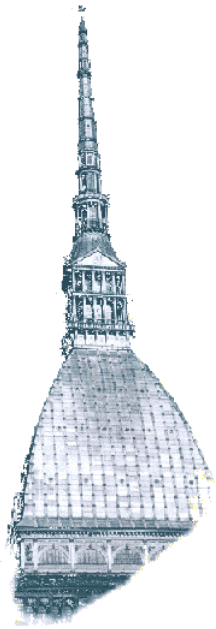
Residential Course on Clinical Pharmacology of Antiretrovirals 2005 – 2015

Laboratorio di Farmacologia Clinica e Farmacogenetica

Gianni Di Perri

Clinica di Malattie Infettive
Università degli Studi di Torino

Ospedale Amedeo di Savoia



- This project took place following the development of a Laboratory of Pharmacokinetics inside the Infectious Diseases Unit of the University of Torino

- Based on the consideration that Torino hosted the third largest italian HIV case series per single clinical center, and that antiretroviral therapy should have been administered for the entire life, we decided to devote ourselves to the study of clinical pharmacology of antiretrovirals in order to try to better understand what we were doing to our patients

- The Residential Course on Clinical Pharmacology of Antiretrovirals has grown up in parallel with our genuine enthusiasm of working in such rapidly developing field, in which most of the novelties we have seen in the last 20 years really contributed to a longer and better life for our Patients

- The Residential Course in Clinical Pharmacology of Antiretrovirals, further to be a unique opportunity for us to learn from our Speakers and Participants, it's a sort of celebration of our happiness to have You All here, to testify how good the idea was and still is, to annually assemble those, pharmacologists, clinicians and non-clinicians, who share the same passion for this special setting

Although the acknowledgments are usually done at the end, please let me anticipate my truly sincere gratitude to two particular Friends and Collaborators Who actually made their best efforts to make this project working….

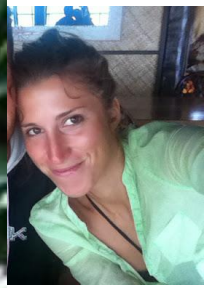
Prof. Stefano Bonora

Dr. Antonio D'Avolio

..together with Mauro Sciandra…

…..but at the very beginning, the very first move of this project was made together with…

Dr. Marta Boffito



Dr. Margherita Bracchi

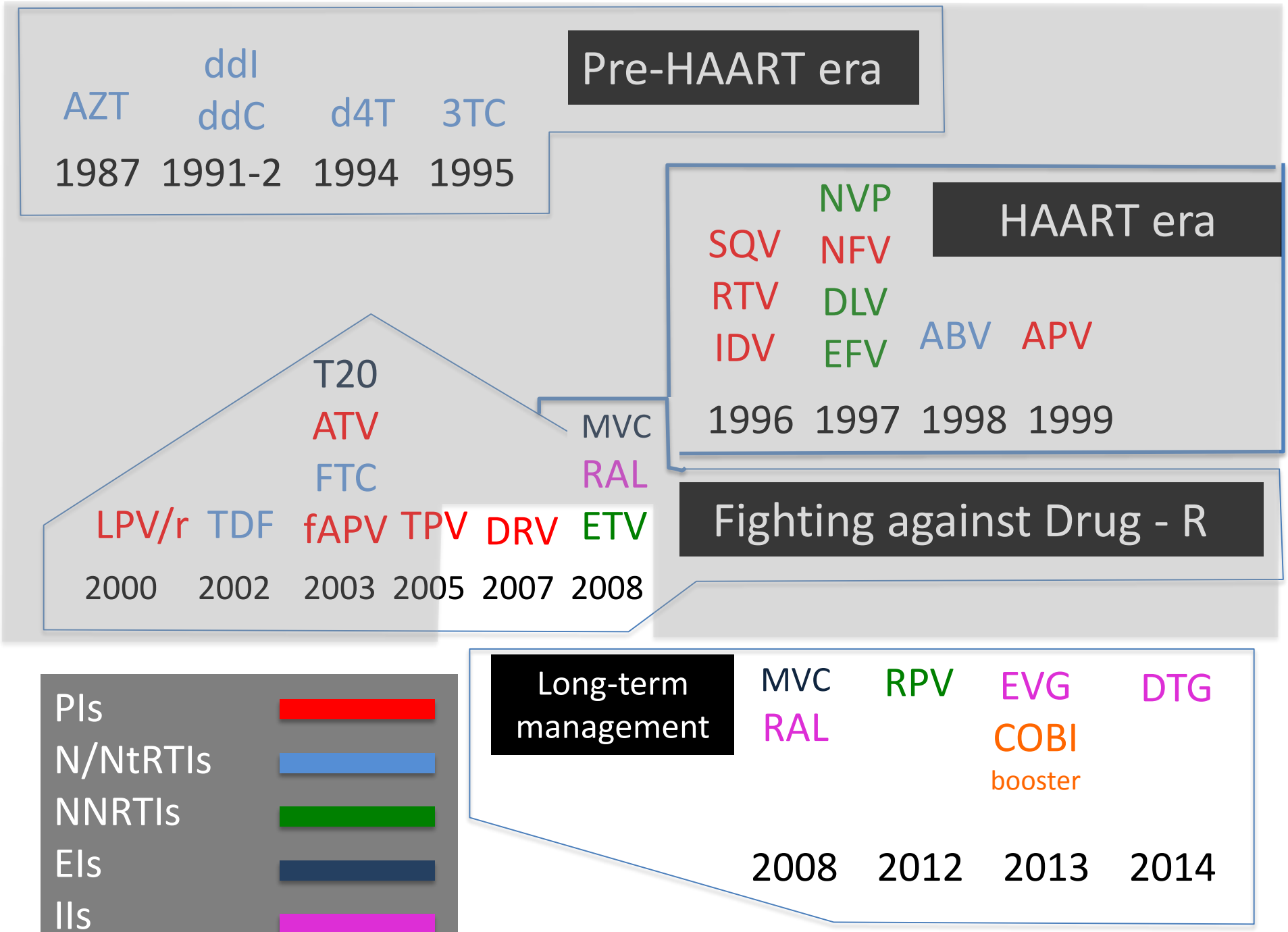
..Who acted as pioneer in establishing our partnership with the David Back's Pharmacology Group in Liverpool before migrating to the Chelsea HIV Unit in London….. We are still sad but truly proud as well!

…and on this line I am also very grateful to Dr. Lorena Baietto (PhD) for Her hard work in the Lab and the efforts She has made in teaching to students, technicians and postgraduates….

Dr. Lorena Baietto

Dr. Marco Siccardi

More recently we also had the privilege to work with Dr. Marco Siccardi (PhD), Who graduated with us, and after having developed remarkable technical skills and successful scientific innovation also migrated to the UK where He joined the Pharmacology Group in Liverpool.
We feel sadly proud, again….


Pre-HAART era
AZT
ddI
ddC
d4T
3TC
1987
1991-2
1994
1995
HAART era
NVP
SQV
NFV
RTV
DLV
IDV
EFV
ABV
APV
1996
1997
1998
1999
T20
ATV
FTC
MVC
RAL
LPV/r
TDF
fAPV
TPV
DRV
ETV
2000
2002
2003
2005
2007
2008
Fighting against Drug - R
PIs
N/NtRTIs
NNRTIs
EIs
IIs
Long-term management
MVC
RAL
RPV
EVG
COBI
booster
DTG
2008
2012
2013
2014

Pharmacology of ARVs: The present and the future.

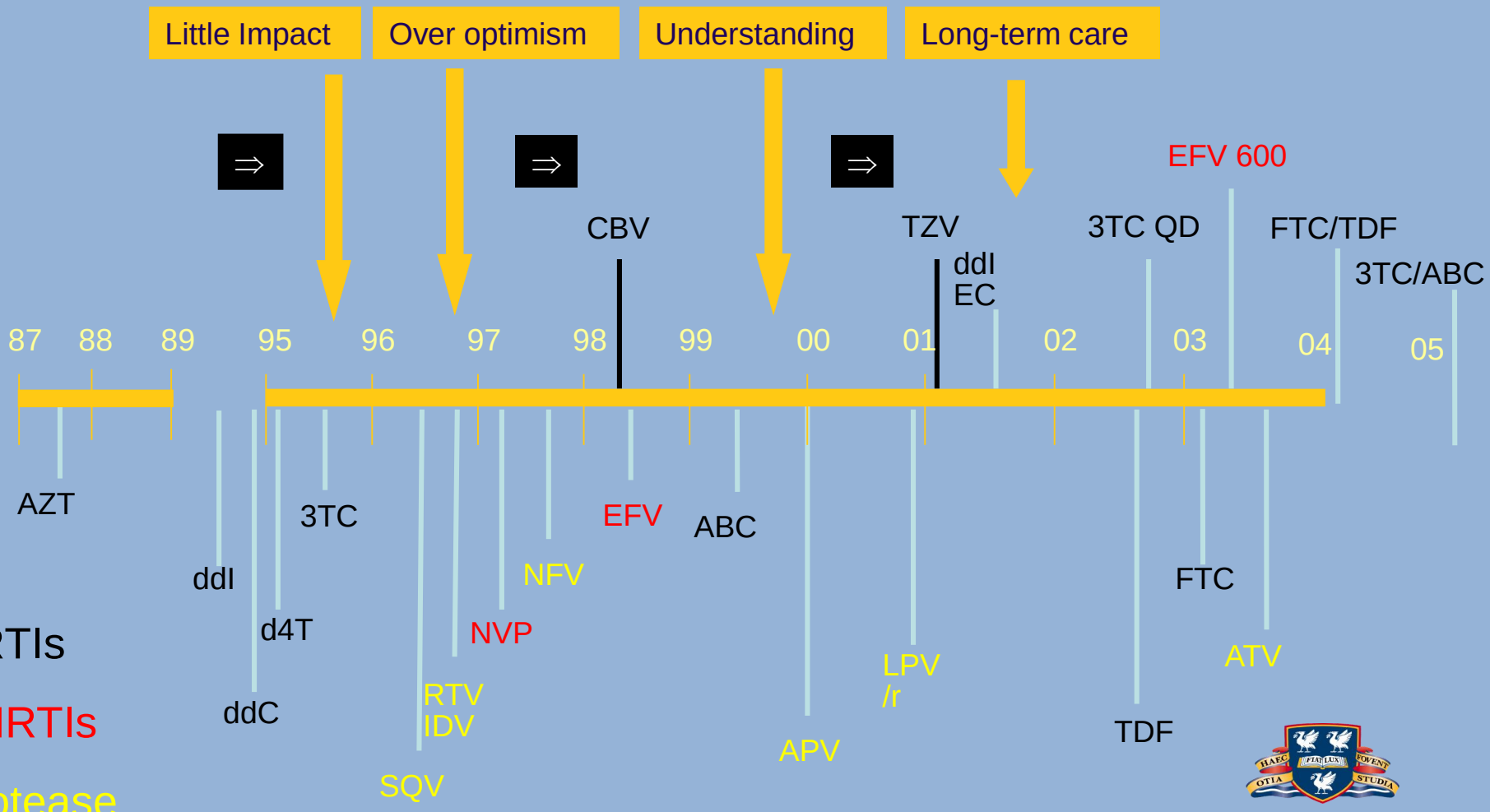
Torino Jan 2005

David Back

THE UNIVERSITY
of LIVERPOOL

…. courtesy of David Back, 1st Residential Course on Clinical Pharmacology of Antiretrovirals, 2005

Anti-HIV Therapy Treatment History



HIV is a disease of long-term care

THE UNIVERSITY *of* LIVERPOOL

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.

How to quantify the "power" or "potency" of our PK exposure?

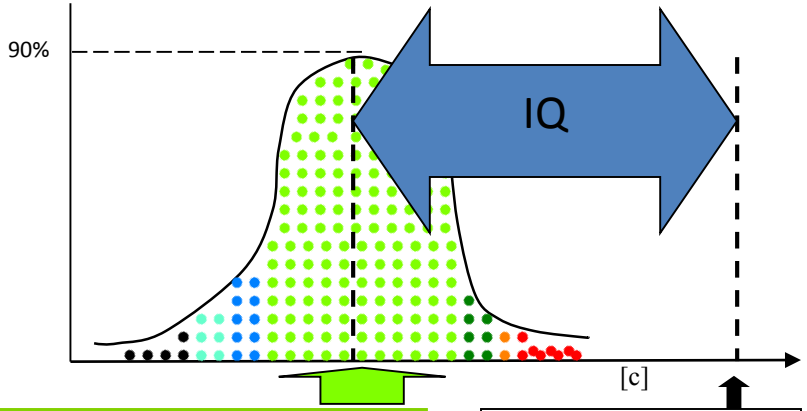
$$IQ = \frac{\text{Pk exposure}}{\text{Viral susceptibility}}$$

$$GIQ = \frac{\text{Plasma } C_{trough}}{\text{n. of relevant mutations}}$$

$$NIQ = \frac{\text{Patient IQ}}{\text{Reference IQ}}$$

$$PIQ = \frac{\text{Plasma } C_{trough}}{IC_{50\text{-}90}}$$

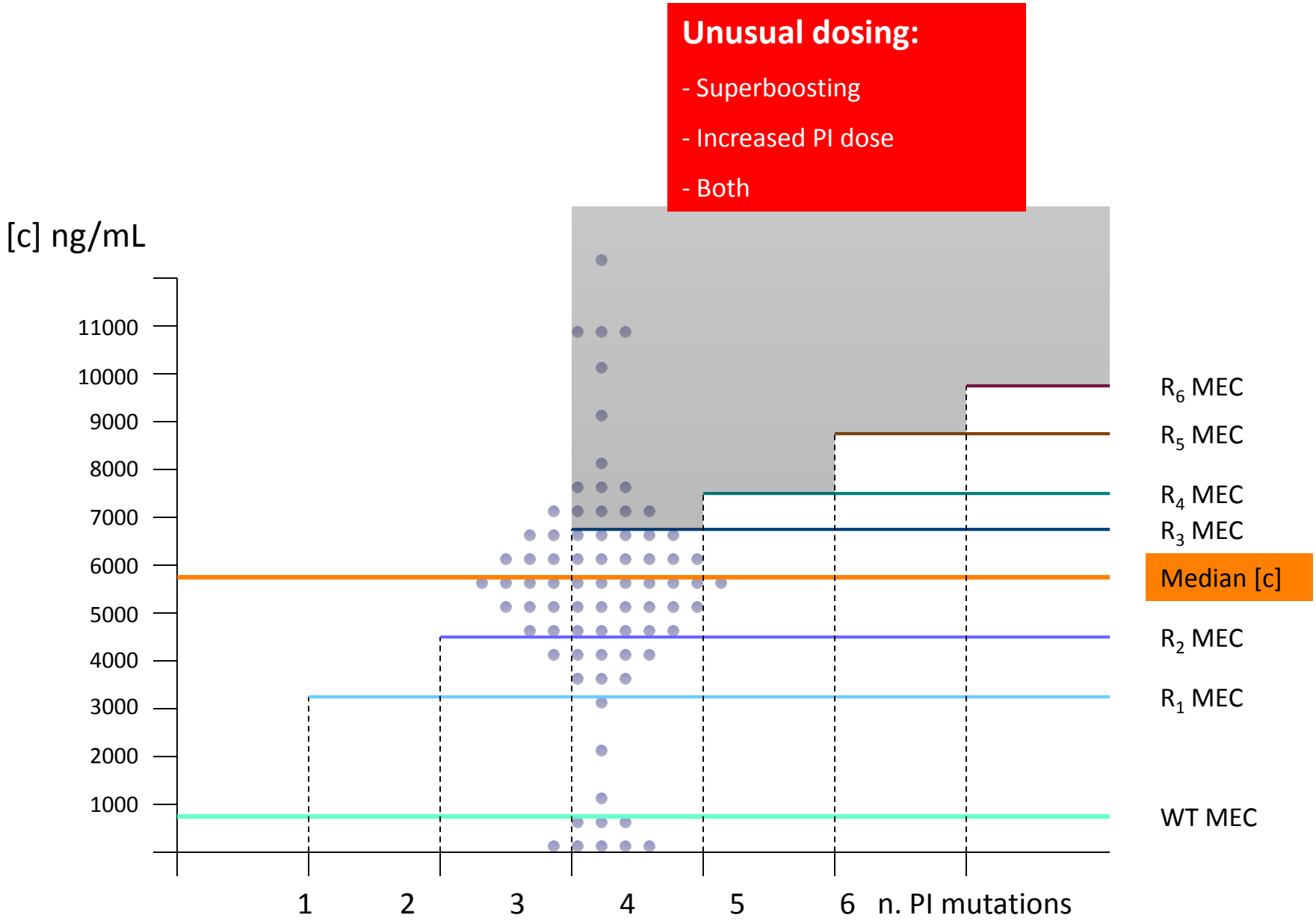
$$VIQ = \frac{\text{Plasma } C_{trough}}{\text{Virtual Phenotype}}$$



Drug [c] corresponding to the EC_{50}

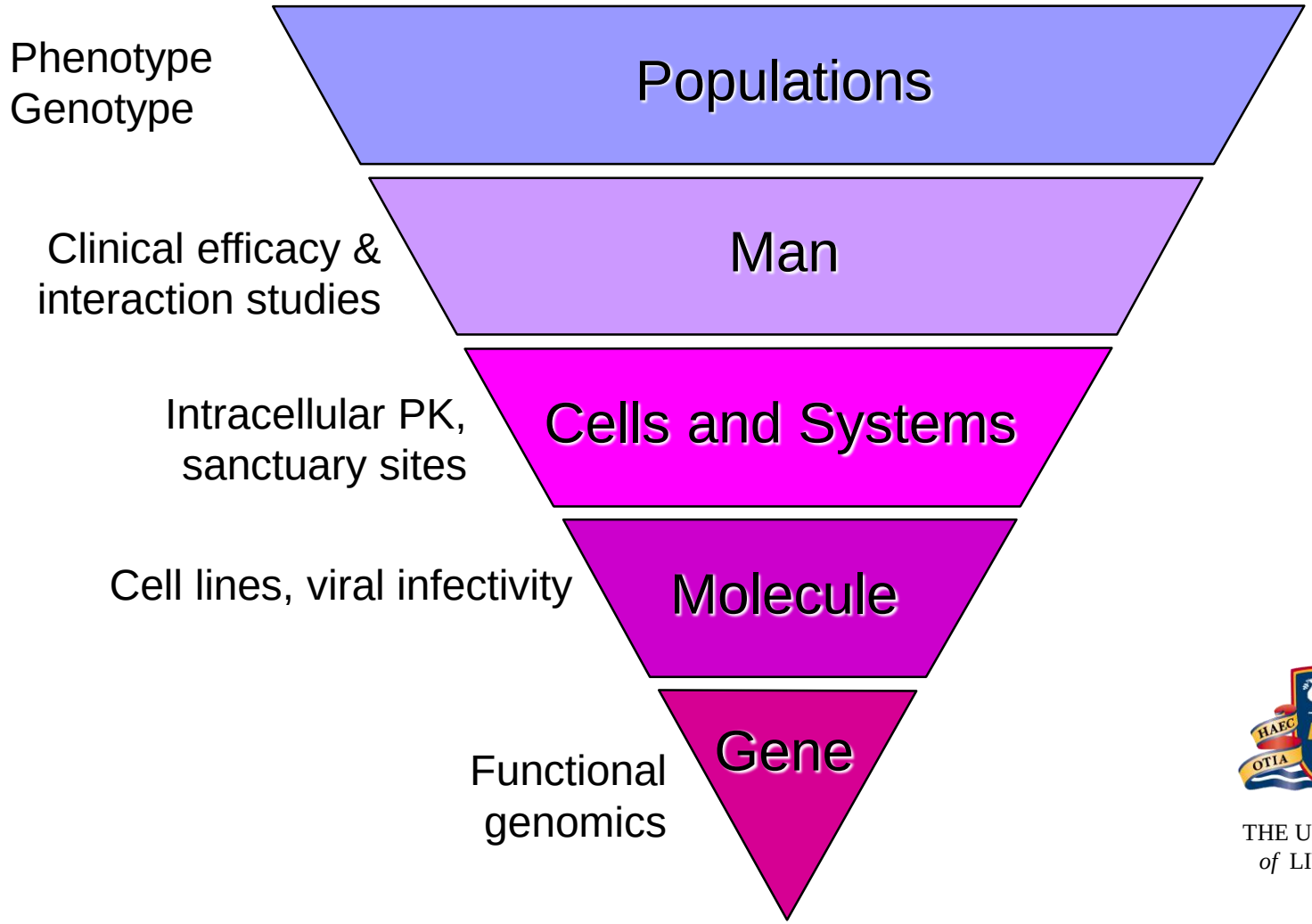
Concentration measured

In studies on PI-experienced pts. IQ has been repeatedly found to have a higher predictive value than drug [c] or sensitivity testing taken alone

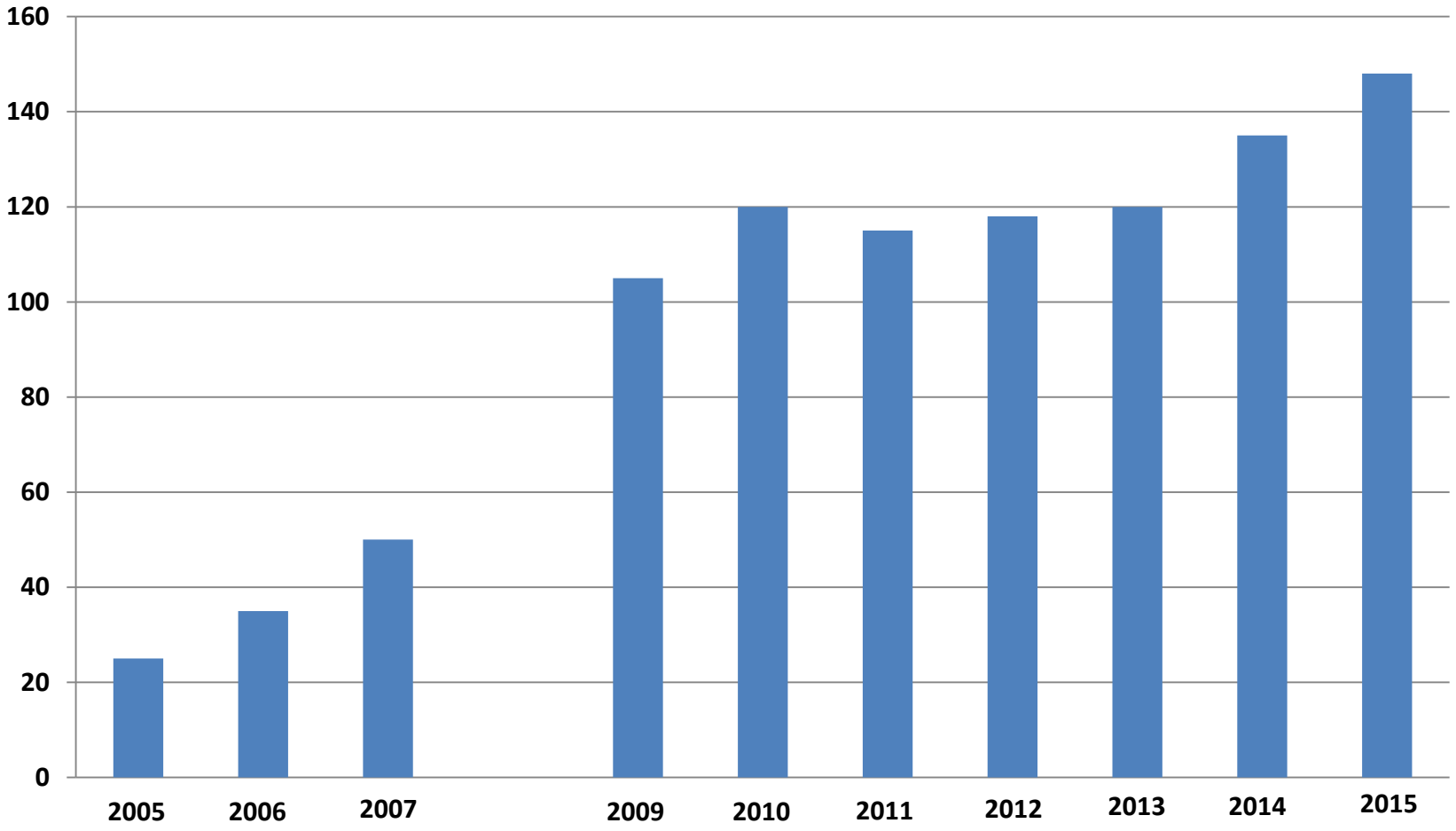

Unusual dosing:
- Superboosting
- Increased PI dose
- Both
[c] ng/mL
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
1
2
3
4
5
6
n. PI mutations
R6 MEC
R5 MEC
R4 MEC
R3 MEC
Median [c]
R2 MEC
R1 MEC
WT MEC

The Future of HIV Pharmacology: Molecule to Man

Studies



THE UNIVERSITY
of LIVERPOOL



PARTICIPANTS TO THE COURSE, 2005-2015

INVITED SPEAKERS 2005-2015

61 speakers

28 international

9
3
3
1
1
6
4
1

Always present !

DAVID BACK

MARTA BOFFITO

SAYE KHOO

CARLO FEDERICO PERNO

SINGLE SPONSOR
2005- 2009

Abbott

A Promise for Life

MULTIPLE SPONSORSHIP
2009 - 2015

Abbott

A Promise for Life

abbvie

2013

janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

MSD

GILEAD

Advancing Therapeutics.
Improving Lives.

ViiV Healthcare

Bristol-Myers Squibb Company

European Cup Final 2006!!
Liverpool v Fiorentina
L·F·C
L·F·C
HAEC
FIAT LUX
FOVENT
OTIA
STUDIA
THE UNIVERSITY
of LIVERPOOL

Page last updated at 20:35 GMT, Tuesday, 29 September 2009 21:35 UK

Stevan Jovetic was Liverpool's tormentor as he scored twice in Fiorentina's surprise win over the Reds in their Champions League Group E tie.

Fiorentina spoil Reds' swan song
Published: Thursday 10 December 2009, 0.30CET
Liverpool FC 1-2 ACF Fiorentina
Alberto Gilardino struck in injury time to complete a comeback win that sealed top spot for the Viola and a sorry Liverpool campaign.

TORINO:

Stefano Bonora
Antonio D'Avolio
Mauro Sciandra
Marco Siccardi
Lorena Baietto
Cristina Tettoni
Sabrina Audagnotto
Letizia Marinaro
Jessica Cusato
Margherita Bracchi
Laura Trentini
Andrea Calcagno
Marco Simiele
Amedeo De Nicolò
Anna Lucchini
Filippo Lipani
Roberto Bertucci
Agostino Maiello
Bernardino Salassa
Francesco G. De Rosa
Chiara Montrucchio
Chiara Alcantarini
Chiara Cardellino

Alessandra Arialdo
Micol Ferrara
Alice Trentalange
Nicole Pagani
Lucio Boglione
Sarah Allegra
Debora Pensi
Pino Cariti
Paolo Bigliano
Ilaria Motta
Silvia Corcione
Maria Laura Stella
Valeria Ghisetti

Acknowledgments

THE UNIVERSITY
of LIVERPOOL

LIVERPOOL:

David Back
Saye Khoo
Andy Owen
Marco Siccardi

ST STEPHEN'S AIDS TRUST

LONDON:

Marta Boffito
Margherita Bracchi

ROMA:

Andrea Antinori
Emanuele Nicastri
Giuseppe Ippolito