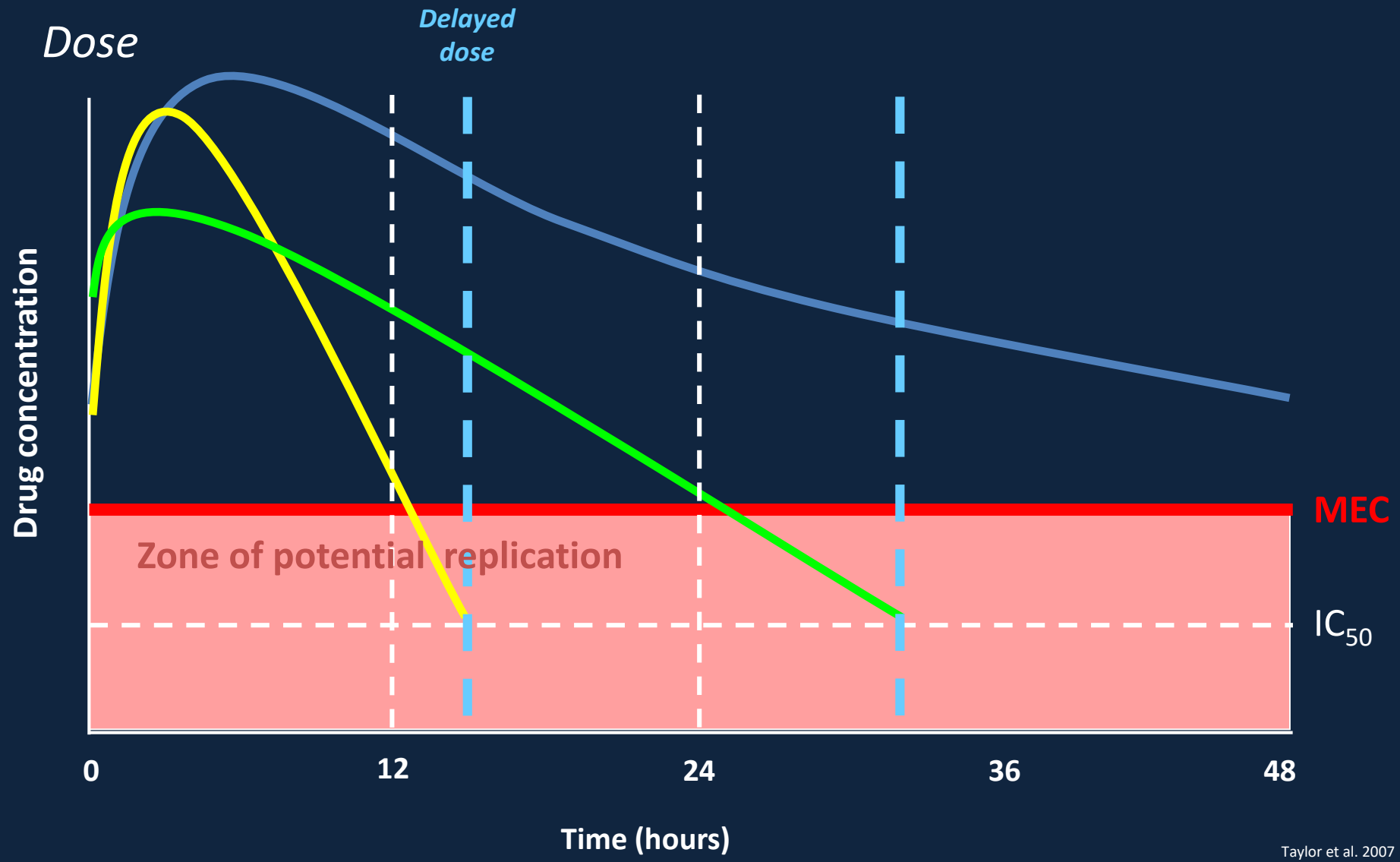
Phosphate Reabsorption







T/2 & “forgiveness”



Taylor et al. 2007

POINT n. 5

Reconsider the previous points by looking at the ongoing innovation

New "conventional" options
With some degree of innovation

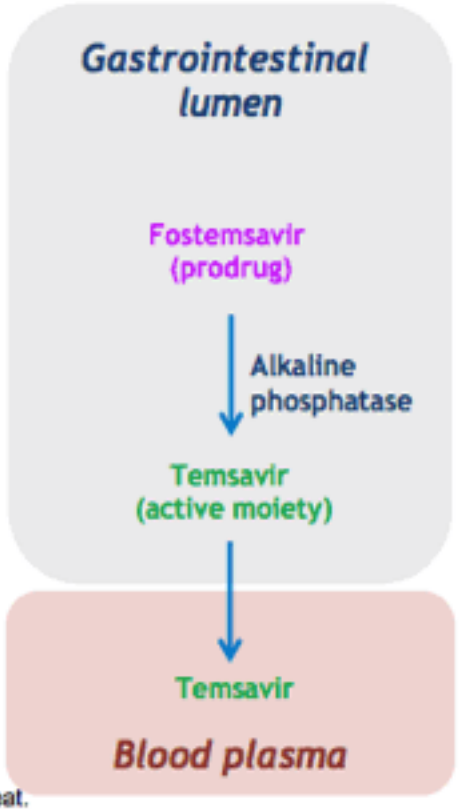
- Raltegravir 1200 mg QD → ***Single daily administration, + 400 mg***
- DRV/COBI/FTC/TAF → ***STR, COBI, no TDF***
- Bictegravir/FTC/TAF → ***STR, no booster, no TDF, not inf. to DTG***
- Doravirine → ***STR +/-, PI-like T/2, lipid neutral, potent, no action on CYP3A***
- DTG/RPV* → ***2 drugs instead of three, not inf. 3 drugs***
- DTG/3TC * → ***2 drugs instead of three, not inf. 3 drugs***

** Not conventional but consisting of conventional drugs*

Overview of Fostemsavir

- Fostemsavir (FTR) is a prodrug metabolised to temsavir (TMR),[1] a first-in-class, investigational attachment inhibitor that is currently being evaluated in HIV-1-infected HTE patients
- Active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1[2–5]
- Unique resistance profile with no *in vitro* cross-resistance to other classes of ARVs[2,5]
- In the Phase 2b study AI438011, FTR demonstrated:[6]
  - Median decreases in plasma HIV-1 RNA of 0.69–1.44 $\log_{10}$ c/mL in a 7-day lead-in monotherapy substudy
  - Generally similar virologic (mITT and observed) and immunologic responses to the ritonavir-boosted atazanavir arm through Week 96
  - A generally well-tolerated safety profile with no FTR-related AEs leading to discontinuation
- Here we present Day 8 and Week 24 efficacy and safety results from the ongoing BRIGHTE study (formerly 205888/AI438-047)

Conversion of fostemsavir to temsavir[1]



HTE, heavily treatment experienced; ARV, antiretrovirals; AEs, adverse events; mITT, modified intent to treat.

1. Brown J *et al. J Pharm Sci* 2013; 102:1742–1751; 2. Nowicka-Sans B *et al. AAC* 2012; 56:3498–3507; 3. Ray N *et al. JAIDS* 2013; 64:7–15; 4. Zhou N *et al. JAC* 2014; 69:573–581; 5. Li Z *et al. AAC* 2013; 57:4172–4180; 6. DeJesus E *et al., CROI* 2016: Poster 472.

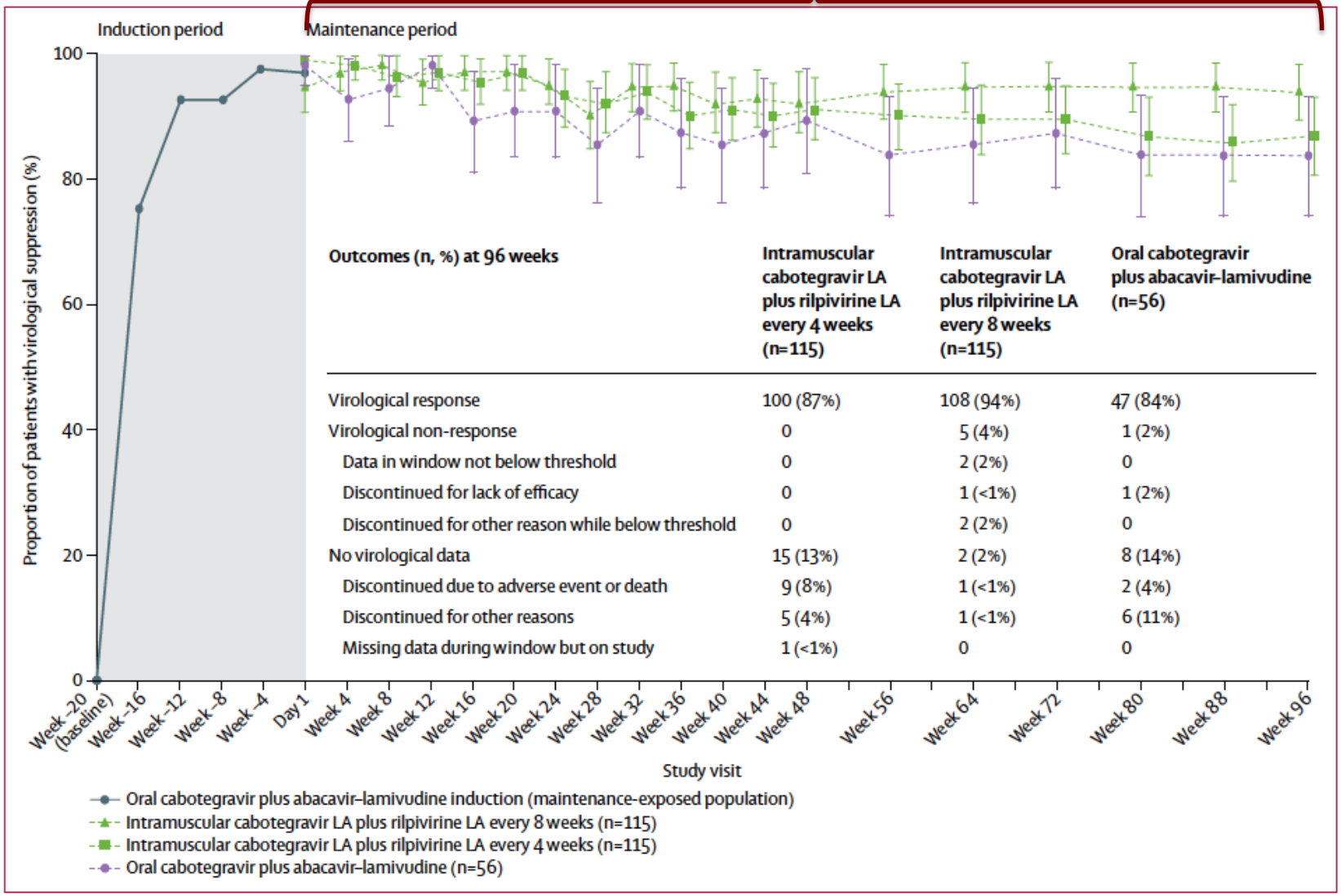
LONG – ACTING AGENTS

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et al

Lancet 2017; 390: 1499–510

SUPERVISED !!



Outcomes (n, %) at 96 weeks	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

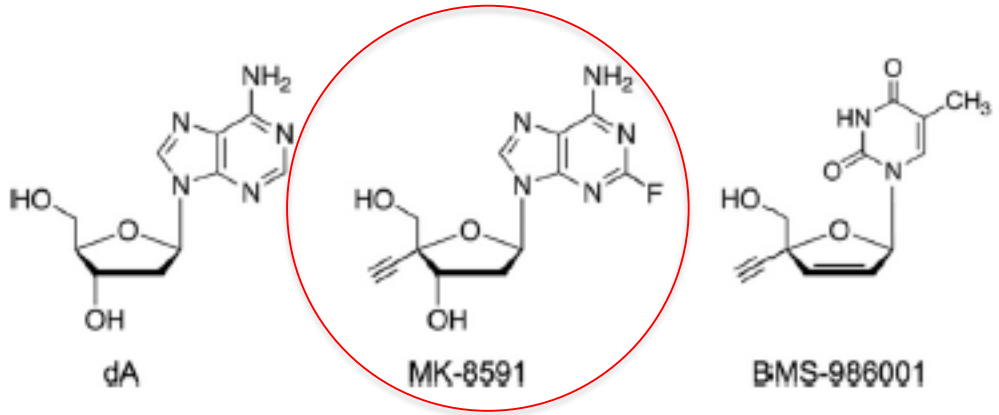
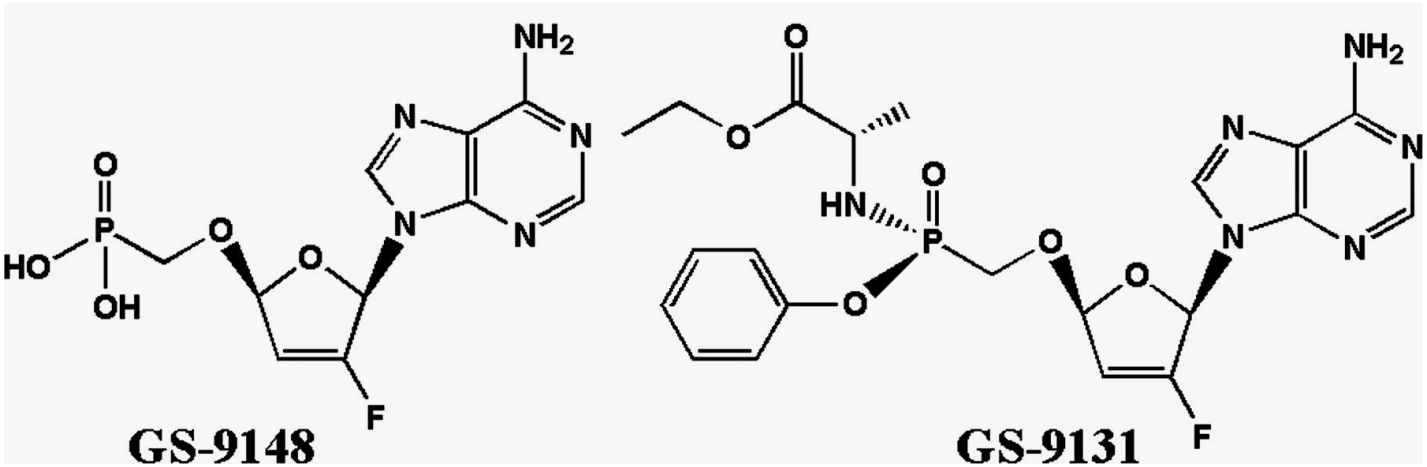


FIG 1 Chemical structures of 2′-deoxyadenosine (dA), MK-8591 (4′-ethynyl-2-fluoro-2′-deoxyadenosine [EFdA]), and BMS-986001 (2′,3′-didehydro-3′-deoxy-4′-ethynyl-thymidine; also known as festinavir, censavudine, 4′-ethynyl stavudine, 4′-ethynyl-d4T, and OBP-601).

GS-9131 is a monoamidate prodrug of the nucleotide analog GS-9148 (phosphonomethoxy-2'-fluoro-2',3'-dideoxydidehydroadenosine). GS-9131 undergoes conversion in lymphocytes to GS-9148 diphosphate, a potent inhibitor of HIV-1 RT.



4’-Ethynyl-2-fluoro-2’-deoxyadenosine (EFdA)

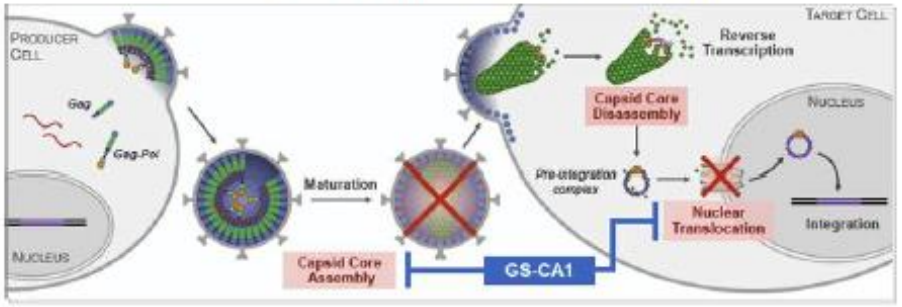
Unique properties

- Exceedingly potent (possible dose in humans of <5 mg/day)
- Lack of cross-resistance with most NRTI’s
- Minor impact of M184V
- More active against HIV-2 than other NRTI’s
- Long half-life of intracellular TP (>72 hours) in rhesus macaques
- Possibility of once-weekly oral dosing
- Possibility of implant formulation with dosing interval of ≥one year

GS-CA1 HIV Capsid Inhibitor: More Potent Than Any Approved Antiretroviral

- Inhibits multiple steps in the HIV replication cycle
  - Capsid core assembly
  - Capsid core disassembly
  - Nuclear translocation
- Highly active against major HIV-1 mutants selected by clinical PIs, NRTIs, NNRTIs, and INSTIs
- No measurable cytotoxicity in target and non-target primary cells
- Single sc injection maintains plasma concentrations 9 times the plasma adjusted EC_{95} for >10 weeks – in rats
- Currently in Phase 1 studies in humans

GS-CA1: Multiple Sites of Action



	EC_{50} (pM)		
	CD4+ T Lymphocytes	Macrophages	Human PBMCs
GS-CA1	60	100	140
Efavirenz	1200	2300	--
Dolutegravir	1000	1900	1200
Atazanavir	6900	8300	19,000

Tse WC, et al. 24th CROI. Seattle, 2017 Abstract 38.

Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

Emu B, et al N Engl J Med 2018;379:645-54.

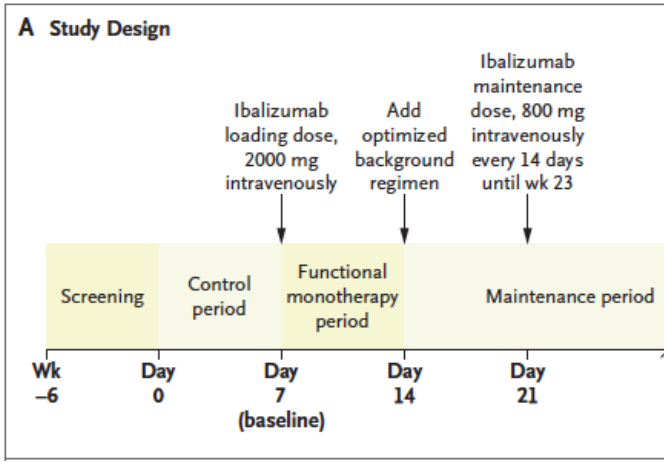


Table 2. Virologic Response before and after Loading Dose of Ibalizumab and at 25 Weeks in the 40 Study Patients.*

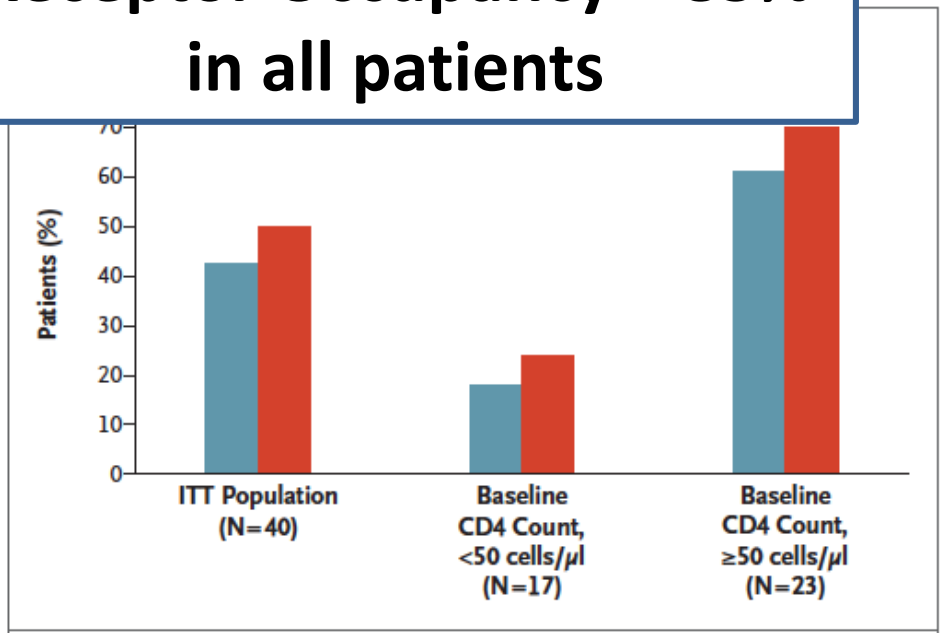
Response	Before and after Loading Dose			Week 25
	Control Period	Functional Monotherapy Period	P Value	
Decrease in viral load of ≥0.5 $\log_{10}$ copies/ml — no. (%)	1 (3)†	33 (83)	<0.001	25 (63)
Decrease in viral load of ≥1.0 $\log_{10}$ copies/ml — no. (%)	0	24 (60)	NA	22 (55)
Mean change in viral load from baseline — $\log_{10}$ copies/ml	0.0±0.2	−1.1±0.6	<0.001	−1.6±1.5

Ibalizumab binds to CD4 extracellular domain 2

Prevention of **conformational change** in the CD4-gp120 complex

Different binding sites from HLA (no interference with CD4-dep. Immunity)

Receptor Occupancy > 85% in all patients



PK profile of VRC01-LS

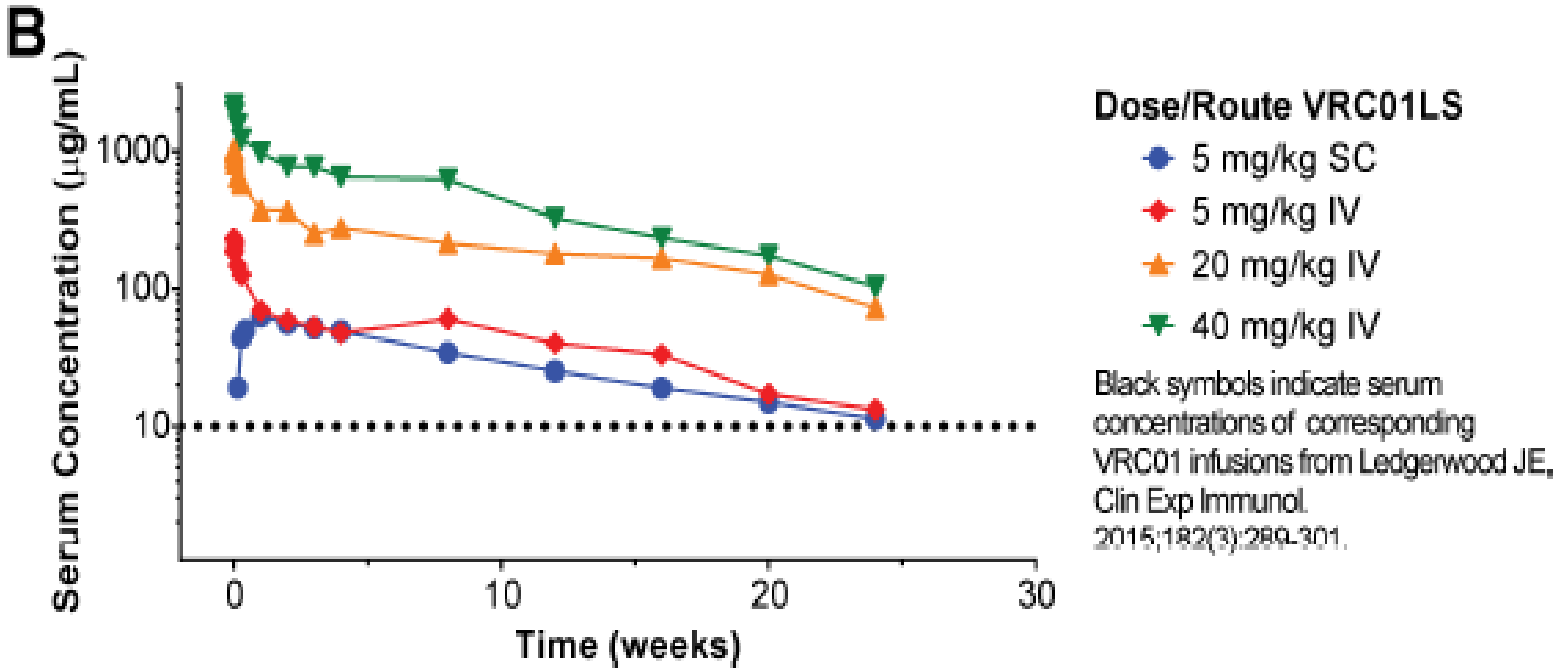
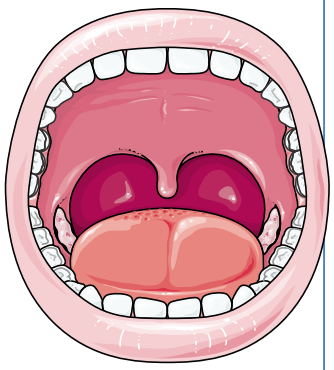


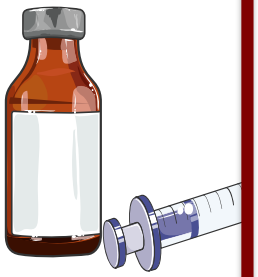
Fig 2. Measurement of antibody serum concentration (µg/mL). (A) Serum VRC01LS concentrations (colored plots) are shown from first measurement through week 24 after a single administration. The infusion dose and route are as specified in the legend. All values are the mean of duplicate samples run in different wells within the same plate. Previously published VRC01 concentrations based on historical data (black plots) after administration at weeks 0 and 4 are shown for comparison. (B) Geometric mean serum VRC01LS concentrations per group over time. The dotted line at 10 µg/mL on each graph is shown as a reference value. IV, intravenous; SC, subcutaneous.

https://doi.org/10.1371/journal.pmed.1002493.g002

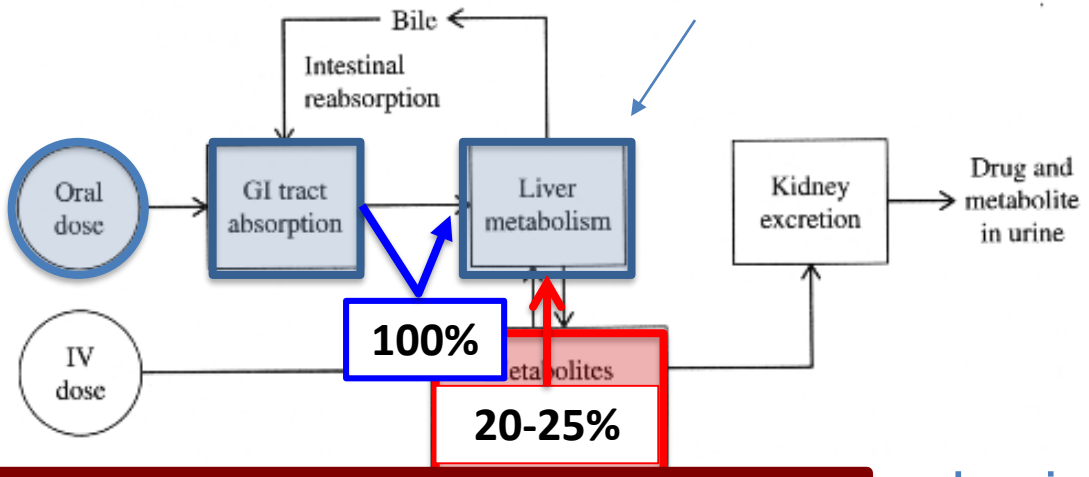
Gaudinski MR et al., *PLoS Med* 2018; January 24

Estrogens	Ethinylestradiol
	Estradiol
Progestins	Desogestrel
	Drospirenone
	Dydrogesterone
	Etonogestrel
	Gestodene
	Levonorgestrel
	Medroxy-progesterone (IM)
	Medroxy-progesterone (oral)
	Norelgestromin
	Norethisterone (Norethindrone)
	Norgestimate
	Norgestrel
Other	Levonorgestrel (EC)
	Mifepristone
	Ulipristal

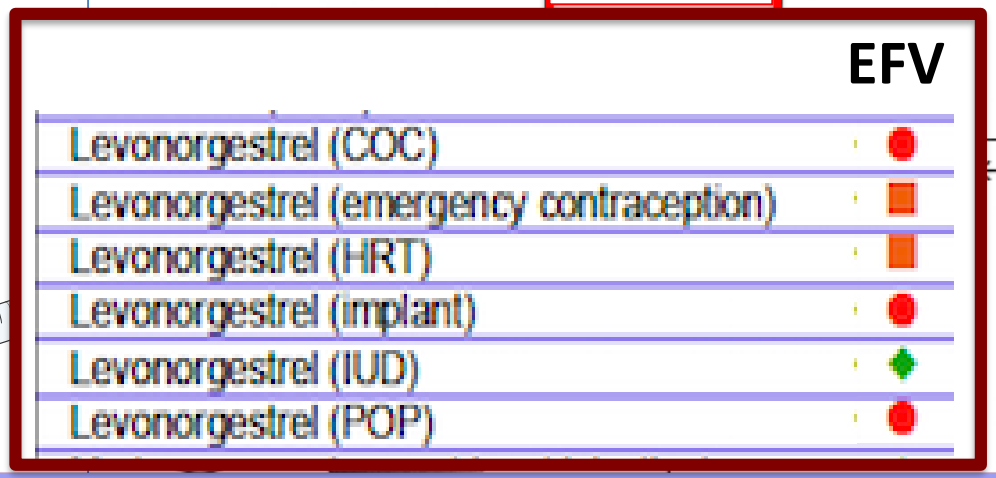




first pass metabolism



brain



	DLV	EFV	ETV	NVP	RPV	RPV + F/TAF
Medroxyprogesterone (IM depot injection)	◆	◆	◆	◆	◆	◆
Medroxyprogesterone (oral)	■	■	■	■	◆	◆

●/○	These drugs should not be coadministered
■/□	Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
◆/◇	No clinically significant interaction expected
✦/✧	There are no clear data, actual or theoretical, to indicate whether an interaction will occur

TORINO:

Stefano Bonora

Francesco G. De Rosa

Andrea Calcagno

Antonio D'Avolio

Mauro Sciandra

Marco Siccardi

Cristina Tettoni

Sabrina Audagnotto

Letizia Marinaro

Jessica Cusato

Laura Trentini

Marco Simiele

Amedeo De Nicolò

Anna Lucchini

Filippo Lipani

Roberto Bertucci

Agostino Maiello

Chiara Montrucchio

Chiara Alcantarini

Marino Bonasso

Ilaria De Benedetto

Stefano Biffi

Paolo Tiralongo

Micol Ferrara

Alice Trentalange

Lucio Boglione

Pino Cariti

Ilaria Motta

Silvia Corcione

Ambra Barco

Tommaso Lupia

Simone Mornese Pinna

Enrica Borgogno

Silvia Scabini

Giancarlo Orofino

Valeria Ghisetti

Valeria Avataneo

Alessandra Manca

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Margherita Bracchi

Nicole Pagani

ROMA:

Andrea Antinori

Adriana Ammassari

Giuseppe Ippolito