Pharmacology of Generics

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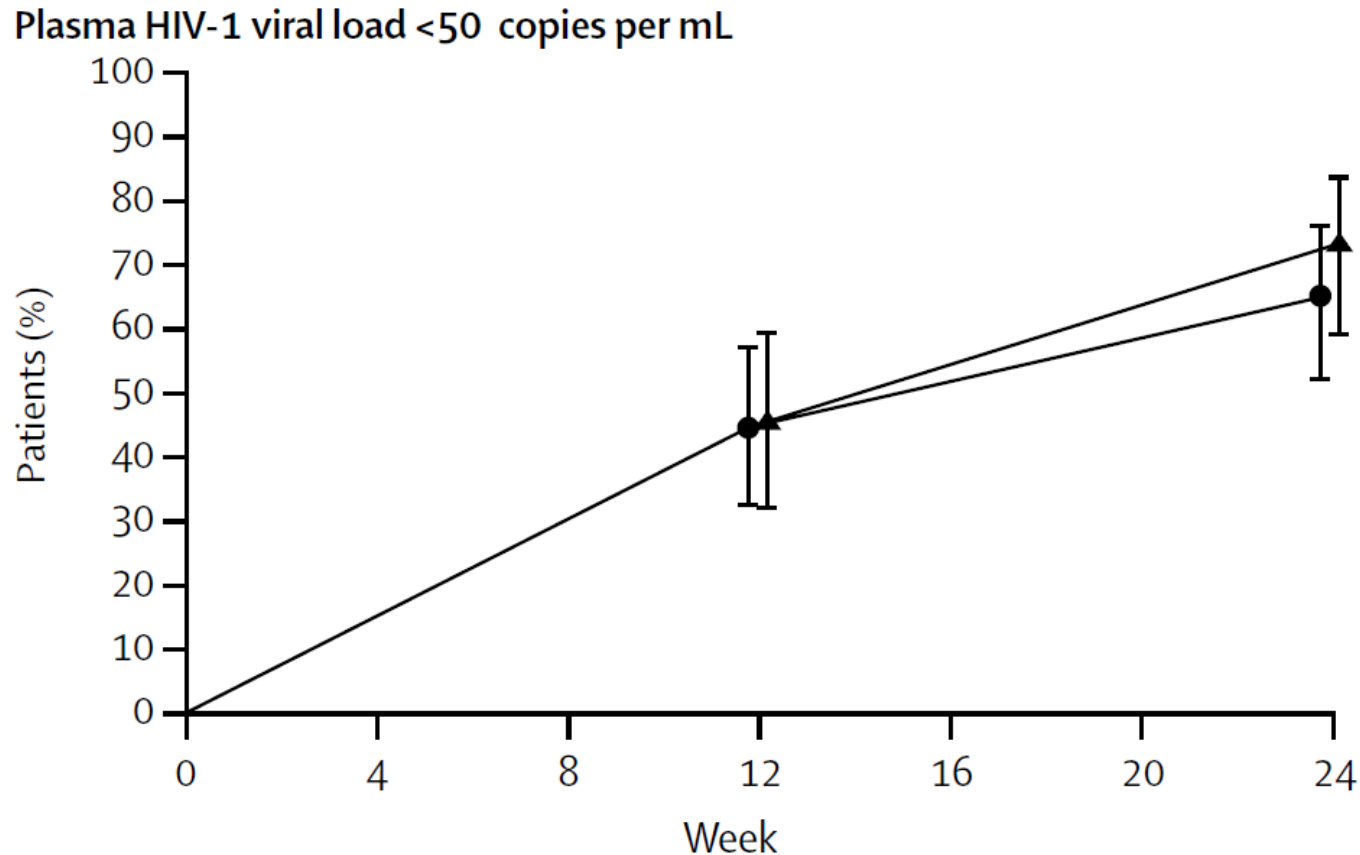# Why to talk of generics today…?

Drug	Trade name	Patent expiration
Lamivudine	Epivir®	2011
Ritonavir	Norvir®	2012
Nevirapine	Viramune®	2013
Lamivudine/AZT	Combvir®	2013
Efavirenz	Sustiva®	2013
Abacavir	Ziagen®	2016
Lopinavir/ritonavir	Kaletra®	2016
Darunavir/ritonavir	Prezista®	2017
Atazanavir/ritonavir	Reyataz®	2017
ABC/3TC	Kyvexa®	2019
Etravirine	Intelence®	2021

Generics are effective drugs…

Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial

Plasma HIV-1 viral load <50 copies per mL

-Laurent, Lancet 2004 -

...that have improved access to therapy...

Impact of generic antiretroviral therapy (ART) and free ART programs on time to initiation of ART at a tertiary HIV care center in Chennai, India

> ✓ 1996-1999:   pregeneric era
> ✓ 2000-2003:   generic era
> ✓ 2004-2007:   free rollout

"...persons in the pregeneric era took 3.25 times longer to initiate ART versus the generic era and persons in the free rollout era initiated ART more rapidly than the generic era..."

...and reduced costs of therapy...

JIAS
Journal of the
International AIDS Society

Oral Presentation – Abstract O216

Predicted savings to the UK National Health Service from switching to generic antiretrovirals, 2014–2018

Hill, Andrew[1]; Hill, Teresa[2]; Jose, Sophie[2] and Pozniak, Anton[3]

- ✓ 67000 individuals in UK taking antiretrovirals in 2014
- ✓ estimated rise: 8% per year
- ✓ Cost of patented drugs taken from the British Formulary (30% discount)
- ✓ cost of generics estimated using a 80% discount from patented drugs

The total predicted saving over five years from a switch to generics was £1.1 billion
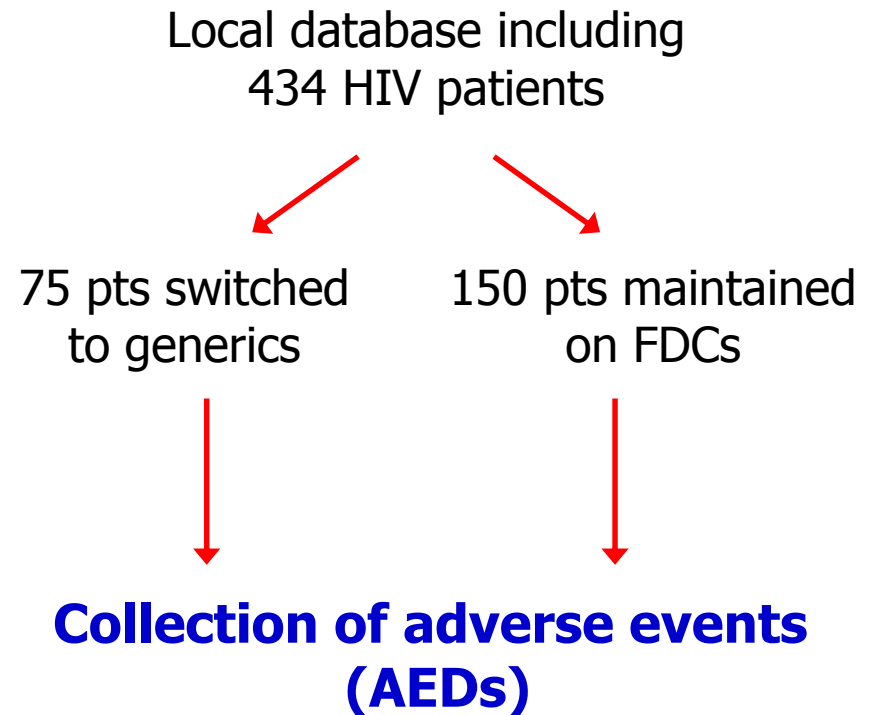
…Concerns from Spanish experience…

Cost analysis of HIV treatment and drug-related adverse events when fixed-dose combinations of antiretrovirals (FDCs) were stopped, versus continuation with FDCs

The Balearic Islands Health Service ordered the discontinuation of the treatment with FDCs in July 2010, but FDCs were reintroduced in August 2010

Local database including 434 HIV patients

75 pts switched to generics   150 pts maintained on FDCs

Collection of adverse events (AEDs)

...Concerns from Spanish experience...

	Exposed group	Non-exposed group
Adverse events (%)	**18.7%**	**1.3%**
Cost of ART (€)	2873	3017
Cost of AEs (€)	230	0
Cost of extra visit (€)	346	0
Total cost (€)	3450	3017
Total cost per day (€)	29	25

Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States

Rochelle P. Walensky, MD, MPH; Paul E. Sax, MD; Yoriko M. Nakamura, BA; Milton C. Weinstein, PhD; Pamela P. Pei, PhD; Kenneth A. Freedberg, MD, MSc; A. David Paltiel, PhD; and Bruce R. Schackman, PhD
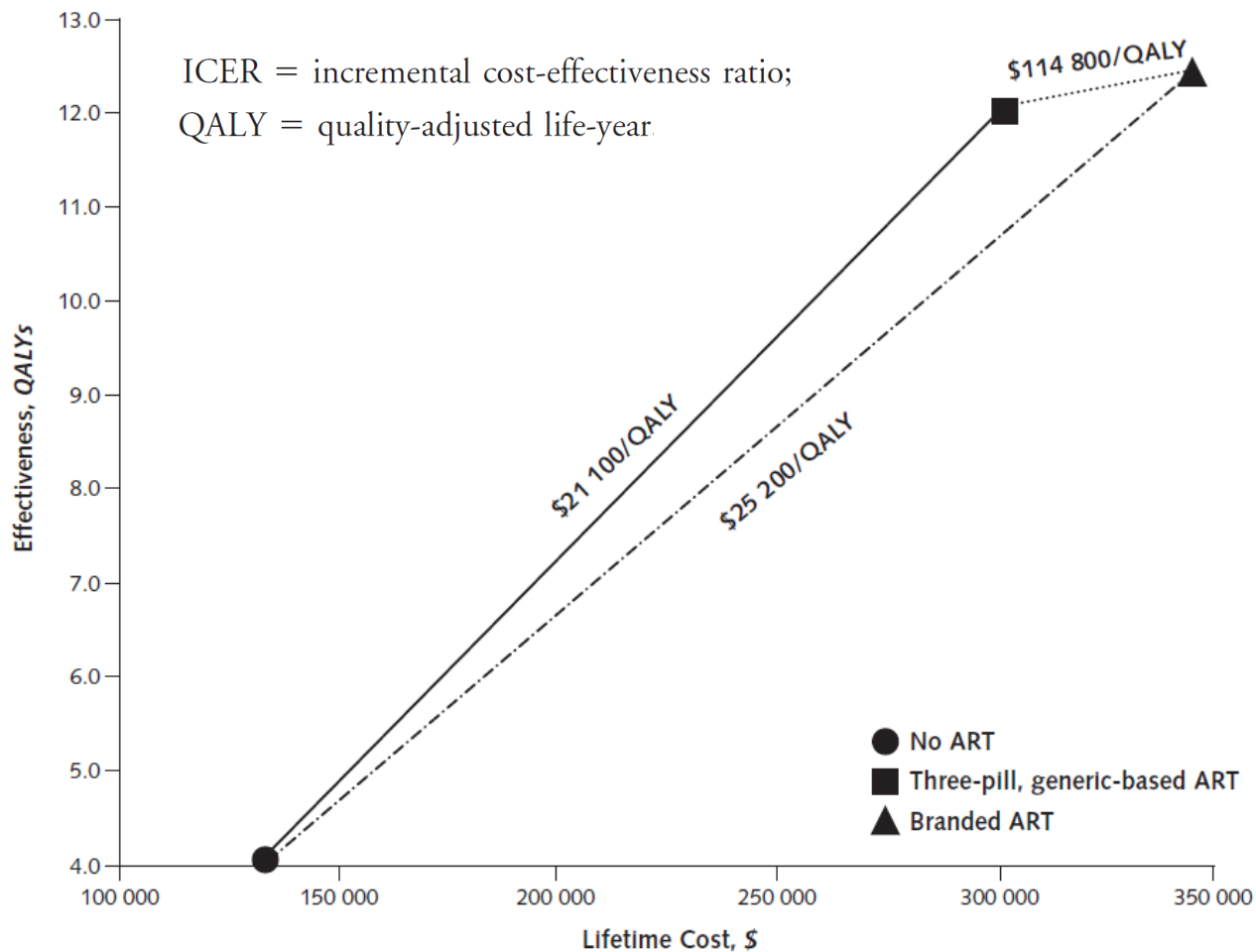
Background: U.S. HIV treatment guidelines recommend branded once-daily, 1-pill efavirenz–emtricitabine–tenofovir as first-line antiretroviral therapy (ART). With the anticipated approval of generic efavirenz in the United States, a once-daily, 3-pill alternative (generic efavirenz, generic lamivudine, and tenofovir) will decrease cost but may reduce adherence and virologic suppression.

Objective: To assess the clinical effect, costs, and cost-effectiveness of a 3-pill, generic-based regimen compared with a branded, co-formulated regimen and to project the potential national savings in the first year of a switch to generic-based ART.

Design: Mathematical simulation of HIV disease.

Setting: United States.

Patients: HIV-infected persons.

Results: Compared with no ART, generic-based ART has an ICER of $21 100/QALY. Compared with generic-based ART, branded ART increases lifetime costs by $42 500 and per-person survival gains by 0.37 QALYs for an ICER of $114 800/QALY. Estimated first-year savings, if all eligible U.S. patients start or switch to generic-based ART, are $920 million.

Why the use of generics may be eventually associated with health losses?

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

Volontari sani → Randomizzazione

Gruppo	Periodo 1	Periodo 2
A	Farmaco test (generico)	Farmaco di riferimento (branded)
B	Farmaco di riferimento (branded)	Farmaco test (generico)

- ✓ randomized, two period, two-sequence with cross-over design
- ✓ single dose
- ✓ washout of at least 5 half-lives
- ✓ healthy volunteers (mainly males, not less than 12 subjects)
- ✓ 18 or older with a BMI between 18.5 and 30 Kg/m2
- ✓ preferably non-smokers and without a history of alcohol or drug abuse
- ✓ bioequivalence studies should be conducted under fasting conditions
- ✓ PK parameters to be evaluated: AUC_{0-t}, AUC_{0-inf}, and C_{max} (T_{max}?)

✓ "…To determine bioequivalence, the parameters to be analysed are AUC(0-t) and Cmax. For these parameters the **90% confidence interval** for the ratio of the test and reference products should be contained within the acceptance interval of **80.00-125.00%.**…"

✓ "…It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. **If bioequivalence has not been demonstrated an additional group can be recruited** and the results from both groups combined in a final analysis…"

1st issue: methodological drawbacks of the guidelines for the assessment of bioequivalence

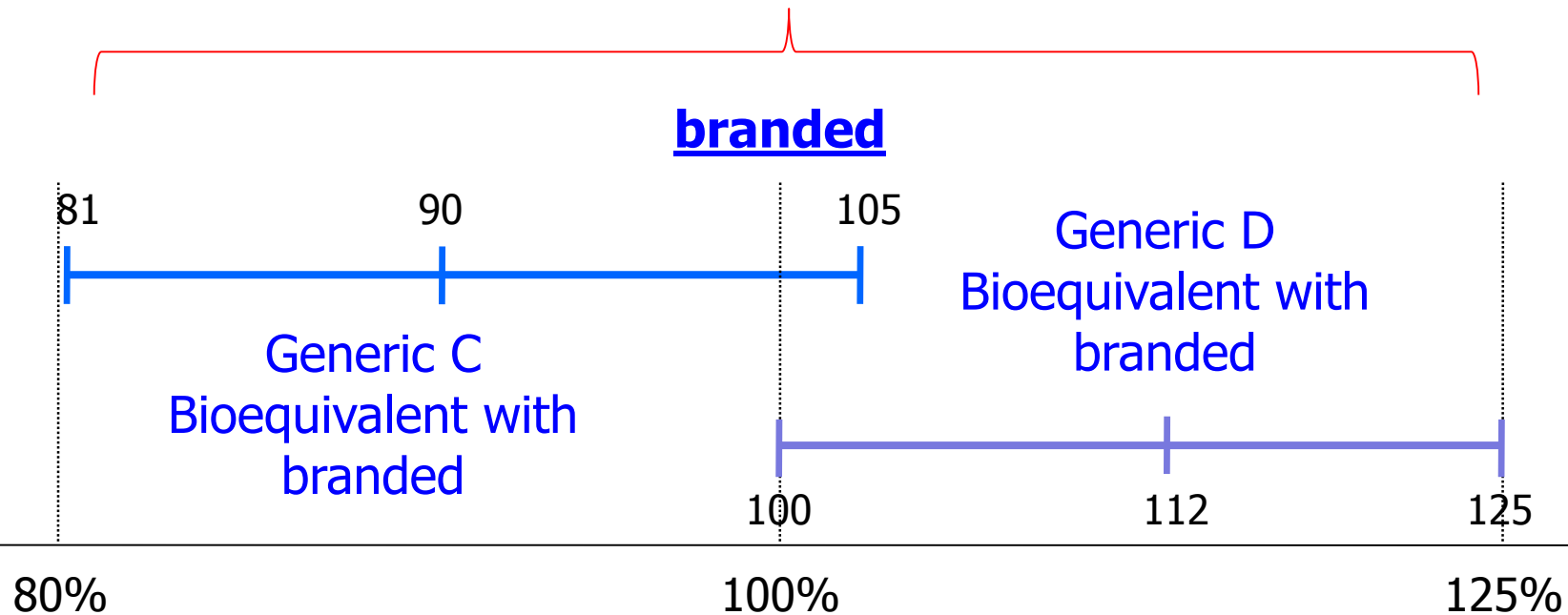Blood drug concentration

○ C$_{trough}$

Doses administerd

Time

Bioequivalence is assessed after the administration of a single drug dose and not at the steady state

2nd issue: generics are not necessarily bioequivalent amongst themselves, although substitution of one generic for another is likely to occur...

"...this guideline does not cover aspects related to generic substitution as this is subject to national regulation..."

Δ: >40%!

branded

81   90   105

Generic C
Bioequivalent with
branded

Generic D
Bioequivalent with
branded

100   112   125

80%   100%   125%

However C and D are not mutually bioequivalent

For each originator there are several generics marketed....

Tacrolimus:

ASTELLAS PHARMA S.P.A.

TEVA ITALIA S.R.L.

ACCORD HEALTHCARE LIMITED

CRINOS S.P.A.

MYLAN S.P.A.

Micophenolate:

ROCHE S.P.A.

ACTAVIS GROUP PTC EHF

CRINOS S.P.A.

MYLAN S.P.A

TEVA PHARMA B.V.

ACCORD HEALTHCARE LIMITED

DR. REDDY'S S.R.L.

SANDOZ S.P.A.

Azathioprine:

SOFAR S.P.A.

HEXAL S.P.A.

THE WELLCOME FOUNDATION LTD

SANDOZ S.P.A.

3rd issue: peculiarities of antiretrovirals

✓ Concentration-dependent activity (efficacy/safety) (PI, NNRTI)

✓ Low genetic barrier with risk to develop cross resistance if drugs are chronically underdosed (NNRTI)

✓ Availability of fixed-dose combinations associated with higher patients compliance compared with single treatments

Accordingly, some (not all!) ARVdrugs could be considered as critical dose drugs

Do EMA guidelines require stringent criteria for the assessment of bioequivalence for critical-dose (NTI) drugs??

- ✓ in specific cases of products with a narrow therapeutic index (NTI), the acceptance interval for AUC <u>should be</u> tightened to 90-111%...

- ✓ where C_{max} is <u>of particular importance</u> the 90-111% acceptance interval should be also applied for this parameter...

- ✓ it is not possible to define a set of criteria to categorise drugs as NTI and it must be decided <u>case by case</u>...

What are narrow therapeutic index drugs?

✓ Any drug for which a 20% or smaller change in dosage, with bioavailability remaining constant, produces clinically significant pharmacodynamic alterations;

✓ Drugs with a LD_{50} to ED_{50} ration less than 2;

✓ Drugs with a ratio of minimum toxic concentration [MTC] to minimum effective concentration [MEC] less than 2;

✓ Drugs whose safe and effective use require careful titration and patient monitoring;

✓ Drugs that exhibit at least a 10-fold pharmacokinetic variability with daily doses remaining constant

Benet LZ, *Transpl Proc* 1999
Levy GA, *Clin Pharmacol Ther* 1998

Is it so difficult to univocally establish which drugs can be or not considered as critical (NTI)?

$$\text{Therapeutic index} = \frac{\text{Maximum safe drug concentration}}{\text{Minimum efficacious drug concentration}}$$

>10   2-10   <2

NB: drugs with TI>10 can be definitively considered as safe (wide therapeutic index drugs)

- Muller, Nature Rev Drug Disc 2012 -

Therapeutic index of antitretroviral drugs

Drug	Therapeutic index
atazanavir	5
efavirenz	4
nevirapine	3/5
lopinavir	6
nelfinavir	5
indinavir	5
tenovofir	4/5
ritonavir	5

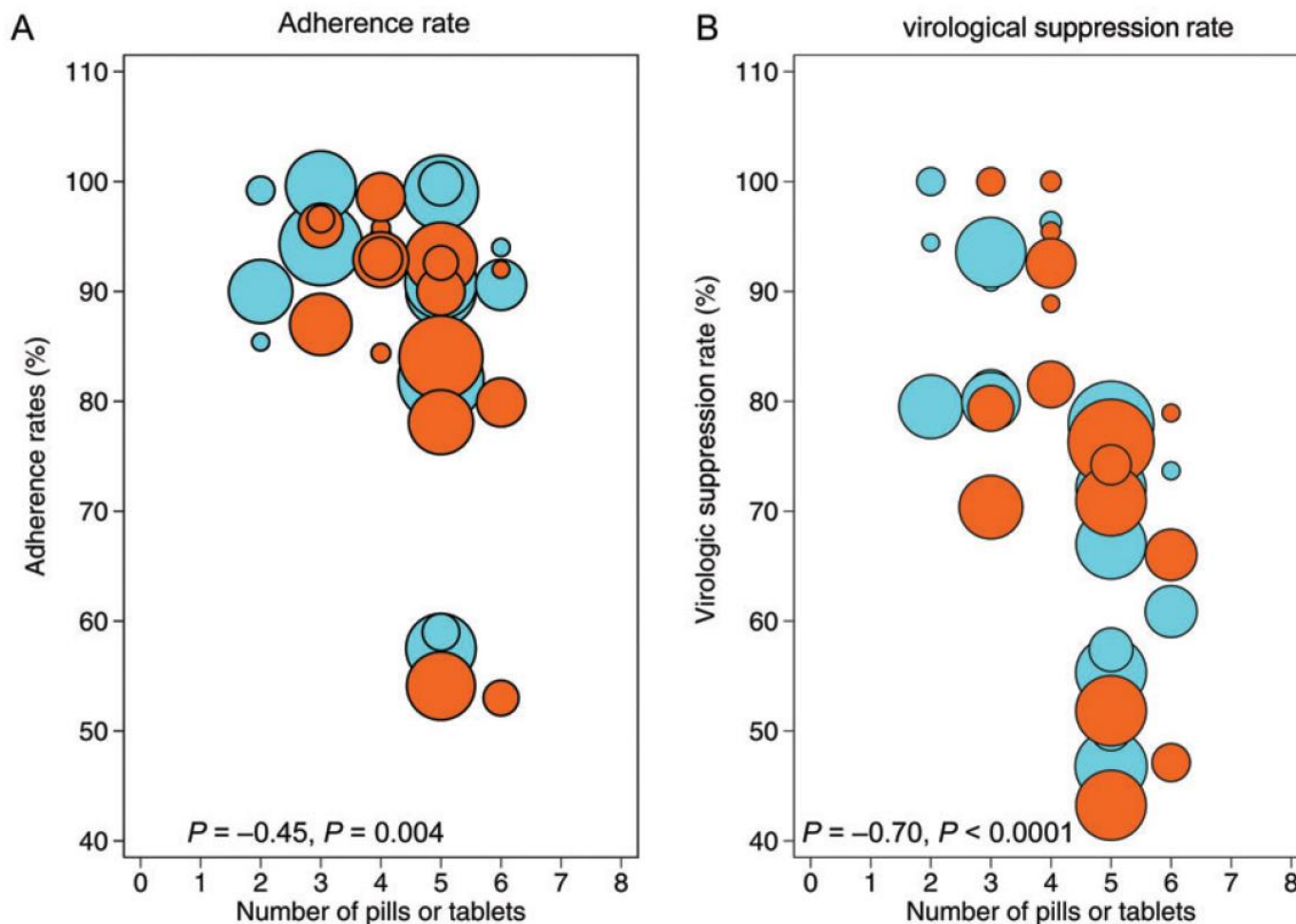| Drug	Therapeutic index
darunavir	??
saquinavir	??
amprenavir	??
abacavir	??
Lamivudine	??
Stavudine	??
emtricitabine	??
didanosine	??
raltegravir	??
etravirine	??
maraviroc	??

✓ No data on the upper therapeutic threshold
✓ No correlation between plasma concentration and clinical outcome

Evidences from literature...

PubMed.gov
US National Library of Medicine National
Institutes of Health

Bioequivalence (BE) studies (2001-2013)	32
✓ <u>BE studies in healthy volunteerrs</u>	26
- Studies showing BE of generic antiretrovirals	22 (85%)
- Studies with BE confirmed at 80-125%	26 (100%)
- Studies with BE confirmed at 90-111%	0

4th issue :the unpacking of FDC...

A — Adherence rate
B — virological suppression rate

A: Adherence rates (%) vs Number of pills or tablets. $P = -0.45, P = 0.004$

B: Virologic suppression rate (%) vs Number of pills or tablets. $P = -0.70, P < 0.0001$

"...Negative significant associations between pill burden and adherence (A) or virologic suppression (B) were found..."

- Nachega, CID May 2014 -

The financial and service implications of splitting fixed-dose antiretroviral drugs – a case study

- Taylor, Int J STD&AIDS 2014 -

Table 1. Assumed average duration and costs of clinical consultations.

Clinical consultation categories	Average consultation time (minutes)[a]	Cost per minute (£)[b]
Medical consultant	20	2.7
Specialist registrar	30	1.22
Nurse[d]	10	0.67
Hospital pharmacist	15	0.68
Midwife[e]	10	0.67

	Cost of clinic visits	Pathology costs
Pre-switch	£135	£115
Post-switch	£190	£142
Difference (95% CI	£56 (£26 to £86)	£26 (-£4 to £57)

	Costs of antiretrovirals	Total costs
Pre-switch	£7,082	£7,332
Post-switch	£7,092	£7,424
Difference (95% CI	£11 (-£501 to £523)	£93 (-£424 to £629)

Acceptability and confidence in antiretroviral generics of physicians and HIV-infected patients in France

Allavena, Clotilde[1]; Jacomet, Christine[2]; Pereira, Bruno[3]; Morand-Joubert, Laurence[4]; Bagheri, Haleh[5]; Cotte, Laurent[6]; Garaffo, Rodolphe[7]; Gerbaud, Laurent[8] and Dellamonica, Pierre[9]

Patients

- ✓ 76% accepted generics
- ✓ 55% have confidence in generics
- ✓ 44% accepted switching of ARVs for generics
- ✓ 17% accepted switching if the pill burden increase

Pysicians

- ✓ 75% would prescribe generics (26% if the combo had to be broken)

Main reasons for non prescription of generics were:

- ✓ previous branded ARV-induced side effects (35%)
- ✓ refusal of generics overall (37%)
- ✓ lack of understanding generics (26%)
- ✓ risk of non-observance of treatment (44%)
- ✓ anxiety/depression (47%/25%)

5th issue: peculiarities of the diseases…..

HIV disease as been associated with:

✓ lower cytochrome activity (altered cytokine production)

✓ elevated gastric pH

✓ altered serum protein concentrations

✓ atrophy of the absorptive surface in the GI tract
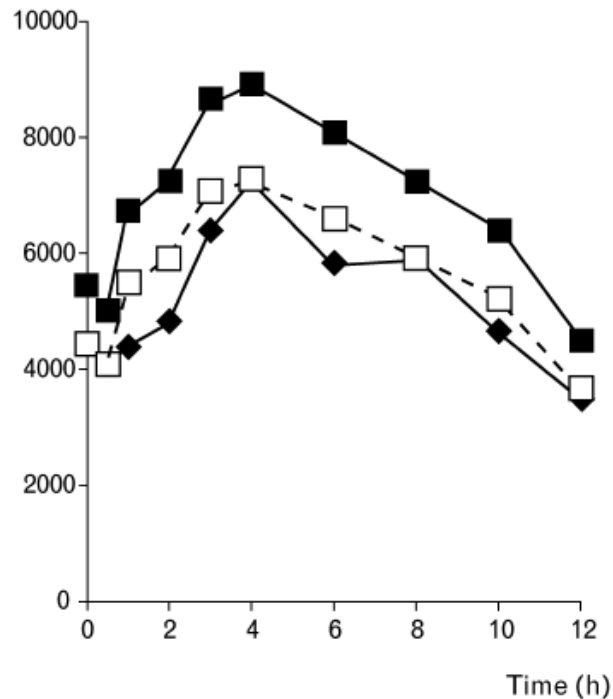
- Mukonzo, Clin Pharmacokinet 2011 -

Are pharmacokinetic/BE studies done in healthy volunteers really representative of what happens in the HIV-infected patients?
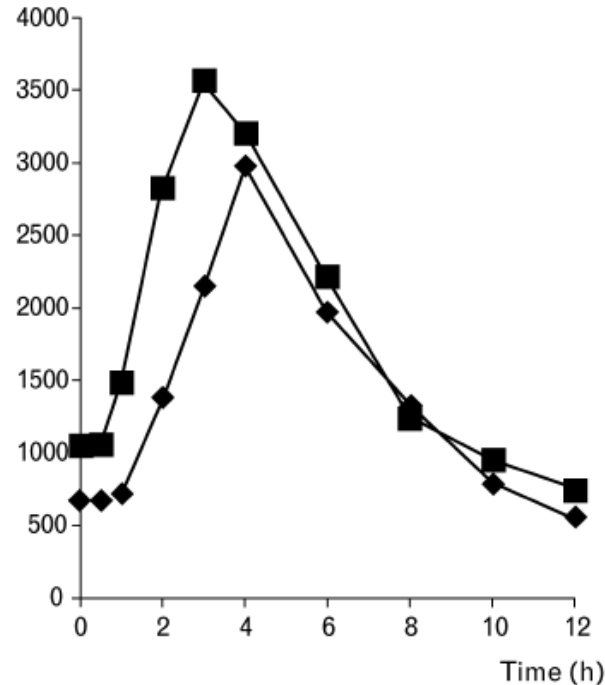
Differences in the pharmacokinetics of protease inhibitors between healthy volunteers and HIV-infected persons
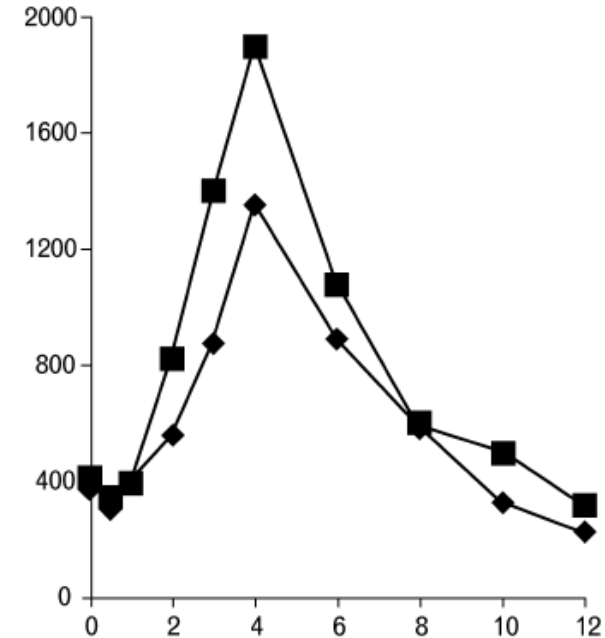Laura Dickinson, Saye Khoo and David Back

Evidences from literature...

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- Studies showing BE of generic antiretrovirals	22 (85%)
- Studies with BE confirmed at 80-125%	26 (100%)
- Studies with BE confirmed at 90-111%	0
✓ <u>BE studies in HIV-infected patients</u>	8
- Studies with BE confirmed at 80-125%	8
- Studies with BE confirmed at 90-111%	0
- Studies carried out at steady state	5
- Studies showing bioequivalence	**1 (12.5%)**

Which differences have been observed?

Comparison between branded and generic FDCs containing stavudine, lamivudine and nevirapine

	Stavudine	Lamivudine	Nevirapine
Cmax	1.4 (**1.2 – 1.7**)	1.1 (0.8 – **1.6**)	0.9 (**0.7** – 1.2)
AUC	1.1 (1.0 – 1.2)	1.1 (**0.7 – 1.3**)	0.9 (**0.7** – 1.1)
Cmax	0.9 (0.8 – 1.1)	1.1 (0.9 – **1.3**)	0.8 (**0.6** – 1.1)
AUC	0.8 (**0.7** – 1.0)	1.0 (0.9 – 1.1)	0.9 (**0.7** – 1.1)
Cmax	1.3 (1.0 – **1.7**)	0.8 (**0.6** – 1.0)	1.1 (0.9 – 1.2)
AUC	1.1 (0.9 – **1.4**)	0.8 (**0.6** – 1.0)	1.1 (1.0 – 1.3)

Ratio (90% CI)

1.Hosseinipour, AIDS 2007 ; 2. Byakika-Kibwika, JAC 2008; 3.Byakika-Tusiiime Plos ONE 2008

Bioequivalence study of two nevirapine tablet formulations in human immunodeficiency virus-infected patients

Table II. Mean pharmacokinetic parameters of nevirapine obtained after administration of either test or reference formulation
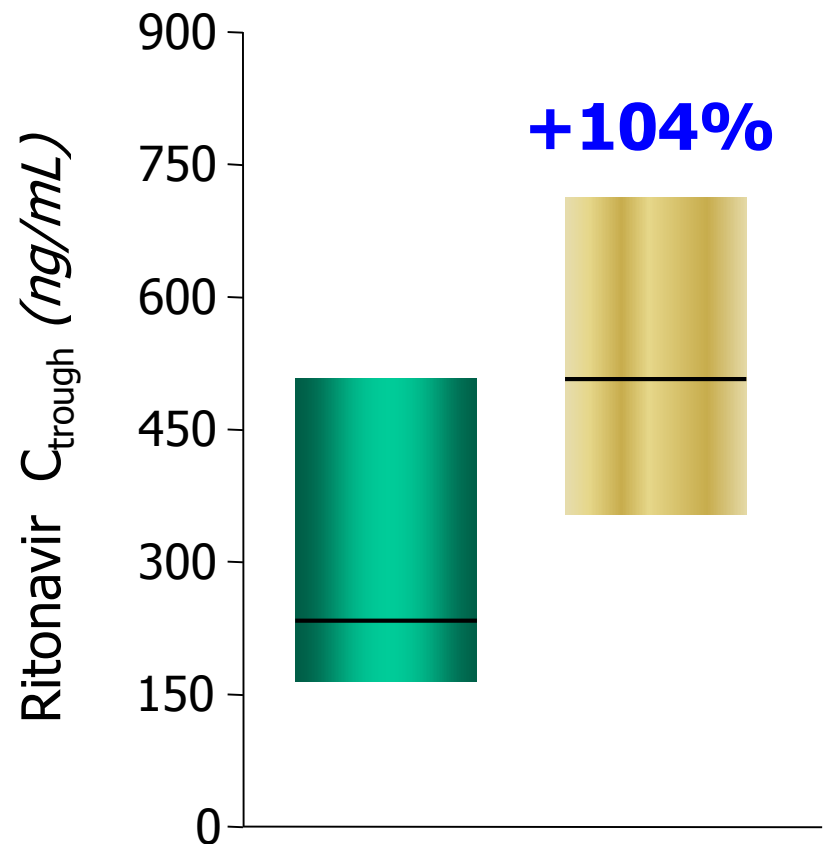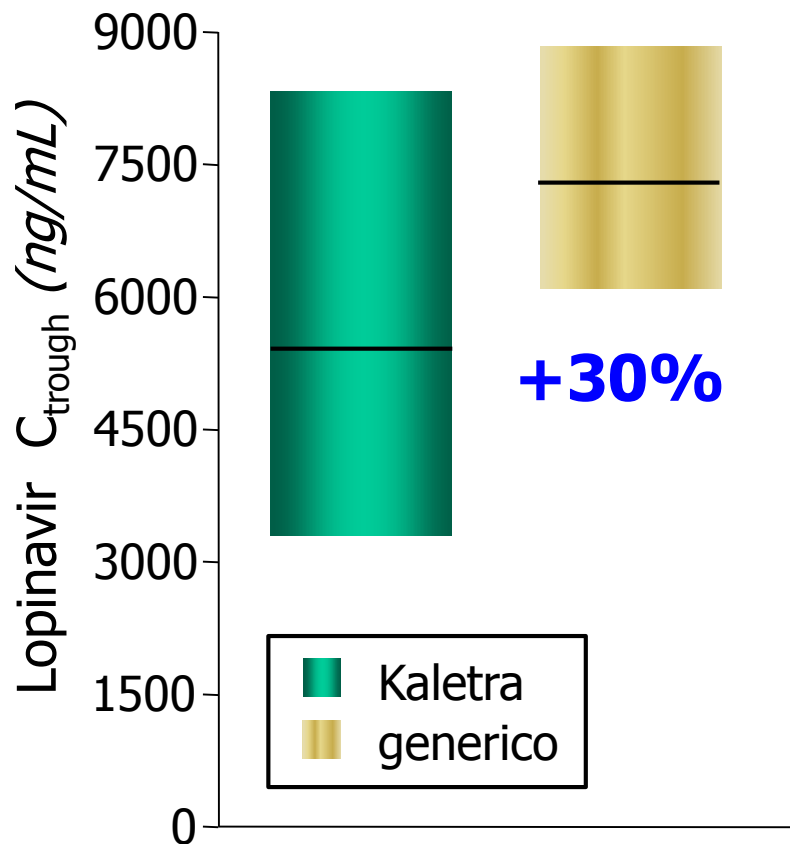
Pharmacokinetic	Test product	Reference product	
C_{max} (µg/ml)	1.91 ± 0.54	1.93 ± 0.52	
T_{max} (h)	3.14 ± 1.72	2.64 ± 1.55	
AUC_{0-12} (µg • h/ml)	15.46 ± 5.50	15.00 ± 4.56	
$AUC_{0-\infty}$ (µg • h/ml)	93.28 ± 145.22	55.73 ± 26.42	**+67%!!!**

C_{max}: maximum plasma concentration; T_{max}: time to C_{max}; AUC_{0-12}: area under the drug concentration-time curve over the 12 h dosage interval; $AUC_{0-\infty}$: area under the drug concentration-time curve over the infinity.

- Tarinas, Farm Hosp 2007 -

Plasma concentrations of generic lopinavir/ritonavir in HIV type-1-infected individuals

✓ 37 HIV-patients on Kaletra were switched to generic lopinavir/ritonavir (Matrix Laboratories)

- van der Lugt, Antiviral Ther 2009 -

Are such differences related to inadequate quantitative and qualitative drug contents?

Generic antiretroviral drugs in developing countries: friends or foes?

We report here on the case of a French subject of sub-Saharan origin who visited Brazzaville (Republic of Congo) and received postexposure prophylaxis following unprotected sexual intercourse. After admission to the main HIV-treatment centre (CTA Brazzaville), he received generic ARVs at the usual doses, containing zidovudine/lamivudine (AZT/3TC) and LPV/r (200/50 mg; Arga–L, McNeil & Argus, India).

- Zucman, AIDS, 2014 -

Generic antiretroviral drugs in developing countries: friends or foes?

✓ Quantitative/qualitative analyses were performed to evaluate the content and quality of the compounds:

- lopinavir: mass 215 mg (theoretical 200 mg)
- ritonavir: mass 50.8 mg (theoretical 50 mg)

- Zucman, AIDS, 2014 -

Generic antiretroviral drugs in developing countries: friends or foes?

✓ Quantitative/qualitative analyses were performed to evaluate the content and quality of the compounds:

- lopinavir: mass 215 mg (theoretical 200 mg)
- ritonavir: mass 50.8 mg (theoretical 50 mg)

✓ Pk evaluations revealed that Arga-L had a **bioavailability of 10%** compared with Kaletra

Trough	400/100 mg ARGA-L		400/100 mg Kaletra	
	LPV (ng/mL)	RTV ng/mL	LPV (ng/mL)	RTV ng/mL
Median (IQR)	158 (108-396)	14 (13-20)	3884 (3592-4526)	98 (89-124)

- Zucman, AIDS, 2014 -

Quality of antiretroviral drugs dispensed from developing countries and internet pharmacies

✓2027 tablets obtained from 8 Countries and 5 internet pharmacies (88 distinct samples)

✓HIV drug tested: zidovudine, lamivudine, efavirenz, nevirapine

✓Quality was assessed using the US Pharmacopoeia (USP 32-NF 27)

✓ samples analyzed for drug content, dissolution, uniformity, breaking force

Drug content %

Drug	# of Samples	USP Specs	# of samples USP Comp	Min	Mean (SD)	Max
SMZ/TMP	32	93–107	32	100·0/93·6	103·5 (1·8)/99·7 (2·3)	105·0/107·2
3TC	15	90–110[a]	15	98·9	102·6 (2·2)	106·3
NVP	9	90–110	9	101·6	104·5 (2·1)	108·4
ZDV	11	90–110	11	92·7	100·2 (3·9)	104
INH	10	90–110	10	95	97·6 (2·0)	100·2
EFV	11	90–110	11	97·6	102·8 (2·7)	106·3

All samples met the USP standards for drug content with a range of 92.7-108.6%

Quality of antiretroviral drugs dispensed from developing countries and internet pharmacies

Dissolution Test (%)

USP, %	# of samples USP Comp	Min	Max
70	31	61·3/94·5	99·9/108
80	15	94·4	105·9
75	9	94·7	103
80	11	86·5	98·5
80	10	93·8	100·5
80	6	77·3	88·4

✓6 out of the 88 samples failed the dissolution test;

✓98% of samples met the USP criteria for content uniformity

✓100% of samples met the USP criteria for breaking force

- Wang, J Clin Pharm Ther 2015 -

20 October 2011
EMA/916997/2011

Assessment report

Efavirenz Teva

International nonproprietary name: efavirenz

Procedure No. EMEA/H/C/002352

✓ 34 healthy volunteers (single dose study: 600 mg)

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic	(CV%)	Geometric			Lower	Upper	
Based on Measured Data									
AUC_{0-72} ($\mu g*h/mL$)	A	56.9727	(21)	55.8726	A vs. B	97.60	93.55	- 101.83	10
	B	58.4186	(22)	57.2440					
Cmax ($\mu g/mL$)	A	2.9865	(28)	2.8682	A vs. B	95.99	89.32	- 103.15	18
	B	3.0882	(28)	2.9882					
Tmax (h)	A	2.92	(44)						
	B	2.94	(45)						

The 90% confidence intervals for the ratio of geometric means of AUC0-72 and Cmax of the test to reference product are within the limits of 80% to 125%. Therefore, the results obtained demonstrate bioequivalence of the 600 mg film-coated with the reference product.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Efavirenz Teva indicated in antiviral combination treatment of human immunodeficiency virus 1 (HIV 1) infected adults, adolescents and children 3 years of age and older is favourable and therefore recommends the granting of the marketing authorisation.

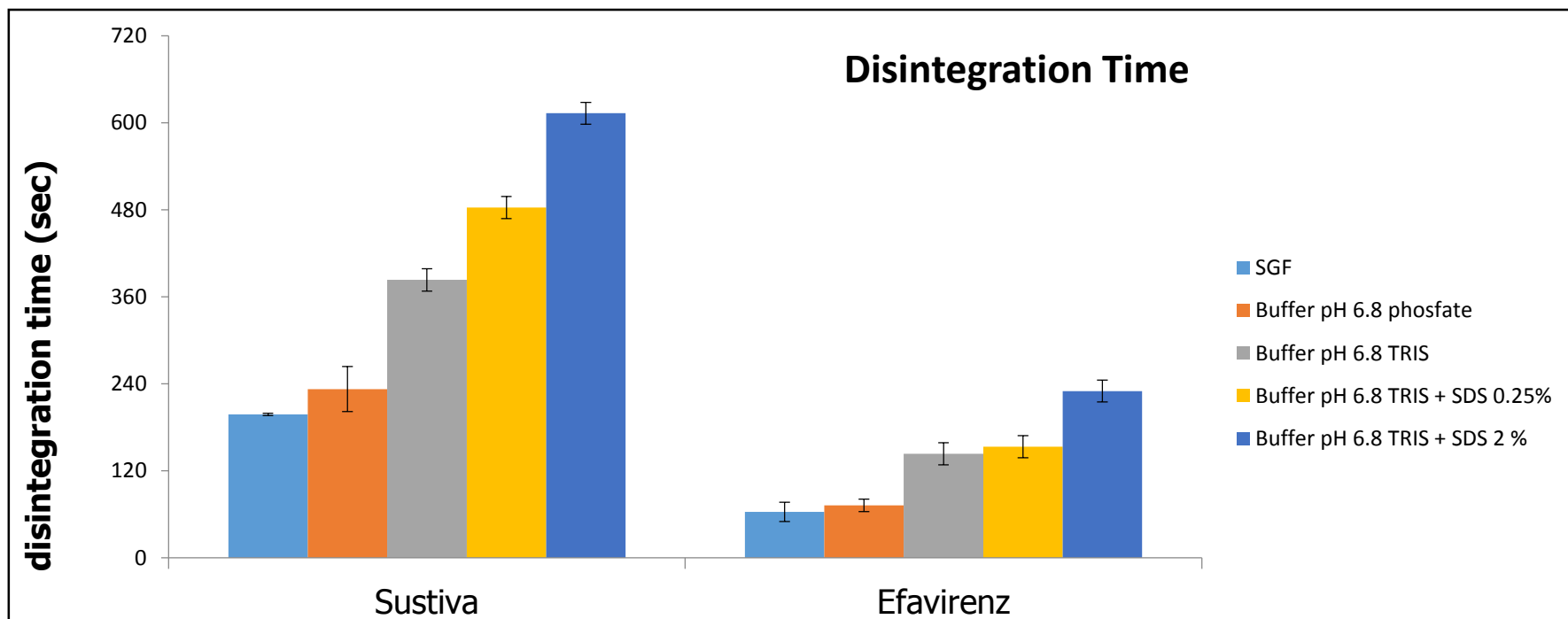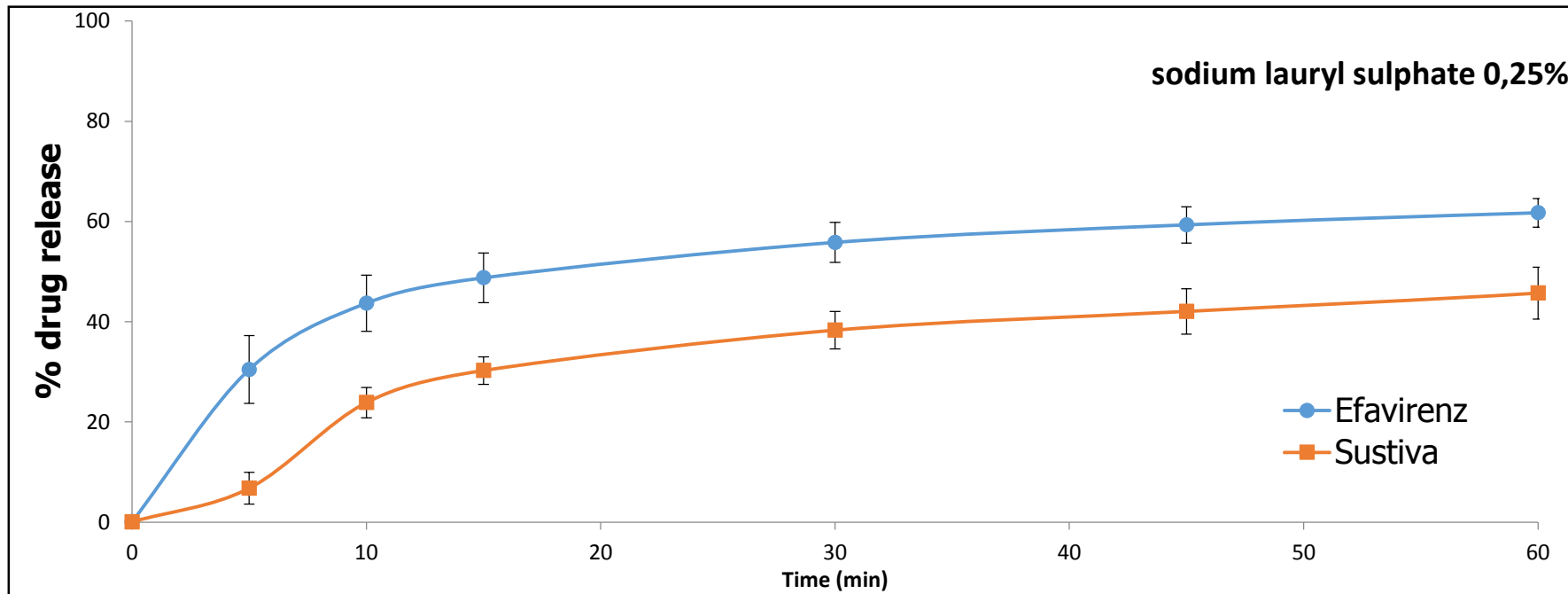**AIC released by EMA: January 9, 2012 (marketed as efavirenz Mylan)**

In vitro and *in vivo* evaluation of branded versus generic efavirenz Mylan formulation
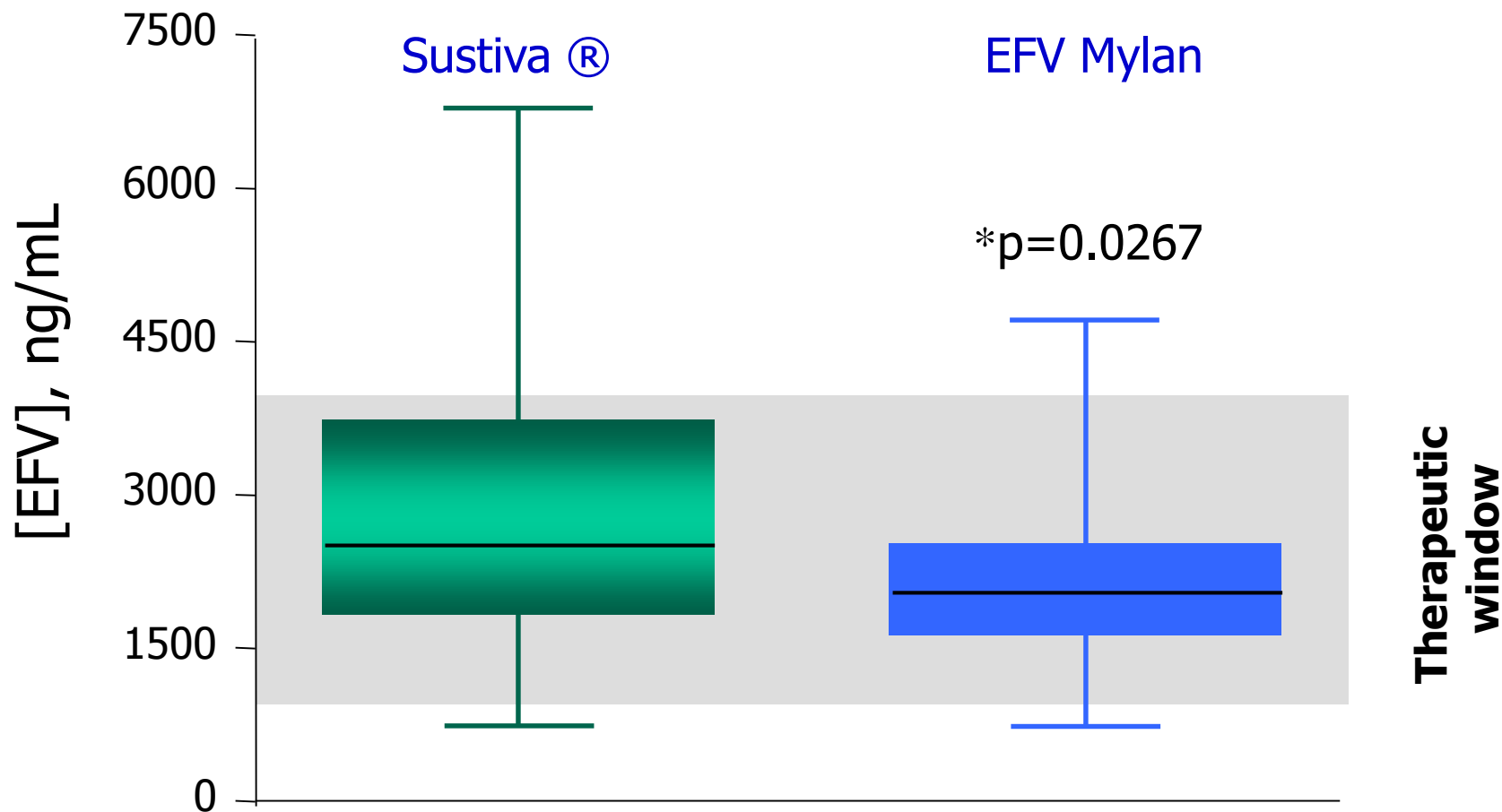
Dept. Infectious Diseases and Unit of Clinical Pharmacology, L. Sacco Universiy Hospital, Milano
Dept. Pharmaceutical Sciences, Università degli Studi di Milano
Dept. Infectious Diseases, Ospedale Galliera, Genova

✓Dissolution tests were conducted according to USP 37 guidelines with 1000 ml dissolution medium at 37±0.5°C and agitated at 50rpm (n=12). The media employed were purified water with 2% (w/v) sodium lauryl sulphate (SLS) as suggested by FDA and by USP, and a modified simulated gastric fluid without enzymes (SGF) with the addition of 0.25% SLS (w/v).

✓Disintegration tests were performed according to USP procedure using SGF and pH 6.8 phosphate buffer in a disintegration apparatus without discs (n=6). Dissolution profiles were compared according to FDA guidelines through the similarity factor (f2).

✓Efavirenz concentrations (collected at 10-16 min after the evening dose intake) were compared *in vivo* in HIV patients given Sustiva® (n=83) or EFV Mylan (n=26) using a parallel design (at steady state).

- Manuscript in preparation -

sodium lauryl sulphate 0,25%

Figure: % drug release vs Time (min) for Efavirenz and Sustiva

Disintegration Time

Legend:
- SGF
- Buffer pH 6.8 phosfate
- Buffer pH 6.8 TRIS
- Buffer pH 6.8 TRIS + SDS 0.25%
- Buffer pH 6.8 TRIS + SDS 2 %

	Sustiva	EFV Mylan
Mean ±SD (ng/mL)	3089±1944	2210±1034 (ratio = 0.72)
% samples <1000 ng/mL	9%	8%
% samples 1000-4000 ng/mL	70%	84%
% samples >4000 ng/mL	21%	8%

…strengths and limitations…

✓ Pk evaluations done in HIV patients
✓ Pk evaluations done at steady state
✓ PK results supported by in vitro assessments

✓ Parallel design
✓ Lack of detailed Pk data (Cmax, AUC)
✓ Differences in the sampling time?
✓ Differences in the genetic background?

In the meantime…what can we do to improve the safe use of generics?

Advisory Committee Recommendations on Generic Substitution of Immunosuppressive Drugs

Ander Åsberg, Oslo, Norway

Benoit Barrou, Paris, France

Klemens Budde, Berlin, Germany

Dario Cattaneo, Milan, Italy

Chris Dudley, Bristol, UK

Magedalena Durlik, Warsaw, Poland

Henrik Ekberg, Malmo, Sweden

Thomas Fehr, Zurich, Switzerland

Josep Grinyo Boira, Barcelona, Spain

Anders Hartmann, Oslo, Norway

Luuk Hilbrands, Nijmegen, The Netherlands

Dirk Kuypers, Leuven, Belgium

Yann le Meur, Brest, France

Ian MacPhee, London, UK

Pierre Marquet, Limoges, France

Herold Metselaar, Rotterdam, The Nederlands

Alfred Mota, Coimbra, Portugal

Daniel Serón, Barcelona, Spain

Jean Paul Squifflet, Liege, Belgium

Teun van Gelder, Rotterdam, The Nederlands

…some key points to be discussed…

- ✓ identification of critical dose drugs (NTI)
- ✓ use more stringent criteria to assess BE for NTIs
- ✓ confirm of BE in patients
- ✓ avoid consecutive substitutions between generics
- ✓ verify the quality of the product
- ✓ verify the pharmaceutical properties of generics
- ✓ Evaluate the impact of generics on adherence (vs FDC)
- ✓ verify efficacy and safety of generics in real life
- ✓ Perform detailed pharmacoeconomics analyses…

Conclusions

✓ The widespread use of generics (that are for sure effective drugs!!) is mandatory to save money and reallocate available funds. Novel, more restrictive criteria are, however, required at least for the approval of critical-dose antiretrovirals

✓ National and international authorities and funding agencies should require that quality-assurance processes are conducted and approved before that generic antiretrovirals are made available to patients

✓ The impact of generic antiretrovirals on PK/clinical outcomes (bioavailability, efficacy, toxicity, adherence) should be monitored in real life scenarios

Thank you!