Effects of cobicistat on tenofovir exposure and its long-term tolerability: is it time to rethink at TAF trials?

Sara Baldelli[1], Andrea Giacomelli[2], Davide Minisci[2], Cristina Mazzali[3], Laura Milazzo[2], Paola Meraviglia[2], Giuliano Rizzardini[2], Emilio Clementi[1], Massimo Galli[2], Dario Cattaneo[1] and Cristina Gervasoni[2]

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8° WORKSHOP NAZIONALE CISAI
PERUGIA, 30 - 31 MARZO 2017
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

- ✓ Tenofovir disoproxil fumarate (TDF) is given at 300 mg daily according to a “one dose fits all” approach

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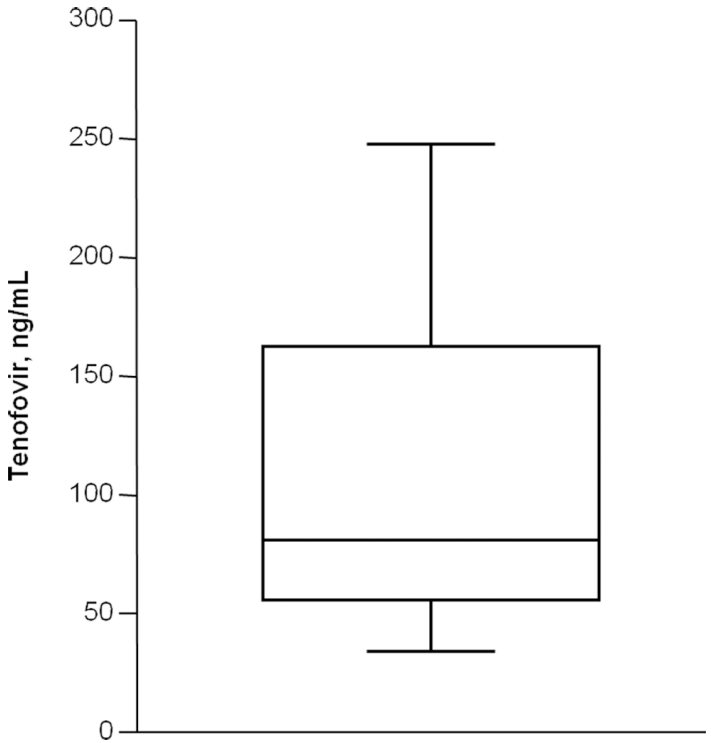
- ✓ It has been demonstrated that there is a large inter-individual variability in the exposure to the drug



Box-plot of Tenofovir (TDF) plasma trough concentrations measured in 100 HIV-infected patients.

Gervasoni at al, PLoS One. 2013

Kunimoto *et al. Journal of Pharmaceutical Health Care and Sciences* (2016) 2:22
DOI 10.1186/s40780-016-0056-5

Journal of Pharmaceutical Health Care and Sciences

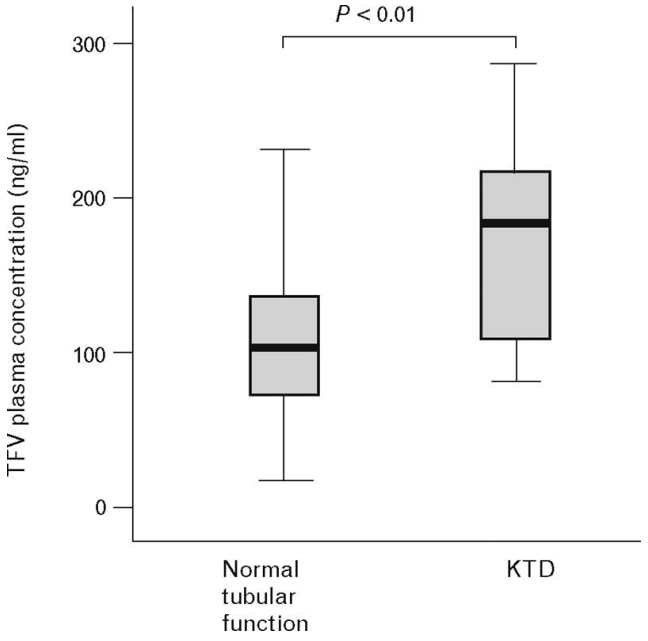
RESEARCH ARTICLE Open Access

Plasma tenofovir trough concentrations are associated with renal dysfunction in Japanese patients with HIV infection: a retrospective cohort study

Yusuke Kunimoto[1*], Hiroshi Ikeda[2], Satoshi Fujii[1], Manabu Kitagawa[1], Kieko Yamazaki[1], Hiromasa Nakata[1], Norimasa Noda[1], Tadao Ishida[3] and Atsushi Miyamoto[1]

Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations

Sonia Rodríguez-Nóvoa[a], Pablo Labarga[a], Antonio D'Avolio[b], Pablo Barreiro[a], Marta Albalate[c], Eugenia Vispo[a], Carmen Solera[a], Marco Siccardi[b], Stefano Bonora[b], Giovanni Di Perri[b] and Vincent Soriano[a]



Rodriguez-Novoa at al, AIDS. 2010

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PLOS ONE

Low Body Weight in Females Is a Risk Factor for Increased Tenofovir Exposure and Drug-Related Adverse Events

Cristina Gervasoni[1*], Paola Meraviglia[1], Simona Landonio[1], Sara Baldelli[2], Serena Fucile[2], Laura Castagnoli[1], Emilio Clementi[3,4], Agostino Riva[1], Massimo Galli[1], Giuliano Rizzardini[1], Dario Cattaneo[2]

Common clinical conditions – age, low BMI, ritonavir use, mild renal impairment – affect tenofovir pharmacokinetics in a large cohort of HIV-infected women

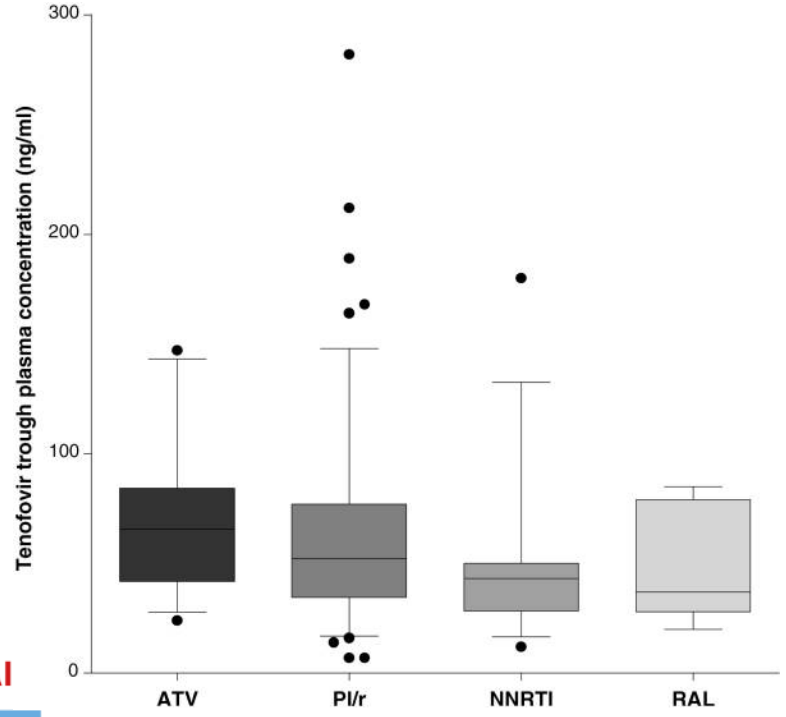
Sanjiv M. Baxi[a], Ruth M. Greenblatt[a,b,c], Peter Bacchetti[c], Rebecca Scherzer[a], Howard Minkoff[d], Yong Huang[e], Kathryn Anastos[f], Mardge Cohen[g], Stephen J. Gange[h], Mary Young[i], Michael G. Shlipak[a,j] and Monica Gandhi[a]

AIDS, 2014

AAC
Journals.ASM.org

Tenofovir Plasma Concentrations According to Companion Drugs: a Cross-Sectional Study of HIV-Positive Patients with Normal Renal Function

A. Calcagno,[a] D. Gonzalez de Requena,[a] M. Simiele,[a] A. D'Avolio,[a] M. C. Tettoni,[a] B. Salassa,[a] G. Orofino,[b] C. Bramato,[a] V. Libanore,[a] I. Motta,[a] P. Bigliano,[a] E. Orsucci,[a] G. Di Perri,[a] S. Bonora[a]



Aims:

1. To identify demographic, hematochemical and clinical covariates potentially associated with TFV plasma trough concentrations

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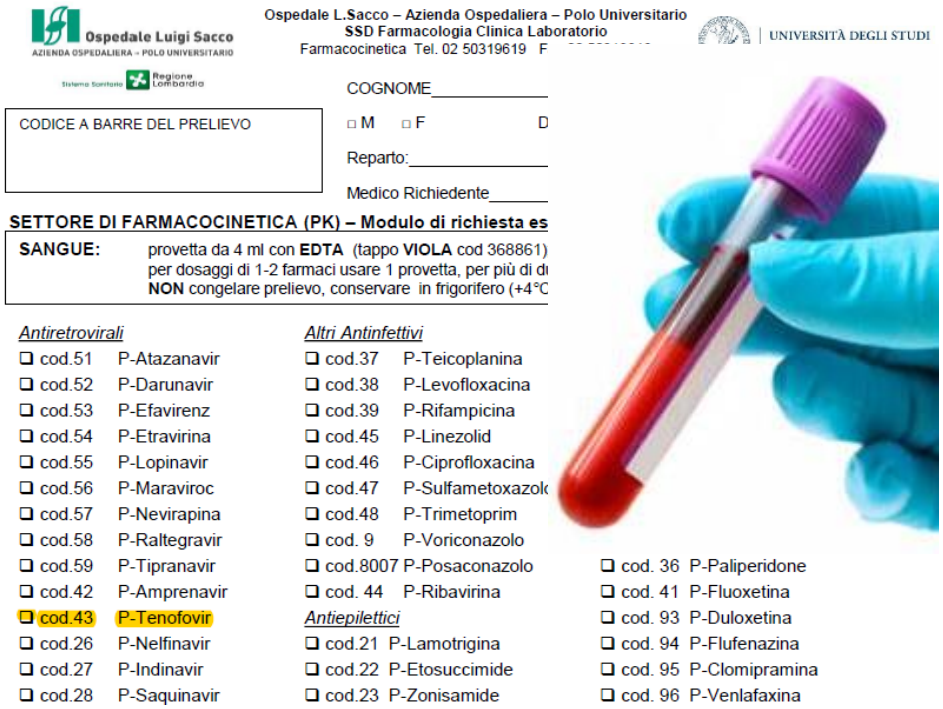
1. To identify demographic, hematochemical and clinical covariates potentially associated with TFV plasma trough concentrations

2. To investigate the potential role of boosting agents (ritonavir or cobicistat) on TDF tolerability

Materials and methods

Patients:



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SSD Farmacologia Clinica Laboratorio
Farmacocinetica Tel. 02 50319619 F

UNIVERSITÀ DEGLI STUDI

CODICE A BARRE DEL PRELIEVO

COGNOME_____
□ M □ F D
Reparto:_____
Medico Richiedente_____

SETTORE DI FARMACOCINETICA (PK) – Modulo di richiesta es

SANGUE: provetta da 4 ml con **EDTA** (tappo **VIOLA** cod 368861)
per dosaggi di 1-2 farmaci usare 1 provetta, per più di d
NON congelare prelievo, conservare in frigorifero (+4°C

Antiretrovirali
- ❑ cod.51 P-Atazanavir
- ❑ cod.52 P-Darunavir
- ❑ cod.53 P-Efavirenz
- ❑ cod.54 P-Etravirina
- ❑ cod.55 P-Lopinavir
- ❑ cod.56 P-Maraviroc
- ❑ cod.57 P-Nevirapina
- ❑ cod.58 P-Raltegravir
- ❑ cod.59 P-Tipranavir
- ❑ cod.42 P-Amprenavir
- ❑ cod.43 P-Tenofovir
- ❑ cod.26 P-Nelfinavir
- ❑ cod.27 P-Indinavir
- ❑ cod.28 P-Saquinavir

Altri Antinfettivi
- ❑ cod.37 P-Teicoplanina
- ❑ cod.38 P-Levofloxacina
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- ❑ cod.46 P-Ciprofloxacina
- ❑ cod.47 P-Sulfametoxazol
- ❑ cod.48 P-Trimetoprim
- ❑ cod. 9 P-Voriconazolo
- ❑ cod.8007 P-Posaconazolo
- ❑ cod. 44 P-Ribavirina

Antiepilettici
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- ❑ cod.22 P-Etosuccimide
- ❑ cod.23 P-Zonisamide

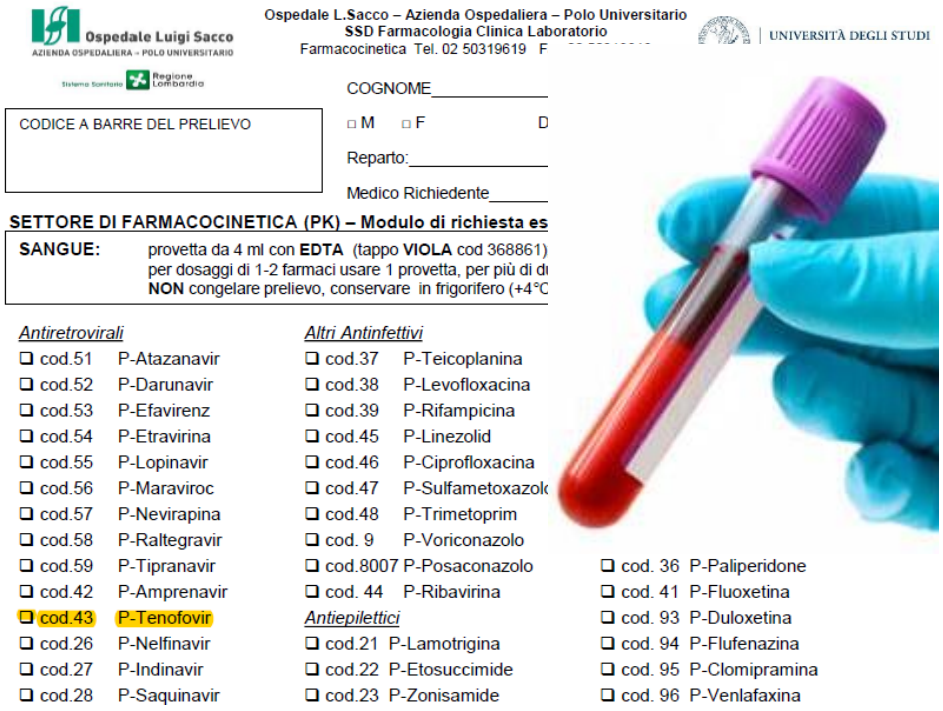
- ❑ cod. 36 P-Paliperidone
- ❑ cod. 41 P-Fluoxetina
- ❑ cod. 93 P-Duloxetina
- ❑ cod. 94 P-Flufenazina
- ❑ cod. 95 P-Clomipramina
- ❑ cod. 96 P-Venlafaxina

Patients included in the study:

- Patients receiving TDF-containing antiretroviral therapies for at least three months
- Patients with at least one request of TDM of TFV plasma trough concentrations

Materials and methods

Patients:



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Patients included in the study:

- Patients receiving TDF-containing antiretroviral therapies for at least three months
- Patients with at least one request of TDM of TFV plasma trough concentrations

Patients excluded from the study:

- Paediatric subjects
- Patients with severe hepatic impairment (defined as Child-Pugh Class B or C)
- Patients with history of kidney or bone disease
- Patients with Cl Cr <80 ml/min before starting TFV

Materials and methods

Statistical analysis:

Uni- and multivariate regression analyses
TFV concentration = dependent variable
Clinical characteristics recorded at the time of TDM = independent covariates

Data were grouped in 4 main drug classes:

- protease inhibitors/ritonavir (atazanavir, darunavir, lopinavir, fosamprenavir)
- non nucleoside reverse transcriptase inhibitors (efavirenz, rilpivirine, nevirapine)
- integrase inhibitors (dolutegravir, raltegravir)
- elvitegravir/cobicistat co-fomulation

Materials and methods

Statistical analysis:

The composite outcome of “TDF toxicity” included:

- patients who discontinued TDF for drug-related toxicity (established by the attending physicians)

- patients that remained on TDF but experienced a clinical worsening in the renal (defined by a >30% increment in serum creatinine concentration from the baseline to the last available) or bone (development of osteopenia or osteoporosis) function

Results 1:

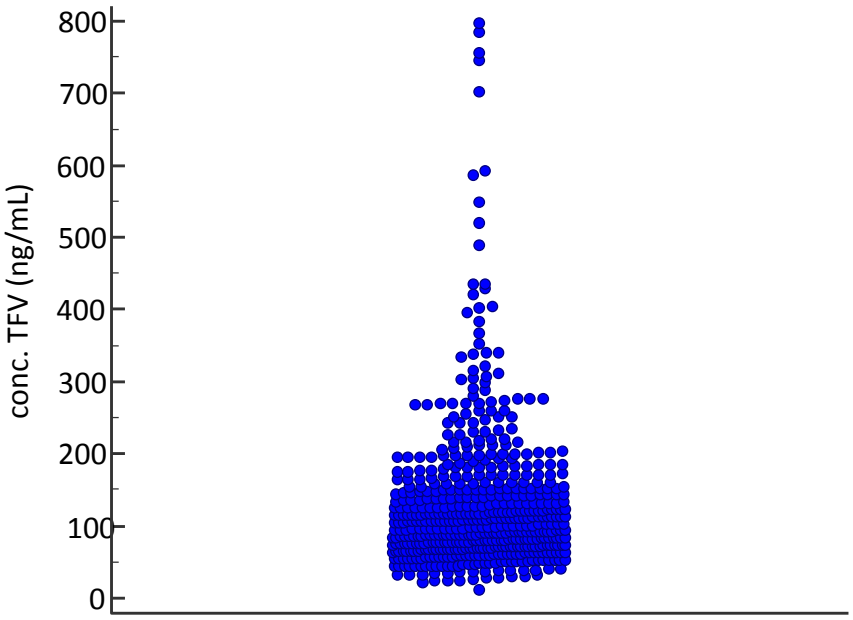
Total Patients: 510

PIs/r (n=207, 41.6%)
NNRTIs (n=178, 34.5%)
INIs (n=49, 9.0%)
ELV/COBI (n=76, 14.9%)

	PIs/r	NNRTIs	INIs	ELV/COBI
Males (%)	63%	77%	67%	85%
Age (years)	47±10	48± 10	48± 9	44±9
Body weight (Kg)	68±16	70±14	69±13	71±12
Tenofovir therapy (days)	1642±1209	1809±1124	1445±1115	455±680
Serum creatinine (mg/dL)	0.9±0.3	0.9±0.2	0.9±0.3	1.0±0.2
Co-infections (%)	43%	23%	49%	23%
Viral load >37 copies/mL (%)	21%	5%	14%	23%
CD4 cell count <250 cells/mL (%)	12%	5%	17%	16%

Results 1:

Distribution of TFV trough concentrations



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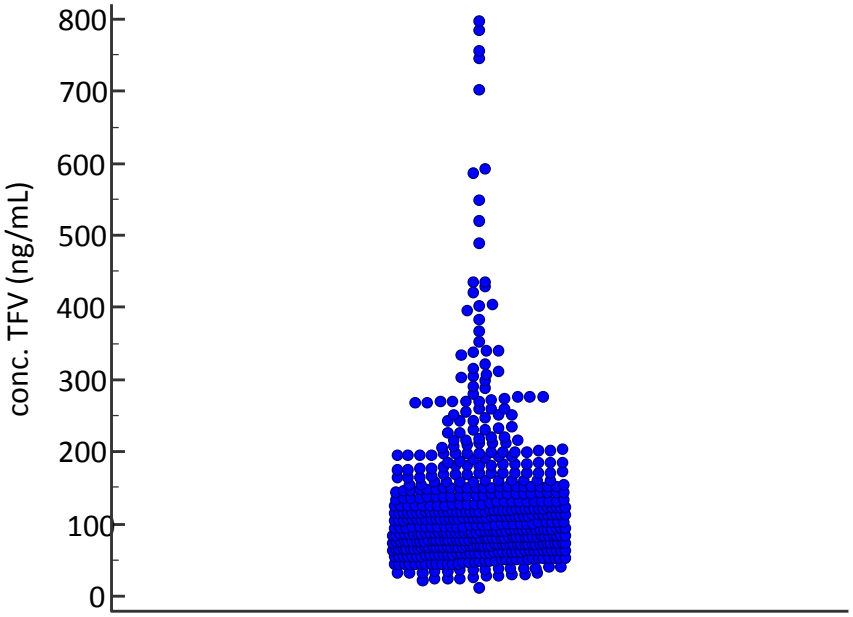
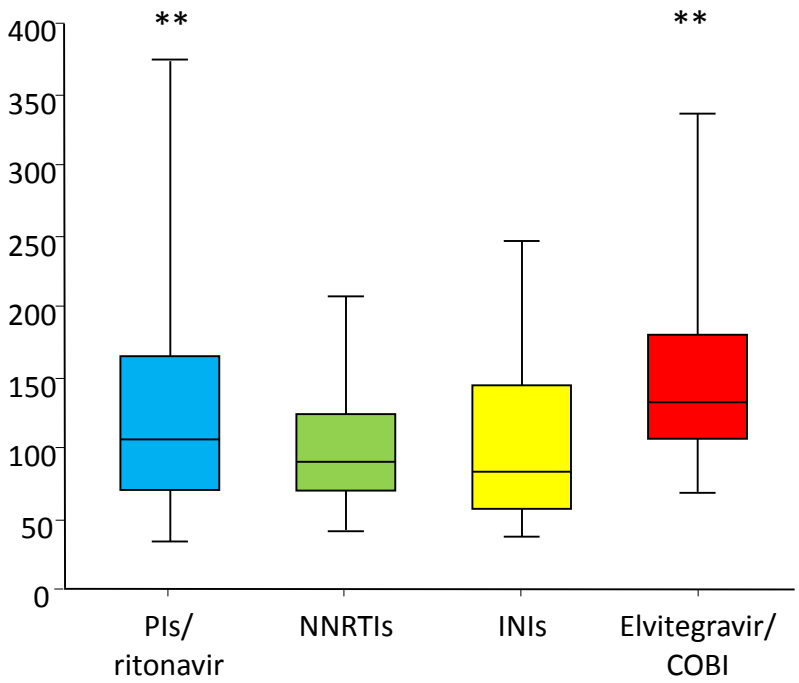


TFV concentrations clustered according to the companion antiretroviral classes



Box and Whiskers plots represent the 5th, 25th, 50th, 75th and 95th percentiles, respectively

**p<0.01 vs NNRTIS and INIs

Results 1:

Uni- and multi-variate regression analyses using TFV plasma trough concentrations as the dependent variable and clinical covariates as independent variables

	Univariate analysis			Multivariate analysis		
	beta	SD	p-value	beta	SD	p-value
Concomitant ART			<0.0001			<0.0001
- ELV/COBI vs. PIs	0.21	0.08	0.011	0.27	0.08	0.001
- INIs vs. PIs	-0.18	0.10	0.064	-0.20	0.10	0.035
- NNRTIs vs. PIs	-0.17	0.06	0.007	-0.12	0.06	0.046
Gender (females vs. males)	0.14	0.06	0.018	0.20	0.08	0.004
Co-infections (NO vs YES)	0.07	0.06	0.275			
CD4 cell count (cells/mL)			0.680			
- [0-250] vs. [250-500]	0.08	0.09	0.385			
- [250-500] vs. [>500]	0.005	0.06	0.936			
Viral load (≥37 vs <37 copies/mL)	-0.01	0.08	0.883			
Duration of TDF therapy			0.722			
- ≤1 yr vs. >6 yrs	-0.05	0.08	0.566			
- (1 yr-3 yrs] vs. > 6yrs	0.05	0.08	0.583			
- (3 yr-6 yrs] vs. > 6yrs	-0.04	0.08	0,628			
Patients' age	0.01	0.003	0.0001	0.01	0.003	<0.0001
Body weight	-0.006	0.002	0.001	-0.01	0.002	0.006
Serum creatinine	0.53	0.10	<0.001	0.32	0.11	<0.0001

Results 2:

Total cases of TDF toxicity: **149**

PIs/r (n=75/207, 36,2%)

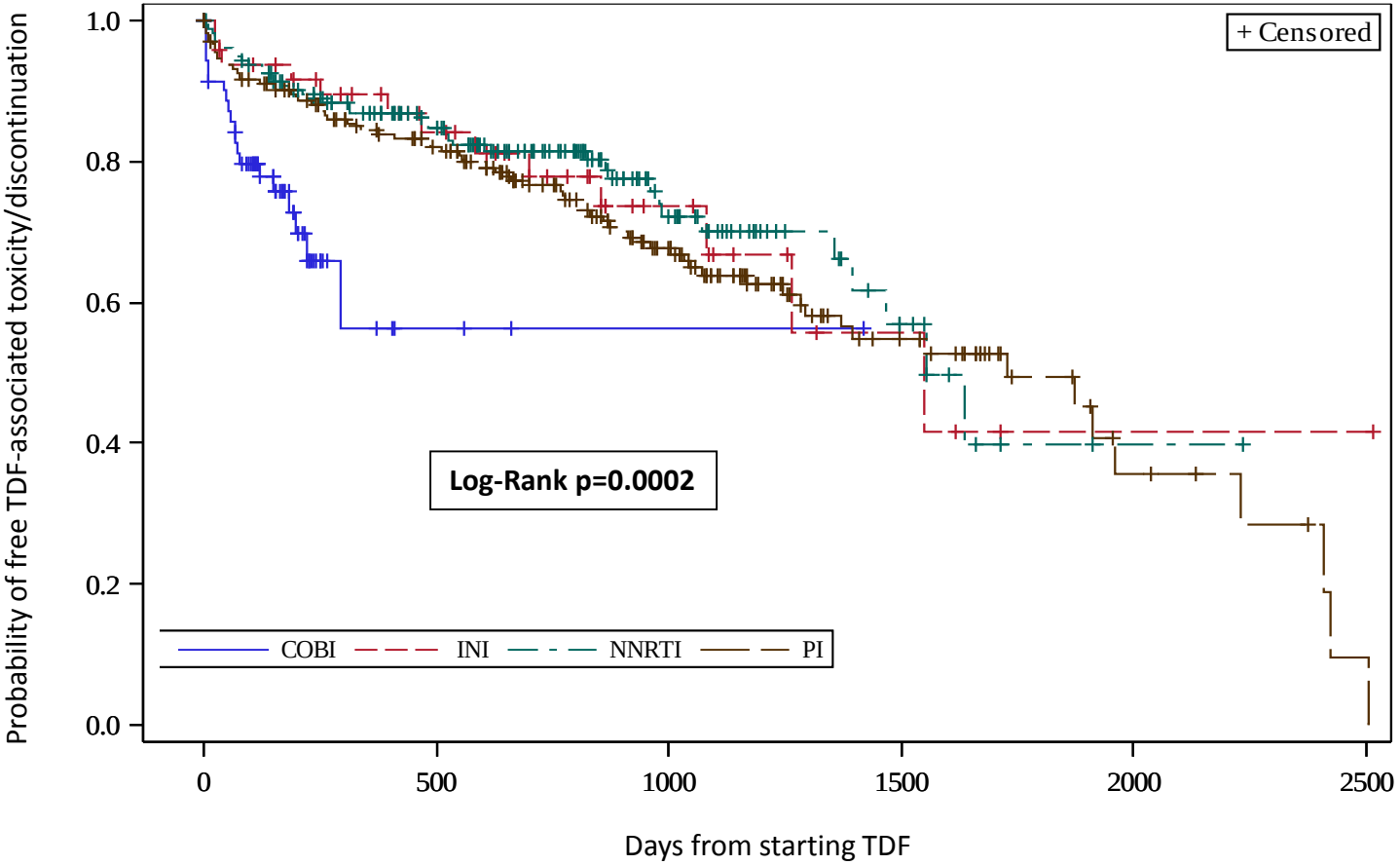
NNRTIs (n=41/178, 23,0%)

INIs (n=13/49, 26,5%)

ELV/COBI (n=20/76, 26,3%)

Results 2:

Kaplan-Meier estimates of risk to develop TDF toxicity clustered according to companion antiretroviral classes



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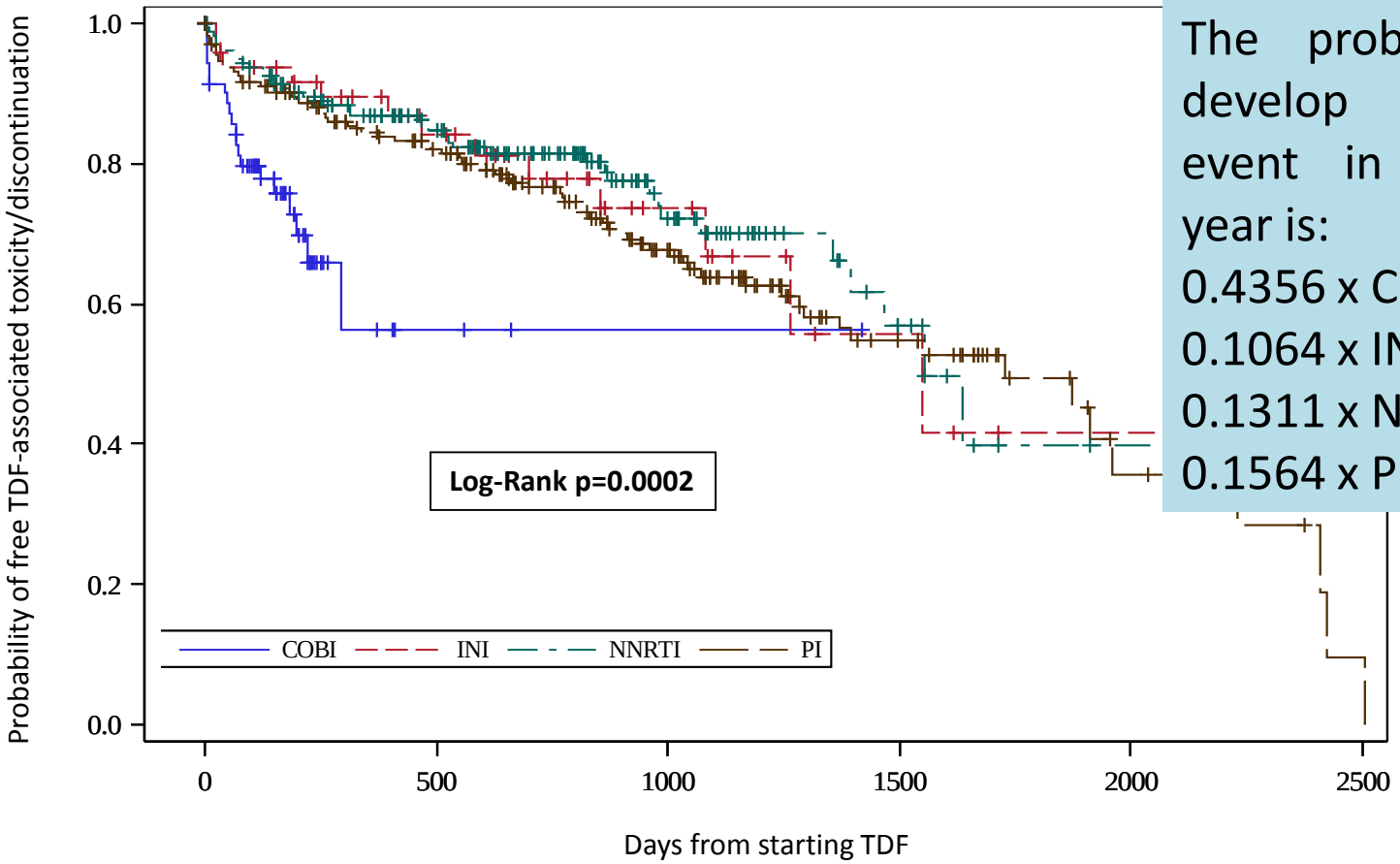

The probability to develop a toxic event in the first year is:
0.4356 x COBI
0.1064 x INI
0.1311 x NNRTI
0.1564 x PI

Results 2:

Cox proportional hazards model to investigate the role of clinical and pharmacological covariates on TDF tolerability (estimated both as development of TDF toxicity or TDF discontinuation)

Parameter	Stratification	Overall Type 3	Probability >Chi-Square	Hazard Ratio	HR-CI	
Antiretroviral therapy[1]		0.0277				
	ELV/COBI		0.0067	2.284	1.257	4.151
	INIs		0.8306	0.936	0.511	1.715
	NNRTIs		0.5607	0.881	0.574	1.351
Serum creatinine		0.1230		1.759	0.858	3.606
Body weight		0.1242		0.988	0.974	1.003
Gender[2]	females	0.7804		1.064	0.687	1.648
Patients' age		0.3861		0.992	0.974	1.010
CD4 cell count[3]		0.1315				
	[250-500]		0.1090	0.636	0.365	1.106
	[>500]		0.7379	0.911	0.529	1.570
Duration of TDF therapy[4]		0.5585				
	[1yr-3yrs]		0.6825	0.894	0.524	1.527
	[3yrs-6yrs]		0.1696	0.686	0.400	1.175
	[>6yrs]		0.5691	0.859	0.508	1.451
Tenofovir concentrations*		0.0048		1,021*	1.006	1.036

[1]PIs as the reference; [2]males as the reference; [3]CD4 [0-250] as the reference; [4] <1 yr as the reference.

•per 10 ng/mL increment of TFV concentrations

Conclusions

- We confirmed the importance of clinical covariates in predicting TDF overexposure. Indeed, in agreement with previous findings we demonstrated that female gender, aging and low patients' body weight were all significantly and independently associated with high tenofovir plasma trough concentrations

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Why despite these evidences all HIV-infected adult patients are still treated with the same TDF dose, irrespectively of their characteristics?

Conclusions

- Co-administration with cobicistat – given co-formulated with elvitegravir – resulted in significantly higher TDF plasma trough concentrations compared with all other ART regimens, including also ritonavir-boosted PIs

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Why HIV- infected adult patients are treated with the same TDF dose, irrespectively of boosted/not boosted ART co-regimen?

Conclusions

TAF:
is used at 25 mg in absence of P-gp inhibitor
is used at 10 mg in presence of P-gp inhibitor

- The possibility that the lack of proper dose adjustment for TDF when given with COBI (or with RTV) could have introduced a bias in the comparison of safety between TAF and TDF during registrative trials, cannot be ruled out