E’ tempo di rivoluzionare la terapia antiretrovirale? Evidenze versus speranze

Milano 24 settembre 2015

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Disclosures

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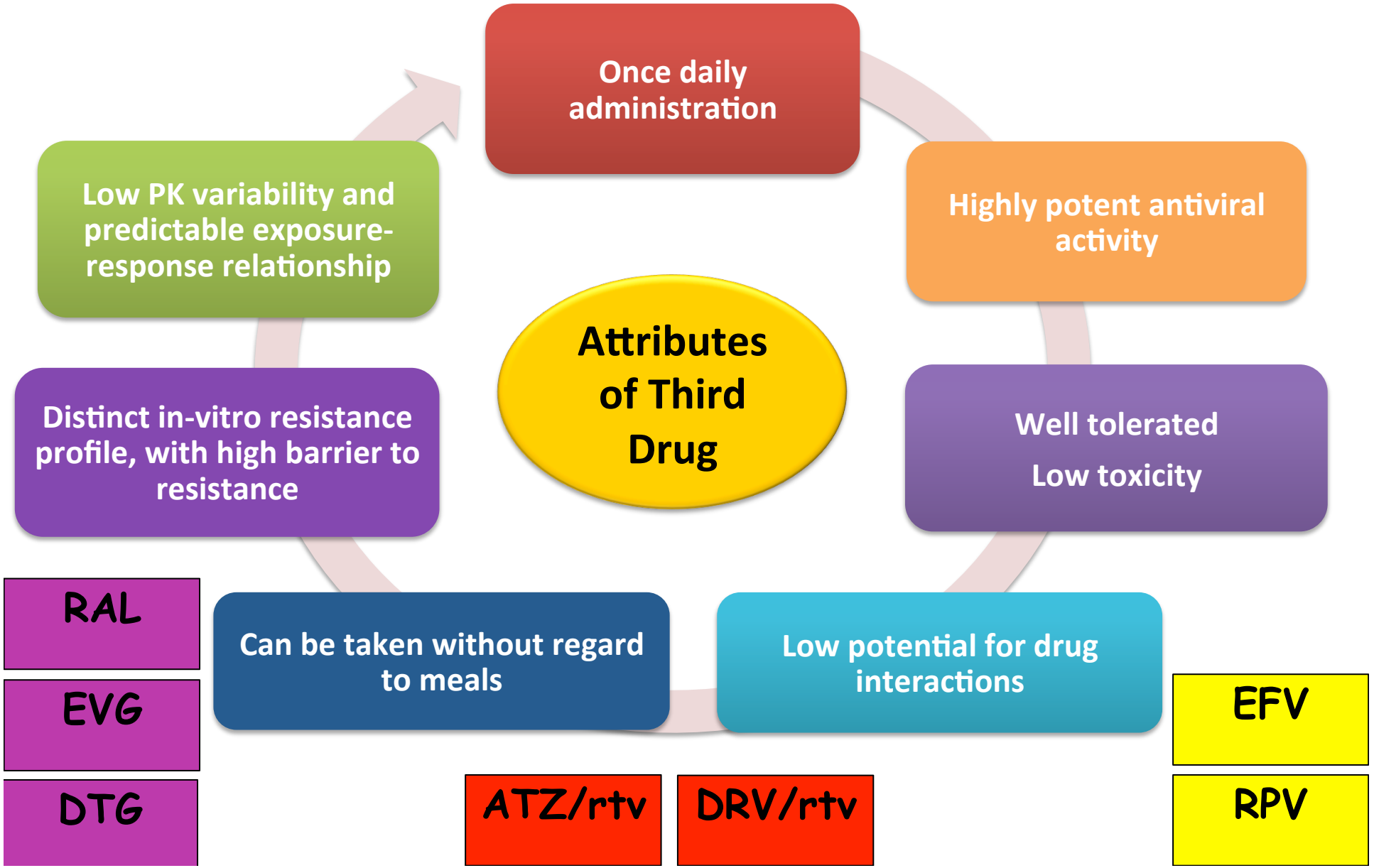
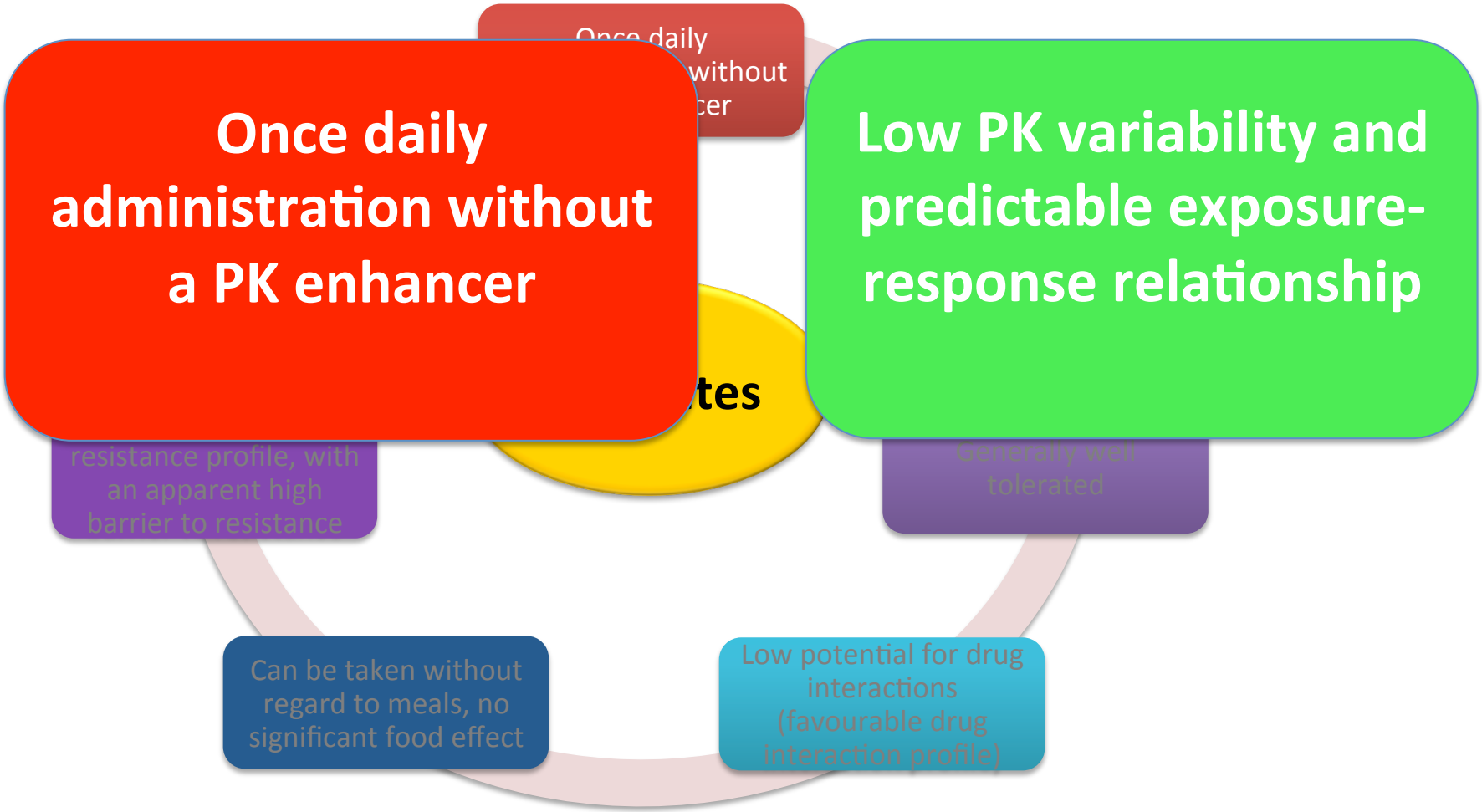
- Gilead Sciences
- Bristol-Myers Squibb
- Janssen-Cilag
- Viiv Healthcare
- Merck Sharp and Dohme
- AbbVie
- Astra Zeneca
- Boheringer Ingelheim
- Pfizer

ATTRIBUTES OF THIRD DRUG FOR USE AS A FIRST-LINE TREATMENT



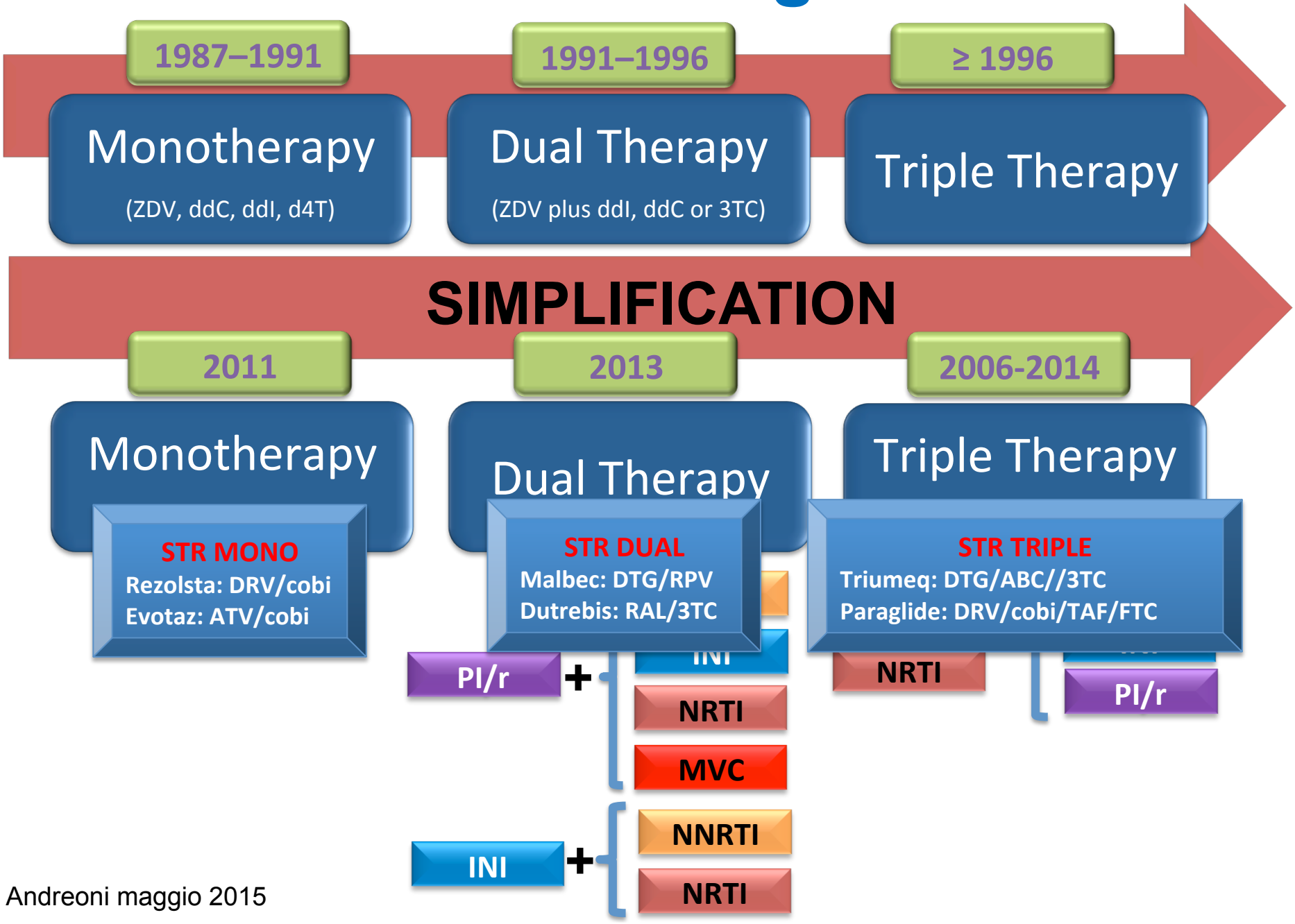
Integrase Inhibitors

ATTRIBUTES OF A DRUG FOR USE AS A FIRST-LINE TREATMENT



PK, pharmacokinetics

How Current Paradigms evolved

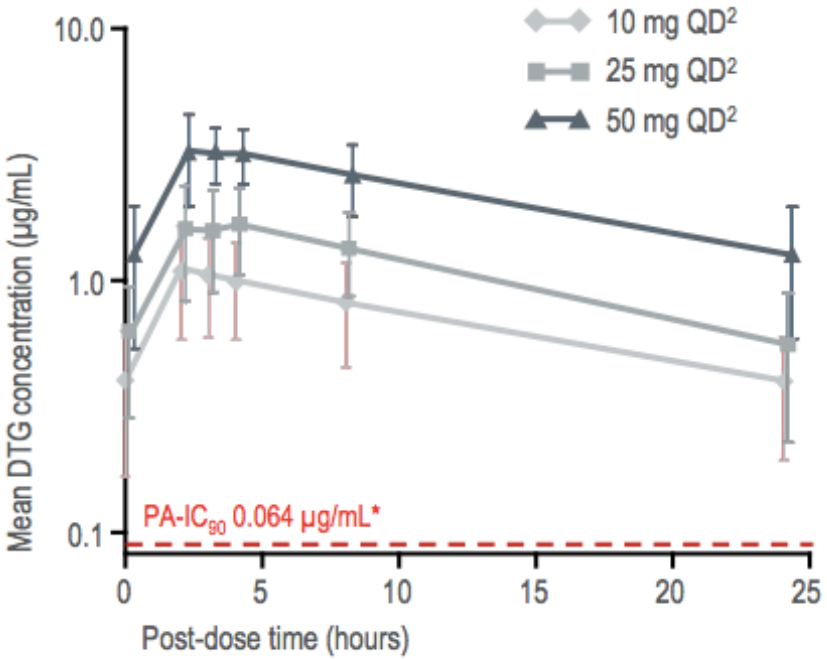


Andreoni maggio 2015

Dolutegravir

CONSISTENT DOSE-EXPOSURE RELATIONSHIP FOR DOLUTEGRAVIR

DTG PK parameters at Week 2 by dose in the SPRING-1 Phase IIb trial[1,2]



Values shown are geometric means (CV%)

QD dose	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg·h/mL)	C_{τ} (µg/mL)	IQ†
10 mg[1,2]	1.10 (37)	16.0 (40)	0.30 (71)	4.7
25 mg[1,2]	1.71 (43)	23.1 (48)	0.54 (67)	8.4
50 mg[1,2]	3.40 (27)	48.1 (40)	1.20 (62)	19

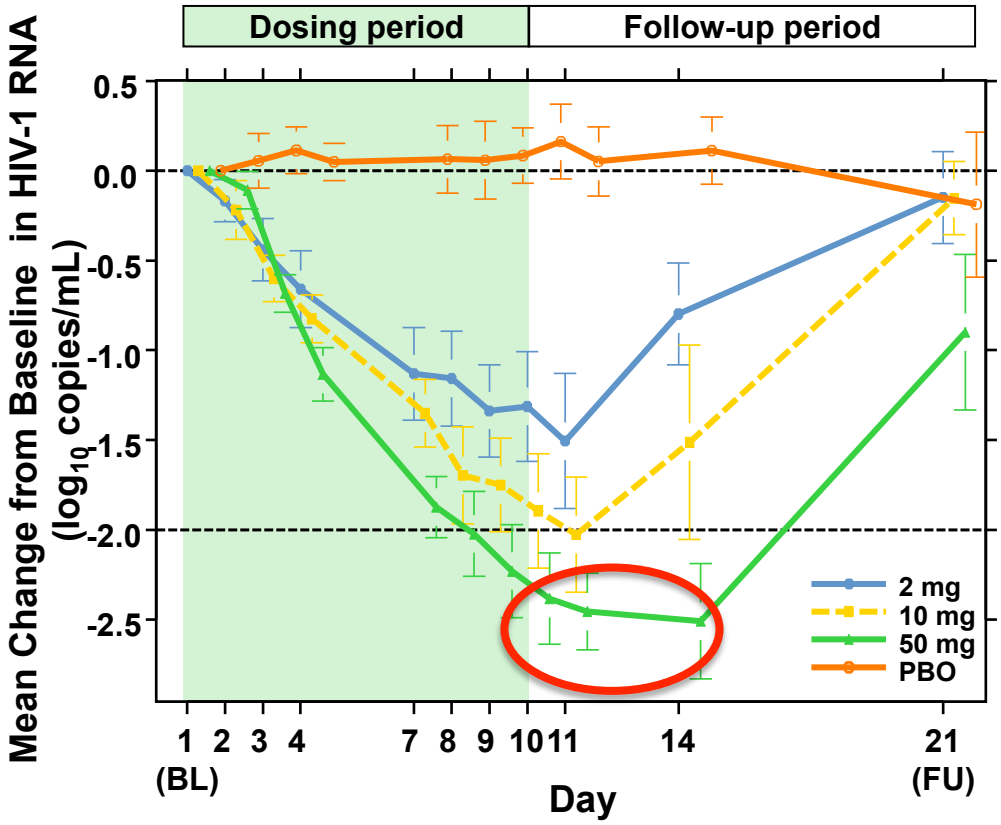
- DTG showed low to moderate PK variability[1,2]
- All drug levels were well above the in-vitro PA-IC_{90} of 0.064 µg/mL[1,2]

*PA-IC_{90} is the protein-adjusted 90% inhibitory concentration
†Inhibitory quotient is defined as C_{τ}/PA–IC_{90}

1. Adapted from van Lunzen J, et al. Lancet Infect Dis 2012; 12:111–8
2. Adapted from Rockstroh J, et al. HIV10 2010. Abstract O50

Dolutegravir Antiviral Activity

10d Monotherapy study in HIV+ subjects

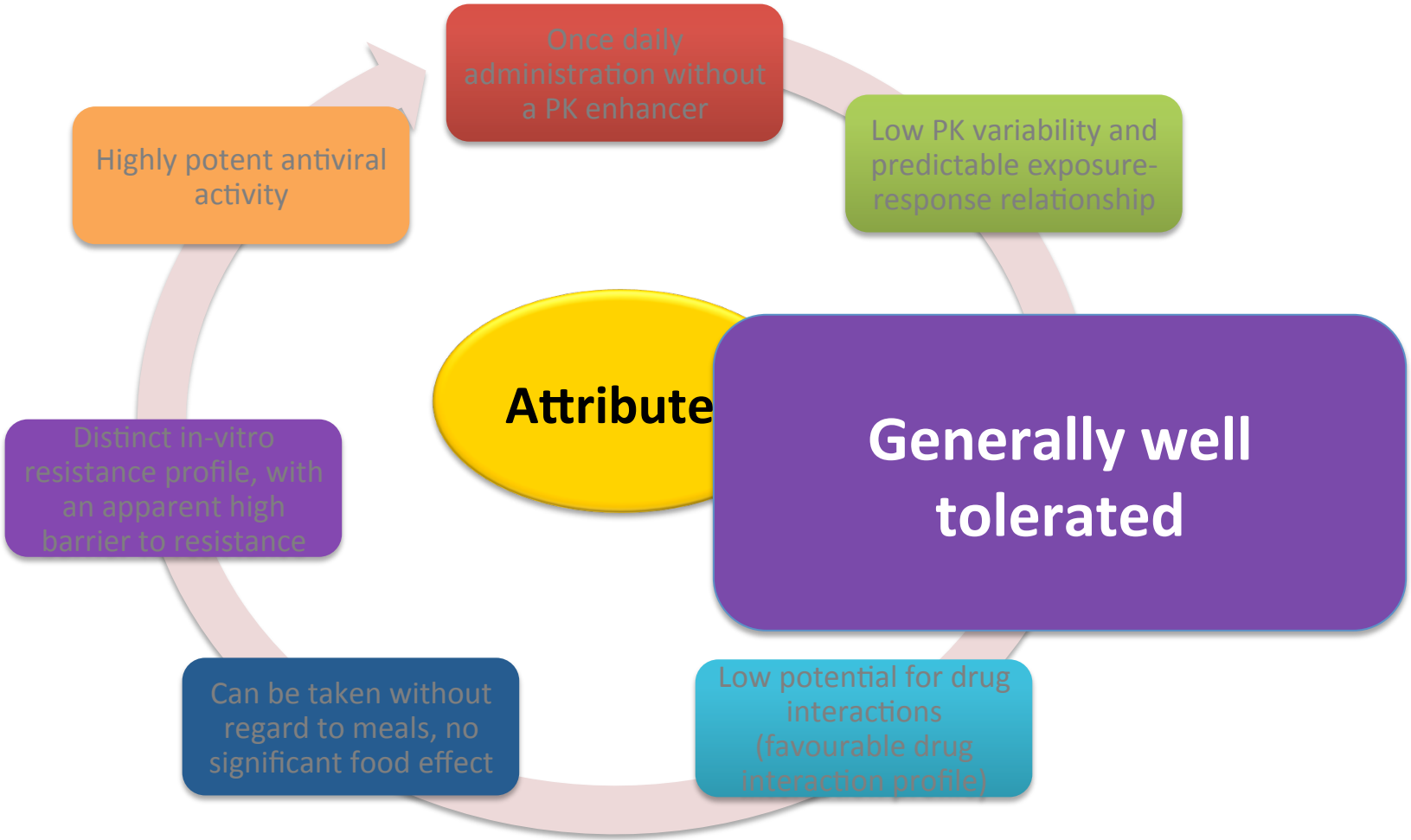


	S/GSK1349572 Dose		
HIV RNA	2mg (n=9)	10mg (n=9)	50mg (n=10)
<400 copies/mL	5/9 (56%)	5/9 (56%)	9/10 (90%)
<50 copies/mL	1/9 (11%)	0	7/10 (70%)

Min, S. et. al. *AIDS*. 2011, 25:1737–1745.

Fujiwara, T. et al. EACS 2009 – 12th European AIDS Conference 11-14 November 2009, Cologne, Germany. PE7.2/4.

ATTRIBUTES OF A DRUG FOR USE AS A FIRST-LINE TREATMENT



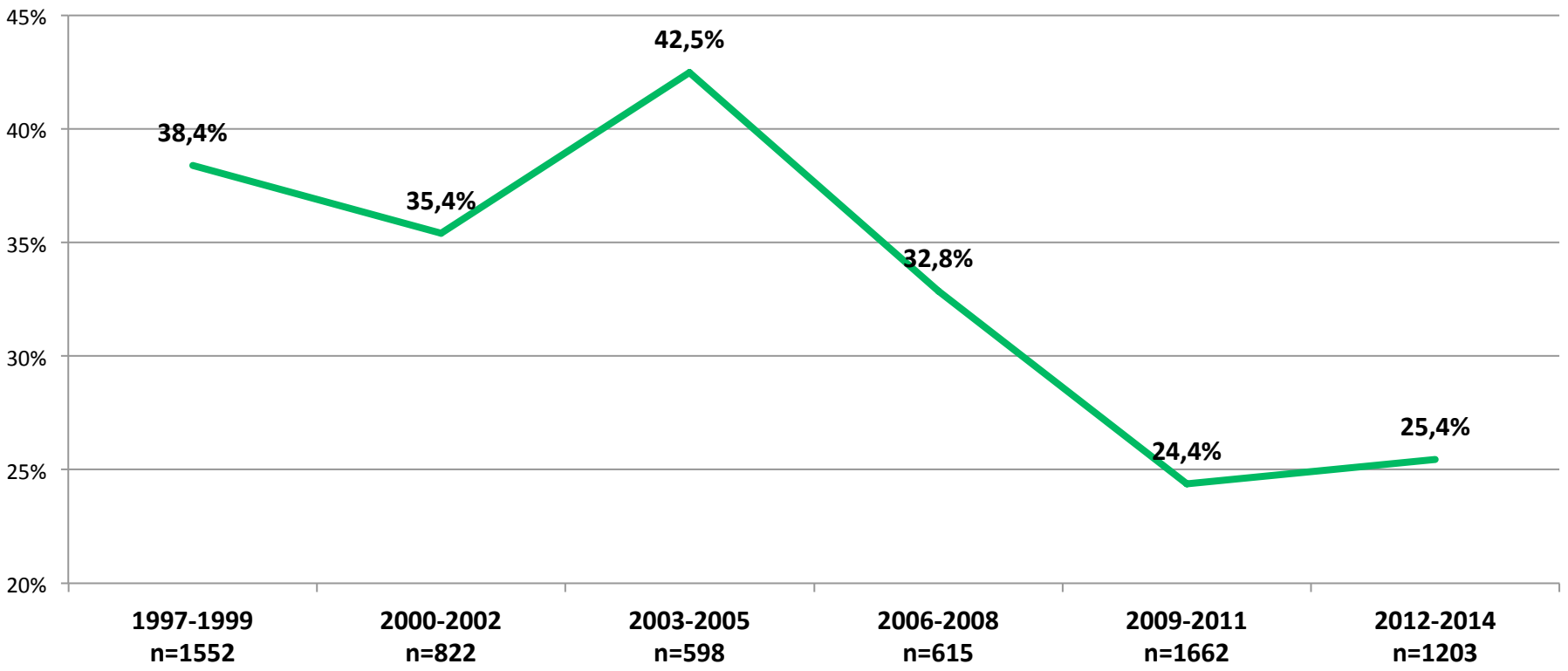
PK, pharmacokinetics

ADVERSE EVENTS

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

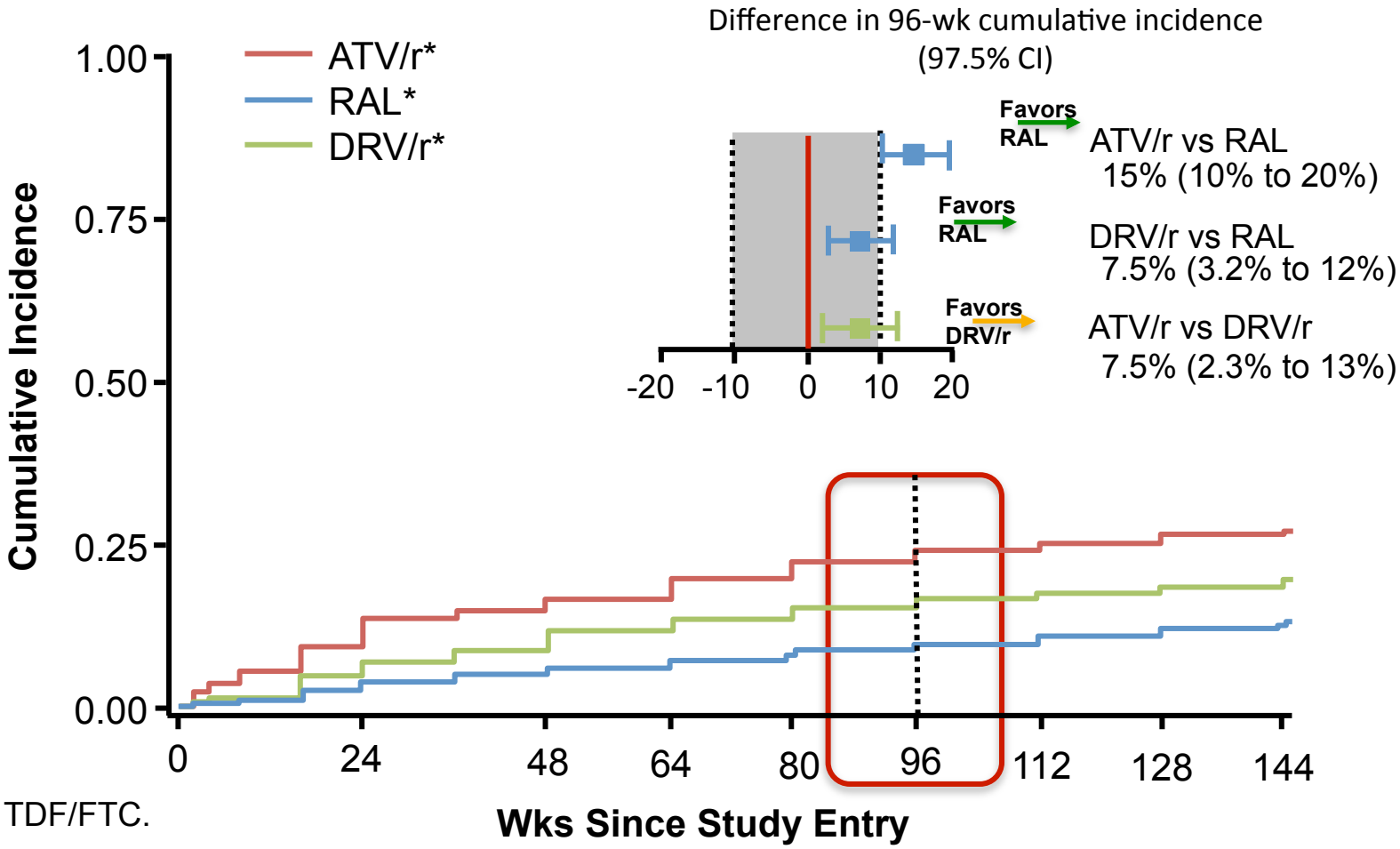
Italian Cohort I. C O. N A. Naive Antiretrovirals

Proportion of patients stopping first HAART regimen within 1 year, according to calendar period



Dec 2014 Report

ACTG 5257: Cumulative Incidence of Virologic or Tolerability Failure



*Plus TDF/FTC.

Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

ACTG 5257: Tolerability Failure

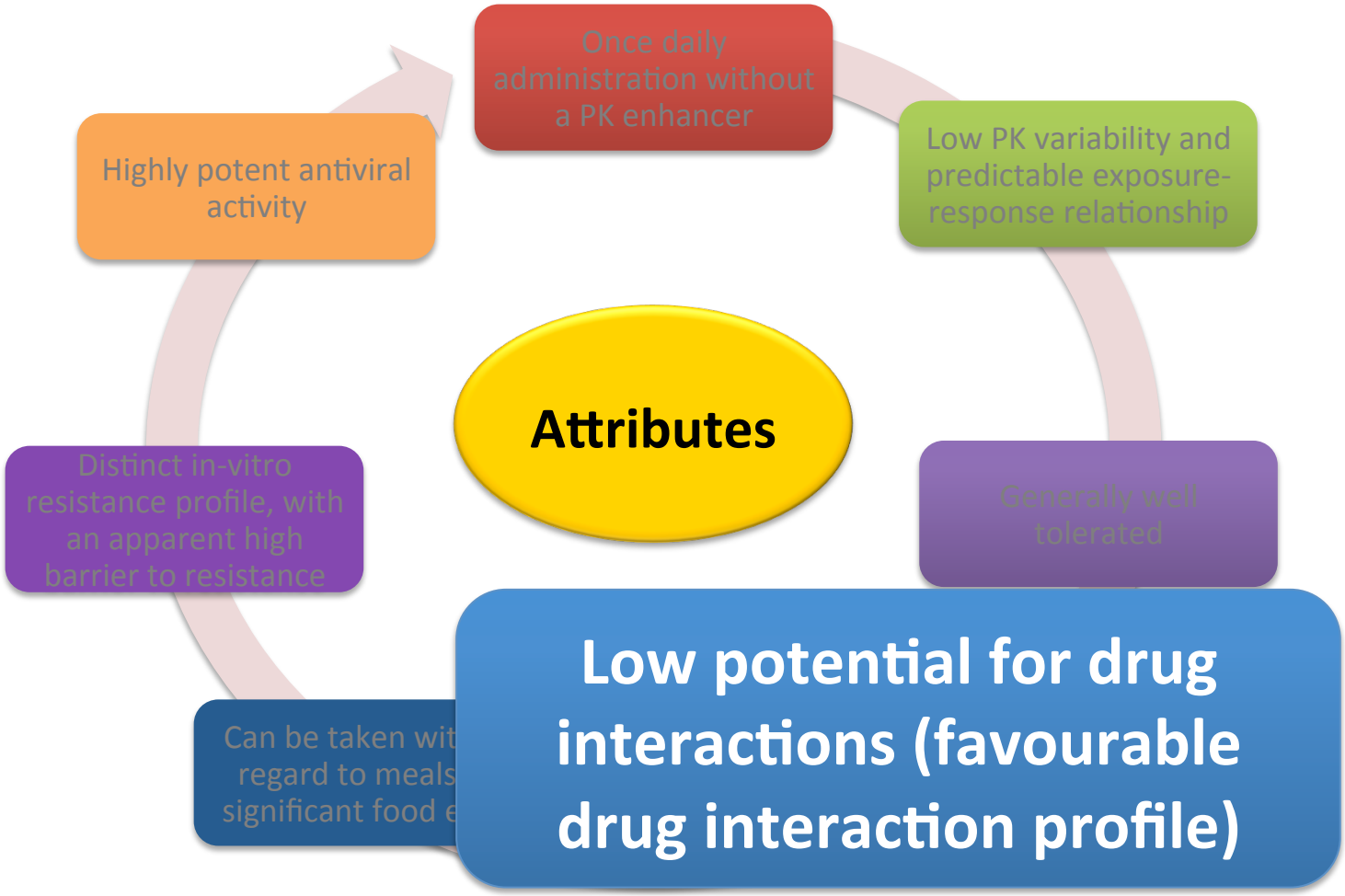
Toxicity-Associated Discontinuation of Randomized ART*

Toxicities Associated With Discontinuation, n (%)	ATV/r† (n = 605)	RAL† (n = 603)	DRV/r† (n = 601)
Any	**95 (16%)**	**8 (1%)**	**32 (5%)**
Gastrointestinal toxicity	25	2	14
Jaundice/hyperbilirubinemia	47	0	0
Other hepatic toxicity	4	1	5
Skin toxicity	7	2	5
Metabolic toxicity	6	0	2
Renal toxicity (all nephrolithiasis)	4	0	0
Abnormal chem/heme (excl. LFTs)	0	0	2
Other toxicity	2	3	4

*Participants allowed to switch therapy for intolerable toxicity.
†Plus TDF/FTC.

Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

ATTRIBUTES OF A DRUG FOR USE AS A FIRST-LINE TREATMENT



PK, pharmacokinetics

Drug–Drug Interactions With Integrase Inhibitors

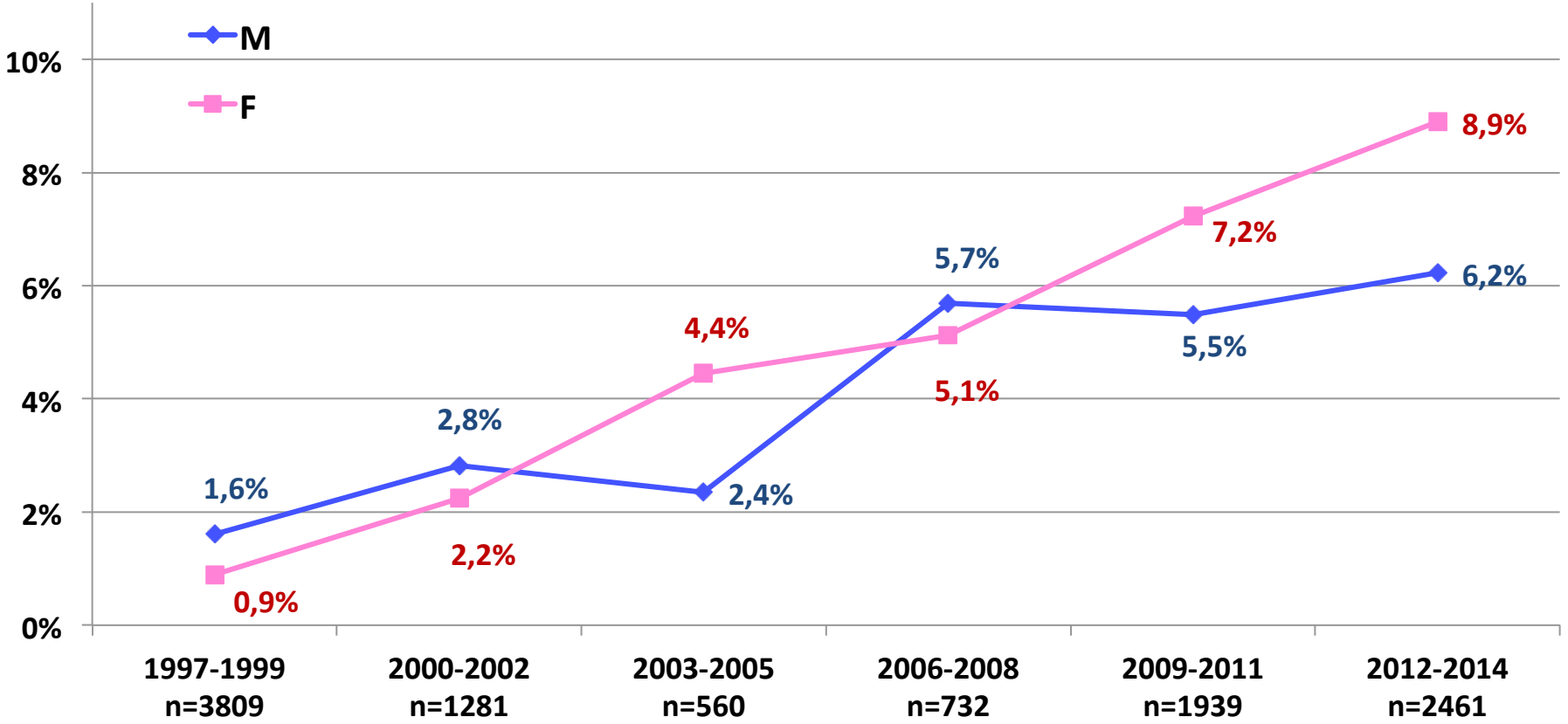
RAL[1,2]	EVG/COBI[1]	DTG[3]
▪ Rifampin ▪ Antacids containing polyvalent cations (Ca++, Mg++)	▪ Antacids ▪ Benzodiazepines ▪ Beta blockers ▪ Calcium channel blockers ▪ Erectile dysfunction drugs ▪ Inhaled/injectable corticosteroids ▪ MVC ▪ OCPs (norgestimate) ▪ Rifampin ▪ Statins	▪ EFV ▪ ETR ▪ FPV/RTV ▪ Medications containing polyvalent cations (Ca++, Mg++), including laxatives, antacids ▪ Metformin ▪ Rifampin ▪ TPV/RTV

*May be a class effect

1. DHHS Adult Guidelines. February 2013. 2. Raltegravir [package insert]. 3. Dolutegravir [package insert].

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of italian patients aged 60 or more according to gender and to period of enrolment

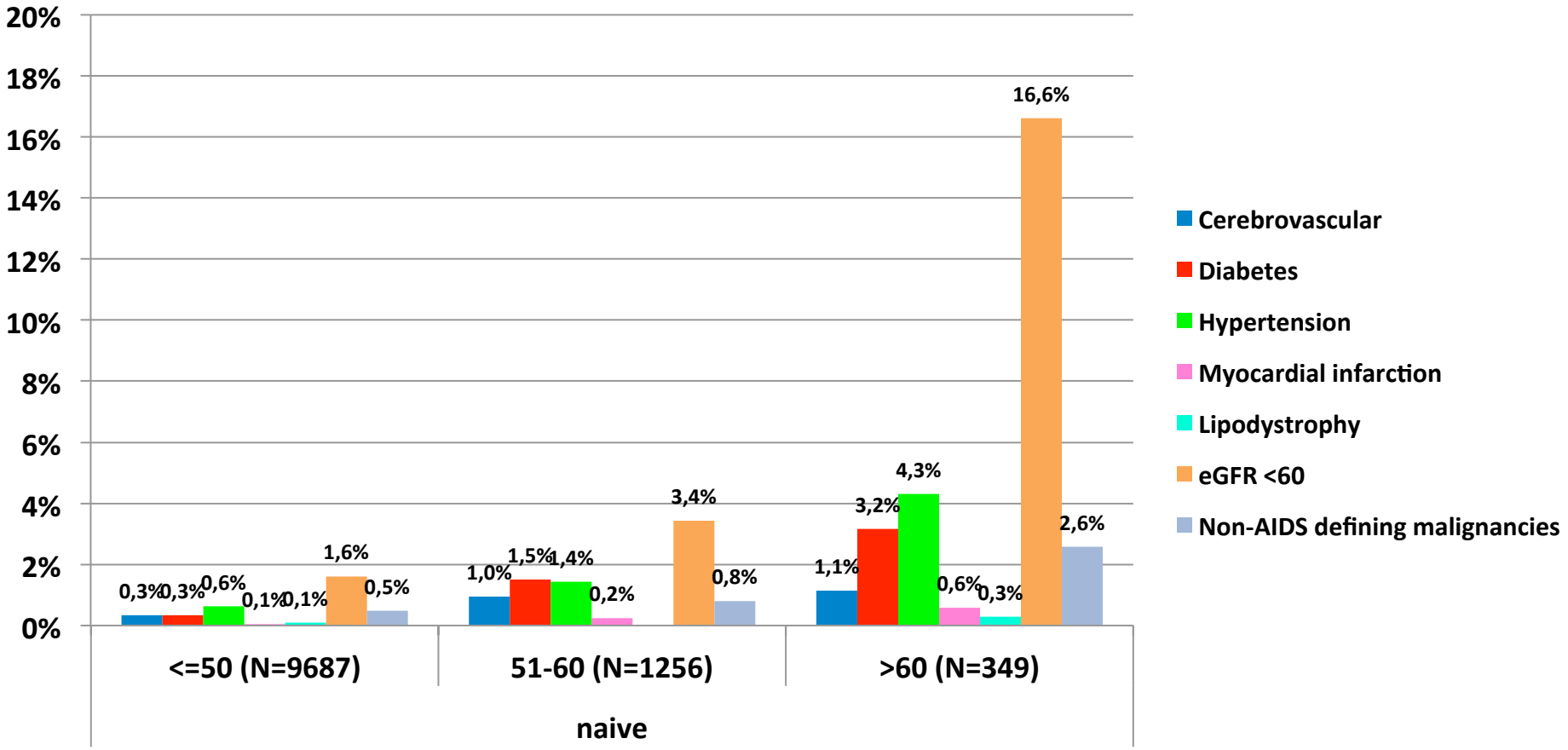


Dec 2014 Report

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Prevalence of different non-AIDS related co-morbidities at different age strata in naive patients

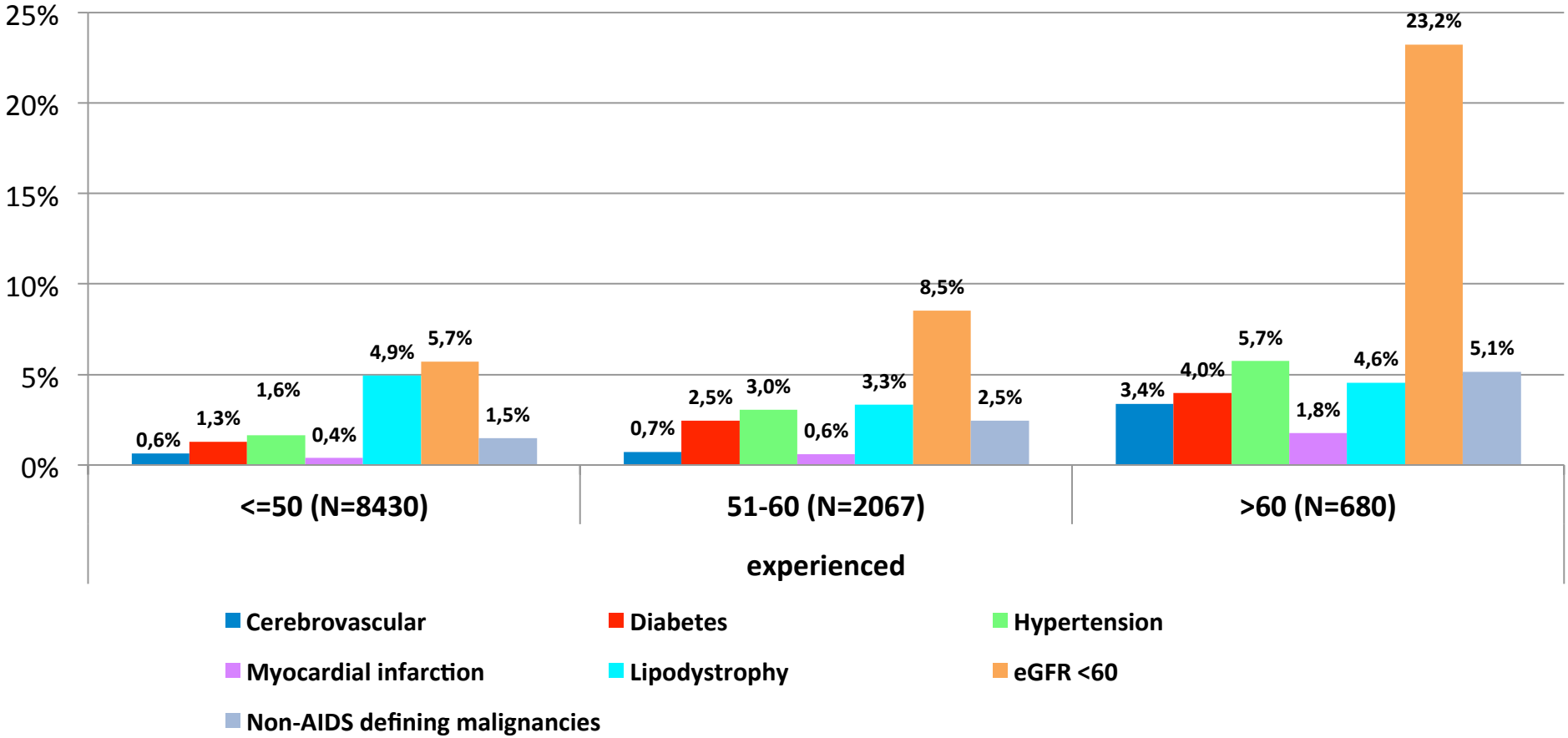


Dec 2014 Report

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

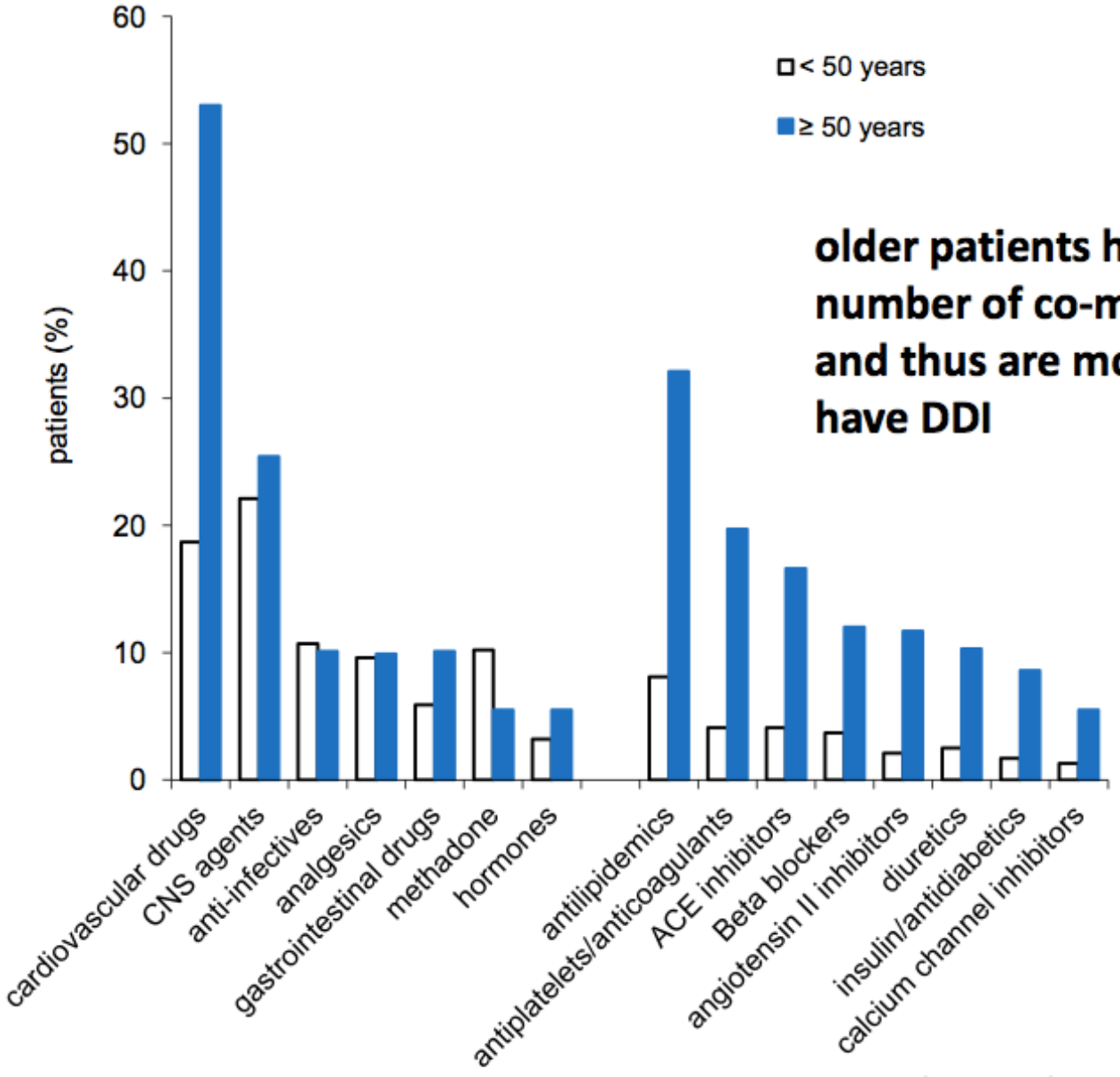
Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Prevalence of different non-AIDS related co-morbidities at different age strata in ART-treated patients



Dec 2014 Report

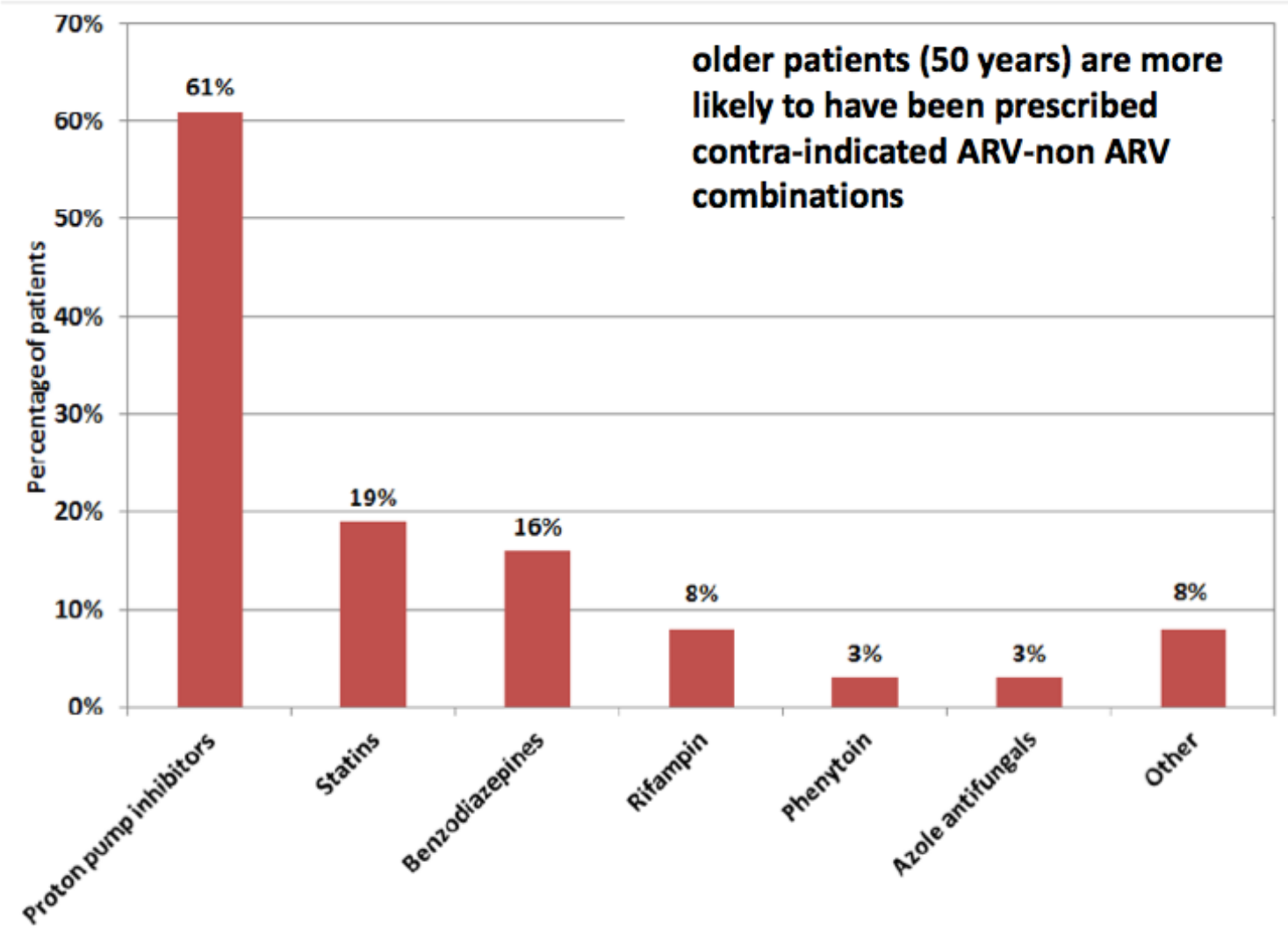
HIV population is aging ➔ increased risk of DDI



older patients have a higher number of co-medications and thus are more likely to have DDI

Marzolini C et al. J Antimicrob Chemother 2011

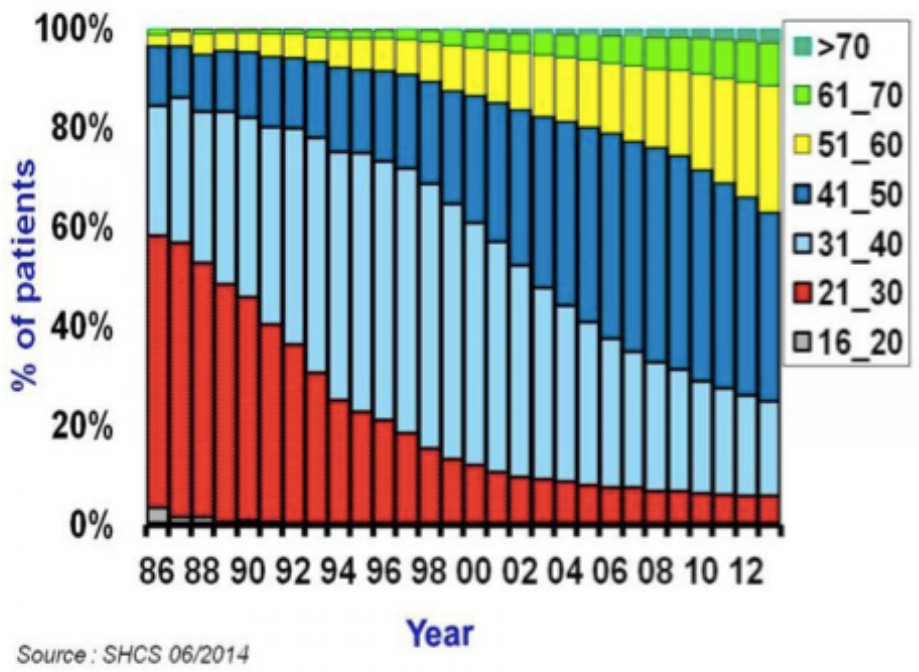
Contra-indicated ARV/non-ARV drug combinations



Holtzman C et al. J Gen Intern Med 2013

Aging and effect on pharmacokinetics

Age distribution of active patients by year in the SHCS, 1986-2013



Source : SHCS 06/2014

proportion of individuals >65 y where PK effects related to age will be noticeable is growing

Table 1. Age-related changes in drug pharmacokinetics and potential effects on antiretroviral drugs

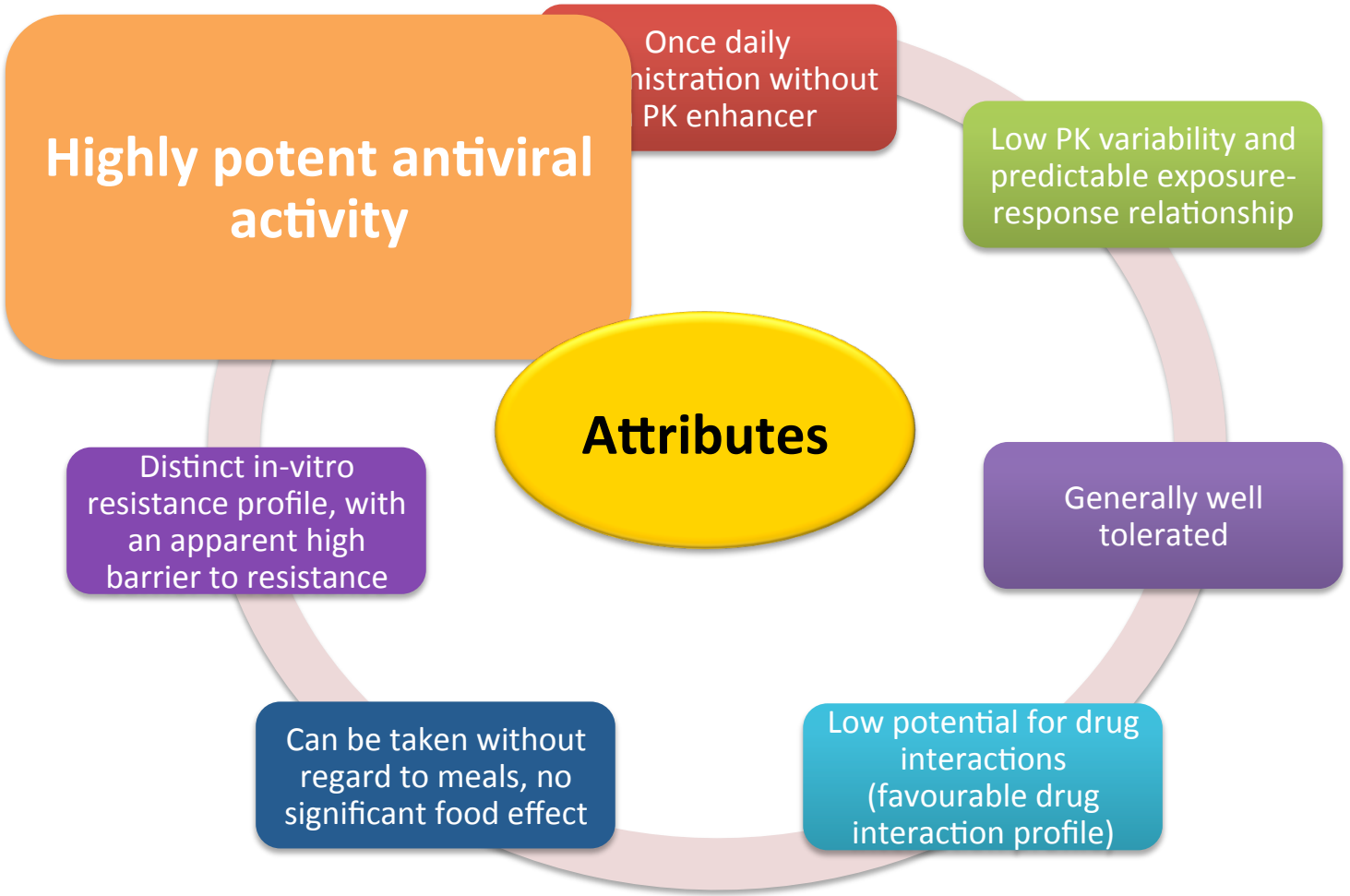
Potential age-related changes to pharmacokinetic characteristics	Potential effects on plasma drug exposure*
Liberation and absorption (absorption rate, bioavailability)	
↑ gastric pH	↓/↑ PIs*
↓ gastric emptying	↑ Rilpivirine*
↓ GI p-gp and CYP activity	↑ Maraviroc
Distribution (volume of distribution)	
↓ albumin	↑ PIs
↑ body fat %	↑ NNRTIs
↓ lean muscle %	↑ Maraviroc
	↑ INSTIs
Metabolism (clearance)	
↓ albumin	↑ PIs*
↓ liver mass	↑ NNRTIs*
↓ hepatic CYP activity	↑ Maraviroc*
	↑ INSTIs
Excretion (clearance)	
↓ renal function	↑ NRTIs** (particularly tenofovir)

➔ mainly ↑ in ARV exposure with ↑ risk of drug toxicity

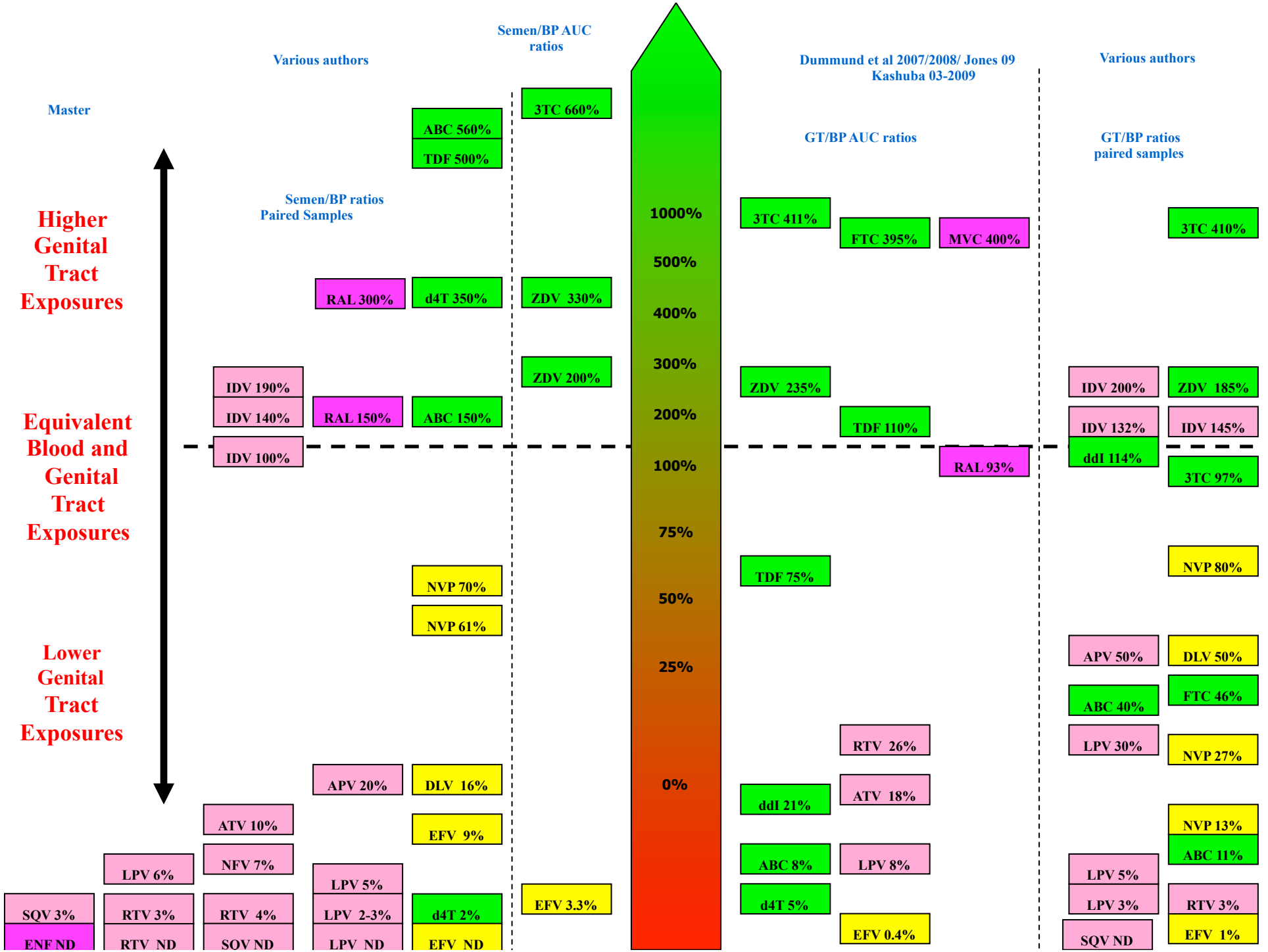
Winston A et al. Curr Opin Infect Dis 2014

SWISS HIV COHORT STUDY

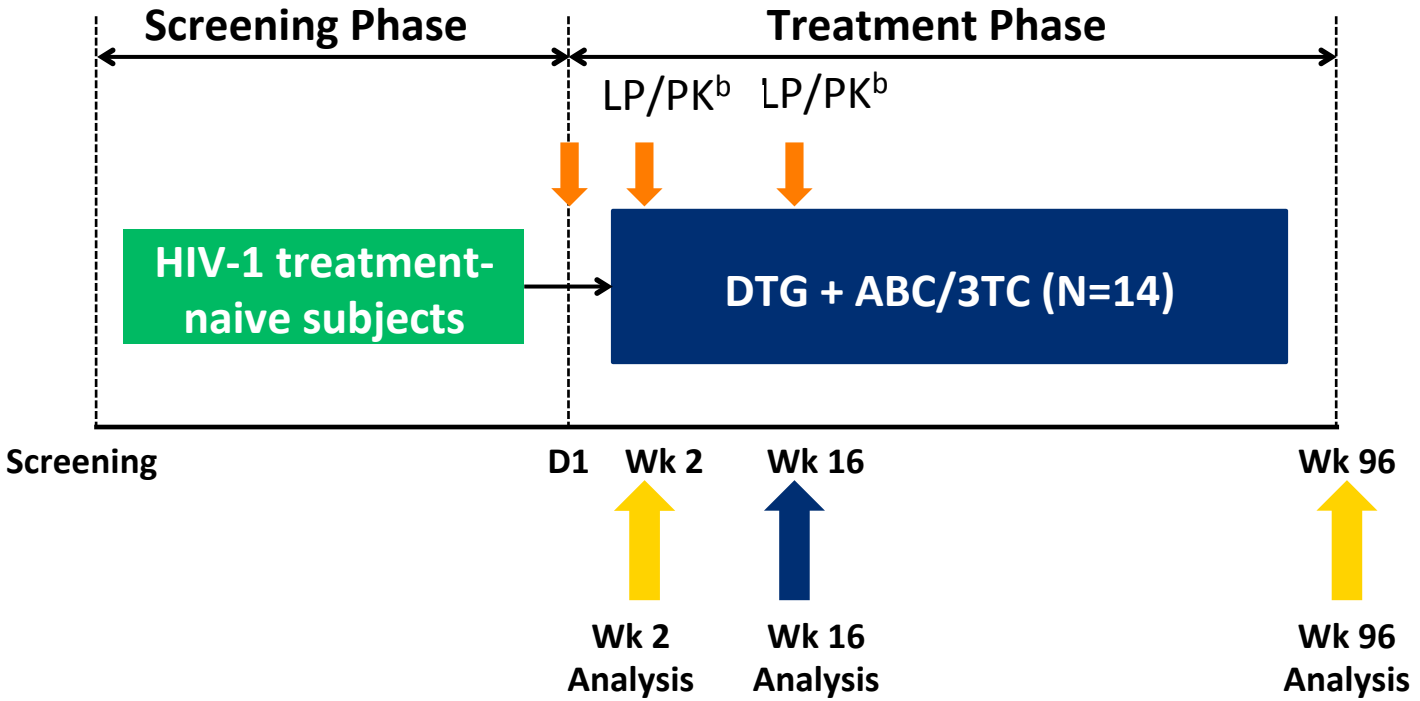
ATTRIBUTES OF A DRUG FOR USE AS A FIRST-LINE TREATMENT



PK, pharmacokinetics


Master
Various authors
Semen/BP AUC ratios
Dummund et al 2007/2008/ Jones 09
Kashuba 03-2009
Various authors
GT/BP AUC ratios
GT/BP ratios paired samples
Semen/BP ratios Paired Samples
Higher Genital Tract Exposures
Equivalent Blood and Genital Tract Exposures
Lower Genital Tract Exposures
1000%
500%
400%
300%
200%
100%
75%
50%
25%
0%
3TC 660%
ABC 560%
TDF 500%
RAL 300%
d4T 350%
ZDV 330%
ZDV 200%
IDV 190%
IDV 140%
IDV 100%
RAL 150%
ABC 150%
NVP 70%
NVP 61%
APV 20%
DLV 16%
EFV 9%
ATV 10%
NFV 7%
LPV 6%
LPV 5%
SQV 3%
RTV 3%
RTV 4%
LPV 2-3%
d4T 2%
ENF ND
RTV ND
SQV ND
LPV ND
EFV ND
EFV 3.3%
3TC 411%
FTC 395%
MVC 400%
ZDV 235%
TDF 110%
RAL 93%
TDF 75%
RTV 26%
ATV 18%
ddI 21%
ABC 8%
LPV 8%
d4T 5%
EFV 0.4%
3TC 410%
IDV 200%
ZDV 185%
IDV 132%
IDV 145%
ddI 114%
3TC 97%
NVP 80%
APV 50%
DLV 50%
FTC 46%
ABC 40%
LPV 30%
NVP 27%
NVP 13%
ABC 11%
LPV 5%
LPV 3%
RTV 3%
SQV ND
EFV 1%

Distribution and Antiviral Activity in Cerebrospinal Fluid (of the Dolutegravir: ING116070 Week 16 Results



[a] CSF/Plasma for HIV-1 RNA only
[b] CSF/Plasma for PK and HIV-1 RNA collected 2-6 hours postdose

Letendre et al. CROI 2013; Atlanta, GA. Poster #178LB.

Clinical Infectious Diseases Advance Access published June 18, 2014

DTG concentrations observed in CSF at both Week 2 and Week 16 exceed the in vitro IC_{50} against wild-type viruses (0.2 ng/mL)[1] for all subjects, suggesting that DTG is able to achieve therapeutic concentrations in the CSF.

	Week 2 N=12		Week 16 N=12	
	Mean (SD)	**Median (min, max)**	**Mean (SD)**	**Median (min, max)**
Plasma total (μg/mL)	3.42 (0.831)	3.36 (2.09, 5.28)	3.03 (1.35)	3.21 (0.64, 4.92)
Plasma unbound (ng/mL)	16.8 (4.10)	17.1 (10.3, 24.0)	23.0 (8.24)	23.9 (3.81, 32.1)
Unbound fraction in plasma (%)	0.495 (0.0823)	0.488 (0.333, 0.655)	0.995 (1.05)	0.701 (0.488, 4.30)
CSF total (ng/mL)	16.2 (5.84)[a]	18.2 (4.0, 23.2)[a]	12.6 (3.64)	13.2 (3.7, 18.3)
Ratio CSF:total plasma (%)	0.467 (0.178)[a]	0.516 (0.115, 0.658)[a]	0.546 (0.480)	0.412 (0.299, 2.04)

[a] N=11, excludes 1 subject with PK samples collected outside the 2-6 hour postdose window

Letendre et al. CROI 2013; Atlanta, GA. Poster #178LB

Clinical Infectious Diseases Advance Access published June 18, 2014.

Virologic Response Data in Plasma and CSF

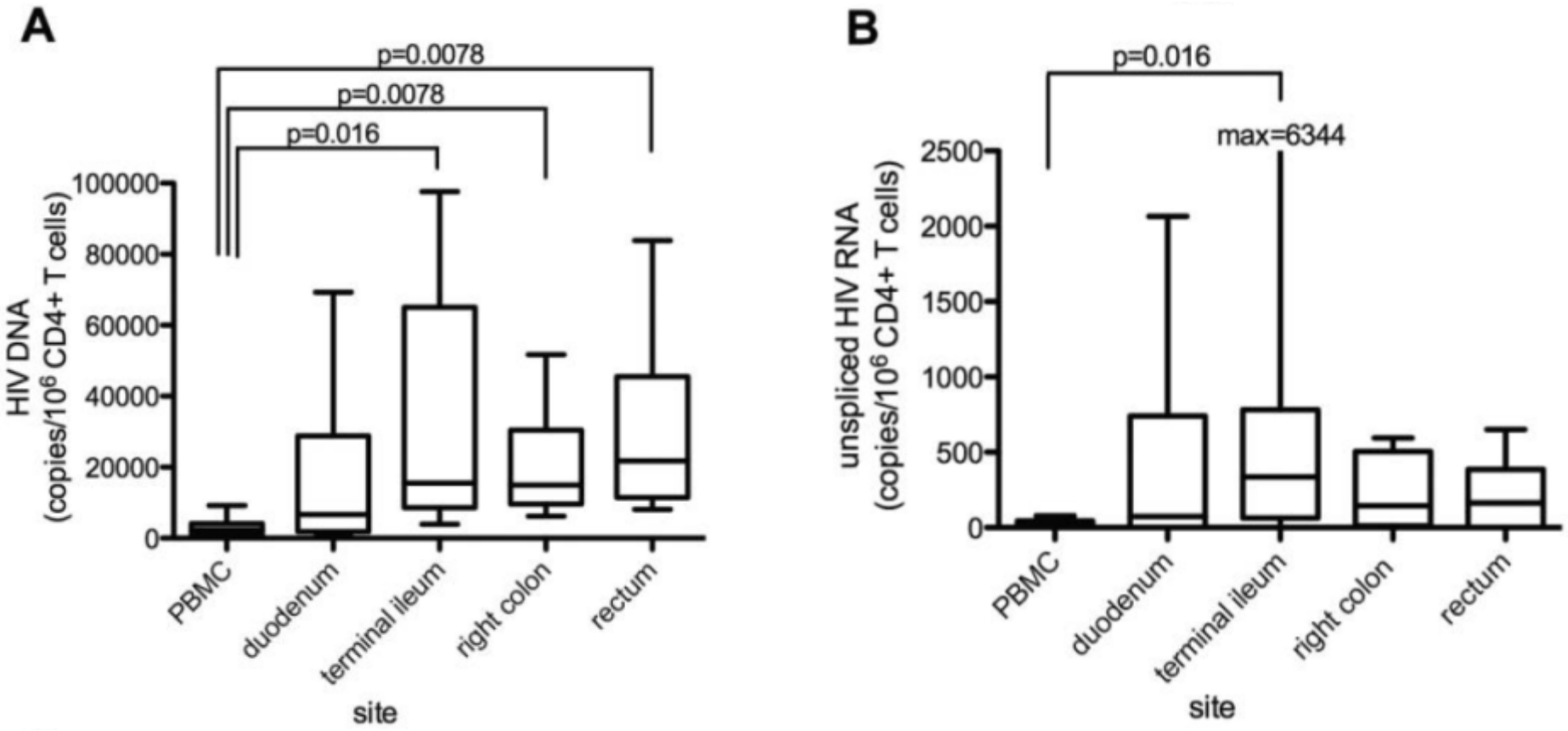
	Plasma HIV-1 RNA			CSF HIV-1 RNA		
Subject	Baseline Absolute Value (c/mL)	Week 16 Absolute Value (c/mL)	Change from Baseline (log_{10} c/mL)	Baseline Absolute Value (c/mL)	Week 16 Absolute Value (c/mL)	Change from Baseline (log_{10} c/mL)
A	38,697	<50	-3.00	2,600	<2	-3.41
B	232,844	<50	-3.78	6,400	<2	-3.81
C	18,483	<50	-2.68	29,000	<2	-4.46
D	47,061	<50	-3.08	450	<2	-2.65
E	24,222	<50	-2.79	29	<2	-1.46
F	137,948	<50	-3.55	1,000	<2	-3.00
G	11,712	<50	-2.48	4,400	<2	-3.64
H	3,976	<50	-2.01	140	<2[a]	-2.15[a]
I	3,684,952	236	-4.19	400,000	<2	-5.60
J	301,078	<50	-3.89	57,000	<2	-4.76
K	53,272	<50	-3.14	460	<2	-2.66
L	74,301	77	-2.98	9,000	5	-3.26

[a] CSF HIV-1 RNA assessment performed on Day 141 (within the Week 24 time window)

Letendre et al. CROI 2013; Atlanta, GA. Poster #178LB

Clinical Infectious Diseases Advance Access published June 18, 2014.

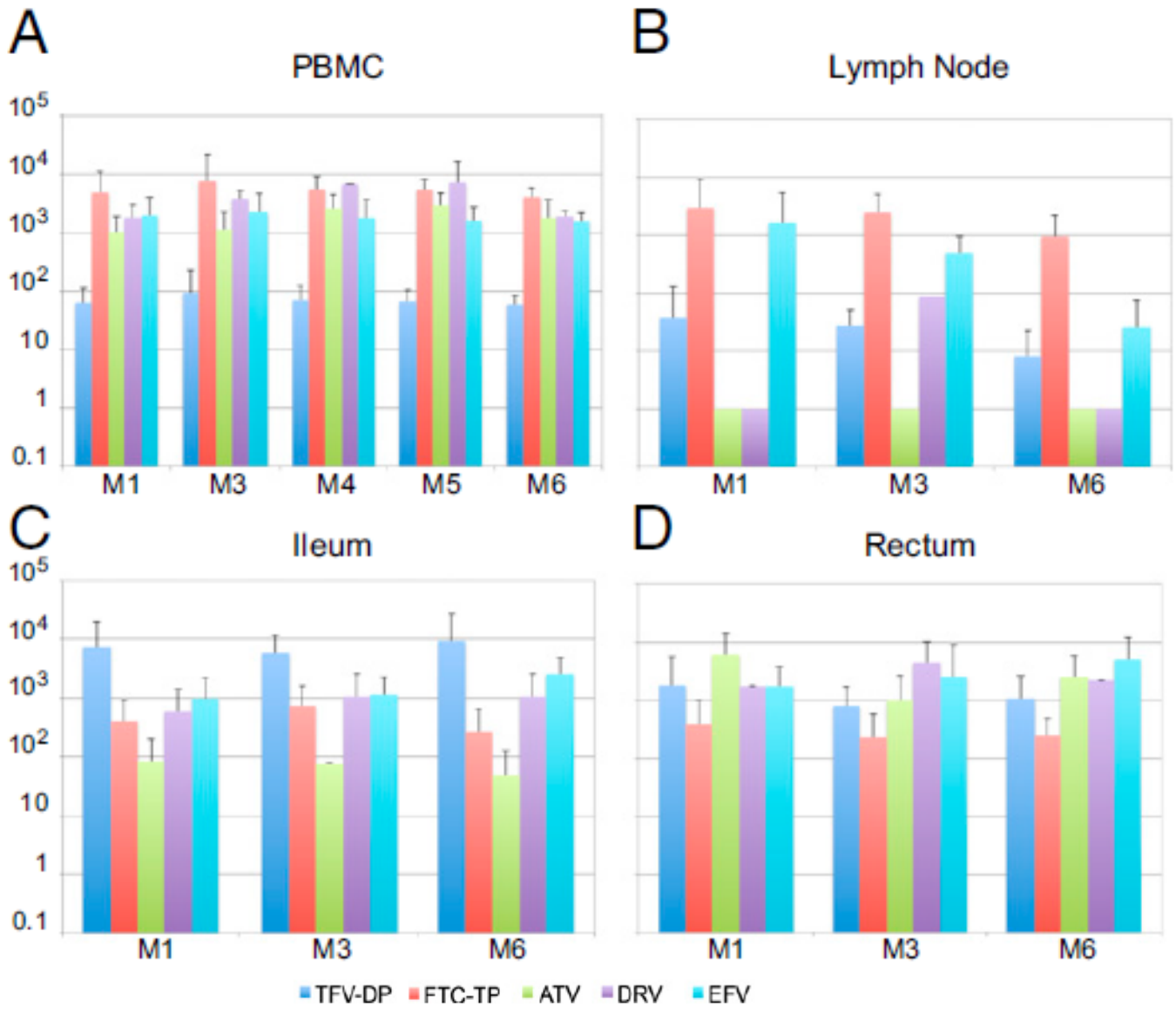
HIV DNA and RNA levels per CD4+ T cell were higher in all 4 gut sites compared with those in the blood.



The Journal of Infectious Diseases 2010; 202(10):1553–1561

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

Fletcher CV, 2014



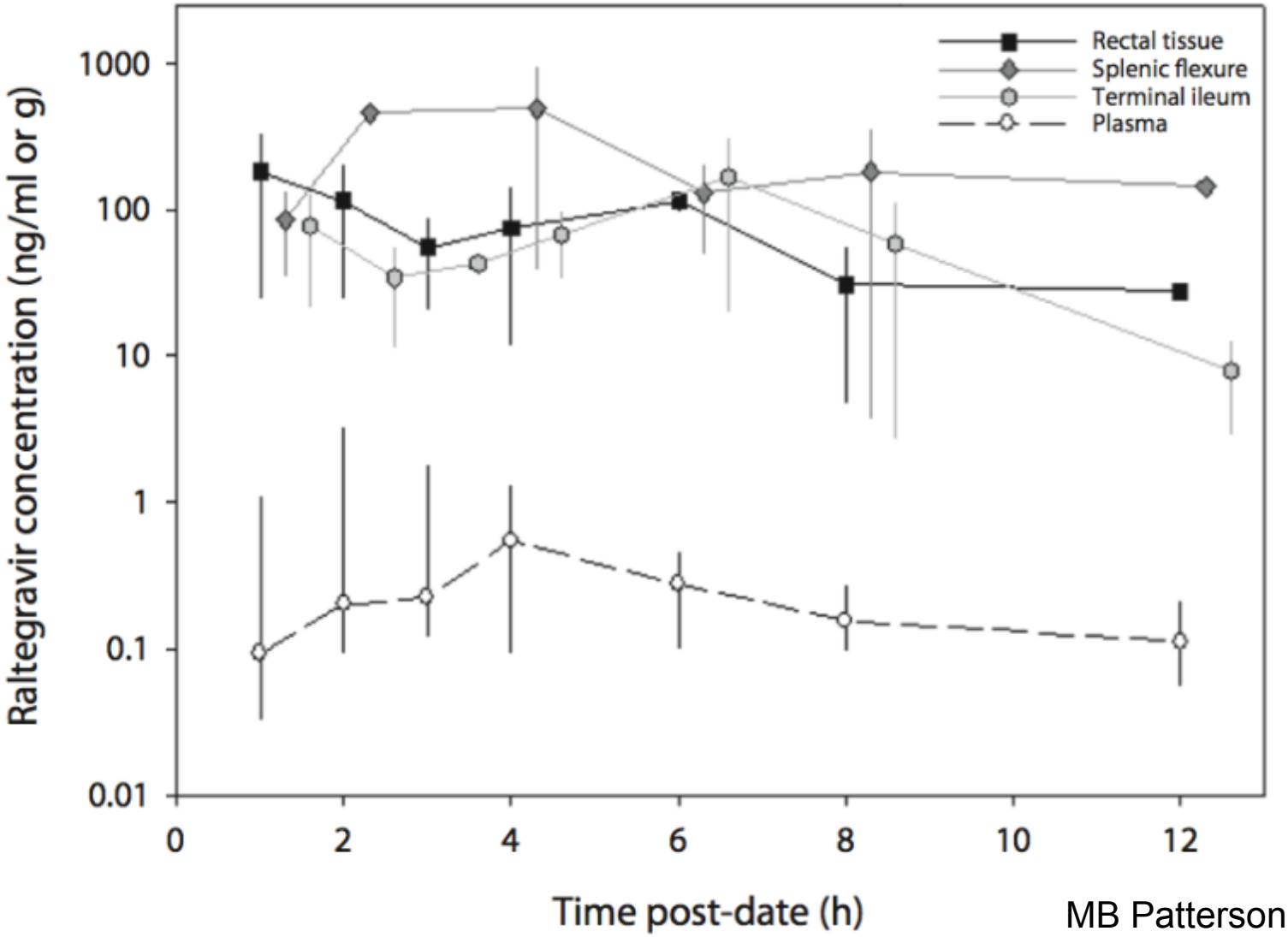
Differential penetration of raltegravir throughout gastrointestinal tissue: implications for eradication and cure

Kristine B. Patterson[a], Heather A. Prince[a], Trenton Stevens[a], Nicholas J. Shaheen[a], Evan S. Dellon[a], Ryan D. Madanick[a], Steven Jennings[b], Myron S. Cohen[a] and Angela D.M. Kashuba[a,b]

AIDS 2013, 27:1413–1419

14 HIV-negative men received RAL 400 mg twice daily for 7 days. Seven blood plasma specimens were collected over 12-h intervals; timed tissue specimens from terminal ileum, splenic flexure, and rectum were also obtained by colonoscopy following the first dose and on day 7 [multiple dose (MD)].

RAL rapidly disseminates into GI tissue and concentrations remain significantly higher than blood plasma.
RAL exposure in GI tissue remains higher than any antiretroviral investigated to date.



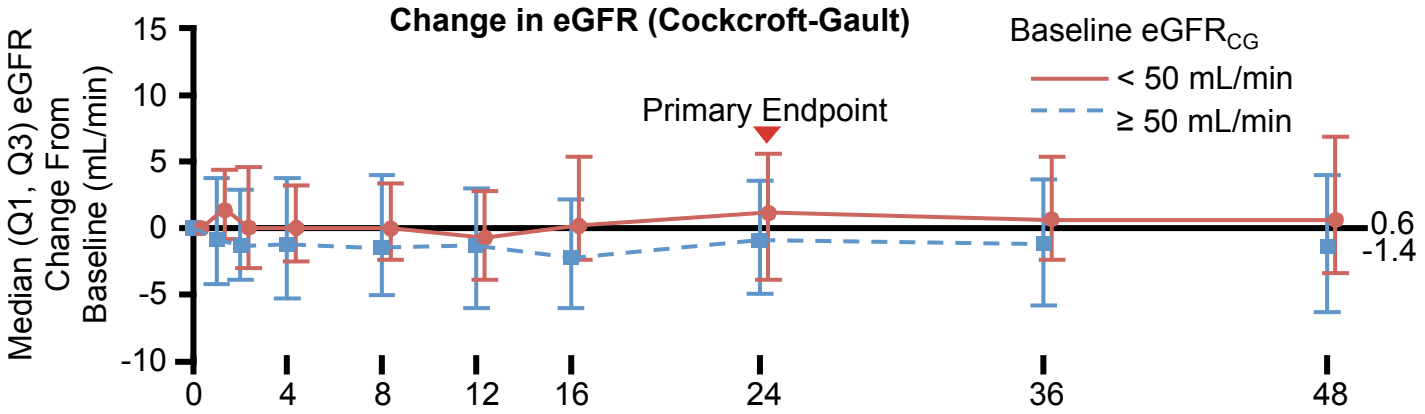
MB Patterson 2013

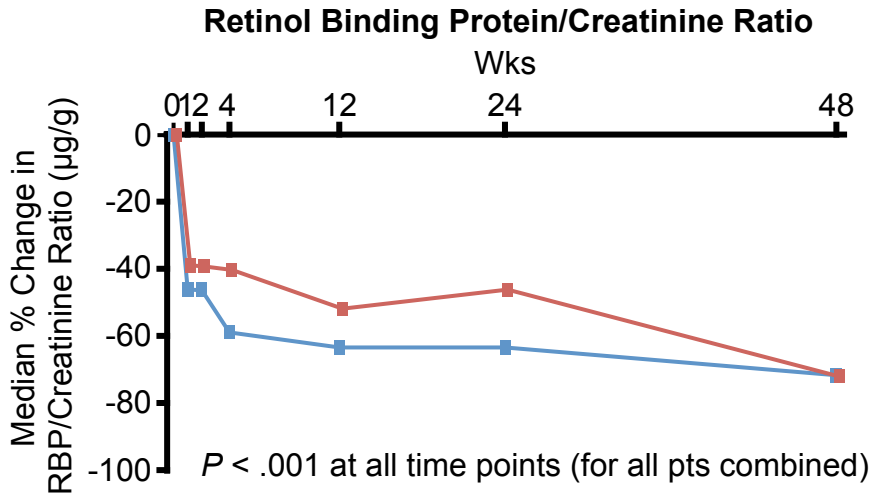
COMING SOON

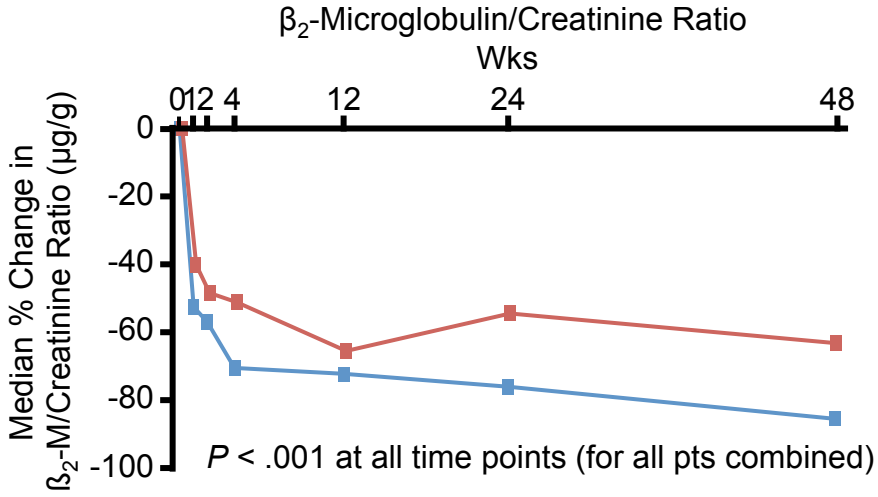
- EVG/COBI/TAF/FTC
- TAF/FTC
- RPV/TAF/FTC

Switch to EVG/COBI/FTC/TAF in Renal Impairment

65% receiving TDF at baseline





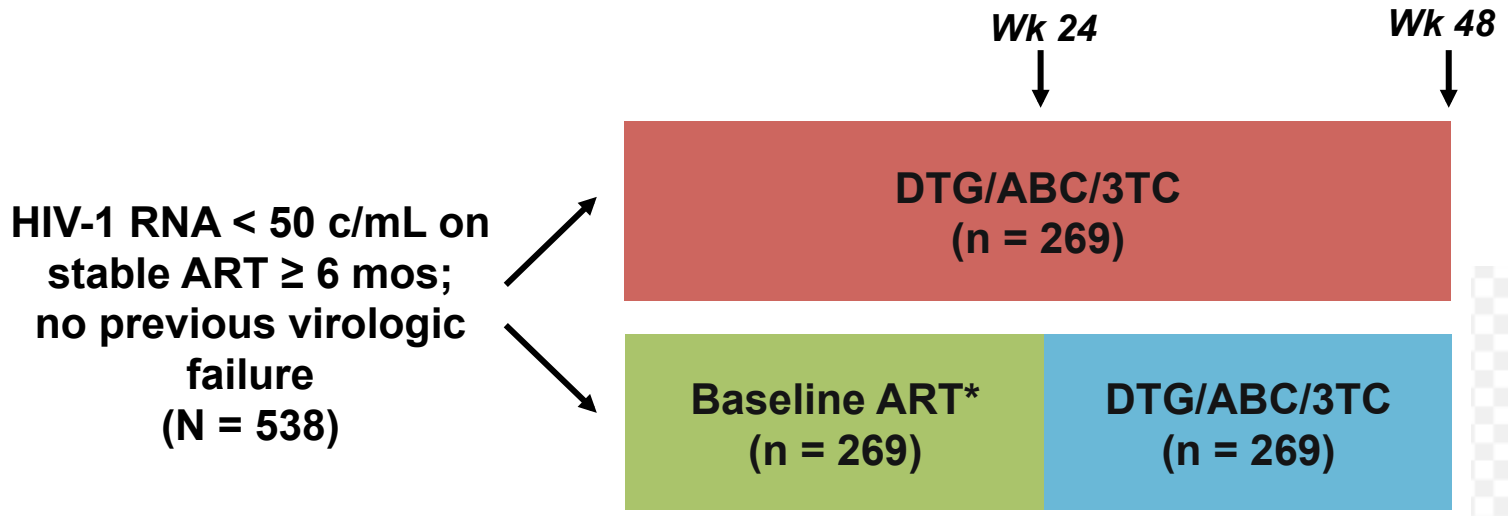


Baseline eGFR < 50 mL/min (n = 80) ≥ 50 mL/min (n = 162)

Pozniak A, et al. CROI 2015. Abstract 795.

STRIIVING: Switch From Suppressive ART to Fixed-Dose DTG/ABC/3TC (Triumeq)

- Ongoing randomized, open-label phase IIIB study
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24



*Containing 2 NRTIs plus a third agent.

ClinicalTrials.gov. NCT02105987.

STR: Strategie per ogni fase della terapia

Naive

Switch per tossicità

NNRTI
Atripla/Eviplera

→

INI Stribild

NNRTI Atripla/Eviplera

INI
Stribild

→

Andreoni Febbraio 2015

STR: Strategie per ogni fase della terapia

Naive

Switch per tossicità

NNRTI
Atripla - Eviplera

→

PI Paraglide

INI Stribild – Triumeq

PI
Paraglide

→

NNRTI Atripla - Eviplera

INI Stribild – Triumeq

INI
Stribild - Triumeq

→

NNRTI Atripla - Eviplera

PI Paraglide

INI Stribild - Triumeq

Andreoni Febbraio 2015

Dolutegravir + Rilpivirine (Malbec) Switch Study (DORISS)

Arms	
Experimental: Arm 1 (intervention)	Active Comparator: Arm 2 (control)
DTG 50 mg/d + RPV 25 mg/d qd orally (intake during a meal)	**Continuation of existing HAART at the time of randomization**

Treatment with suppressive **triple HAART (2 NRTI + either 1 PI/r, or 1 NNRTI, or INI),** unchanged for > 6 months, Intra-class substitution within past 6 months is not considered as a treatment change.
HAART in Patients With Plasma HIV RNA ≤ 50 Copies/mL for at Least 2 Years

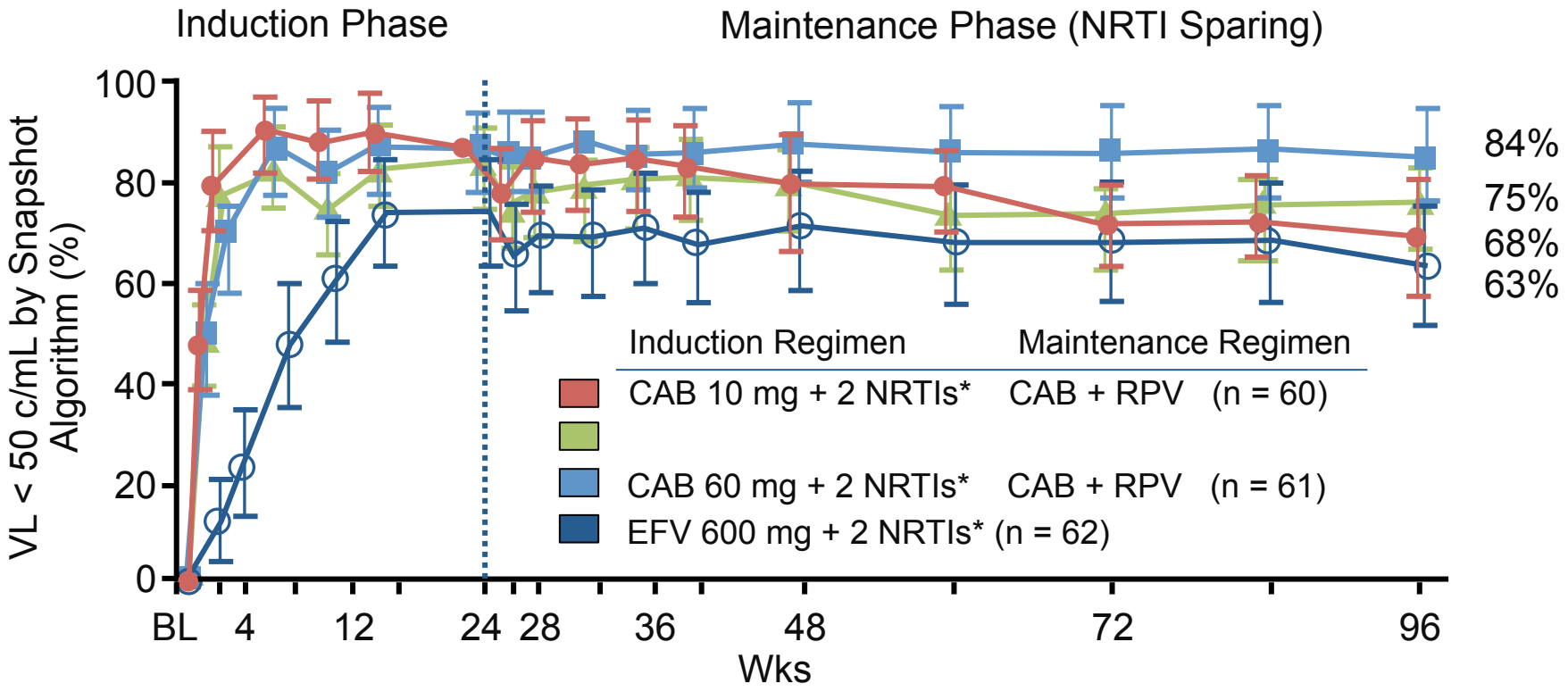
Primary Outcome Measures:

Pilot phase: Percentage of Pts with HIV-RNA/ml ≤ 50 copies from Day 0 to W16
Designated as safety issue

Non-inferiority phase: Percentage of Pts with HIV RNA maintained ≤ 50 copies/mL throughout 24 weeks
Designated as safety issue

ClinicalTrials.gov Identifier: NCT02069834
Sponsor: Nantes University Hospital

LATTE: NRTI-Sparing Maintenance With Cabotegravir + Rilpivirine



- 6 pts in CAB arms with PDVF at Wk 96; 4 additional pts since Wk 48

Margolis D, et al. CROI 2015. Abstract 554LB.

In the Pipeline

- DRV/COBI/TAF/FTC: STR
- Doravirine[1]: NNRTI
  - Active against K103N, Y181C
- Ibalizumab[2]: entry inhibitor
  - Monoclonal antibody binds CD4
  - Being studied for treatment and prevention
- BMS-663068[3]: entry inhibitor
  - Blocks attachment by binding to gp120
- BMS 955176[4]: maturation inhibitor
  - Disrupts processing of gag protein
  - Trial in naive pts planned

1. Morales-Ramirez J, et al. CROI 2014. Abstract 92LB 2. Ernst J, et al. ICAAC 2014. Abstract H-995.
3. Lalezari J, et al. CROI 2014. Abstract 86. 4. Hwang C, et al. CROI 2015. Abstract 114LB.

What to Start?

- **No comorbidities or interacting medications**
  - DTG/ABC/3TC
  - EVG/COBI/FTC/TDF
- **High cardiac risk**
  - RAL + TDF/FTC
  - DTG + TDF/FTC
  - EVG/COBI/TDF/FTC
- **Kidney disease (low cardiac risk)**
  - DTG/ABC/3TC (expect fall in eGFR)
  - RAL + ABC/3TC
- **RTV or COBI interactions**
  - DTG/ABC/3TC
  - DTG + TDF/FTC
  - RAL + TDF/FTC

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How to Choose?

- **Adverse effects or desire for simplification on a suppressive regimen**
  - DTG/ABC/3TC (no switch data yet, but why not?)
  - EVG/COBI/TDF/FTC
  - RPV/TDF/FTC
- **Known or predicted nonadherence**
  - DRV/COBI + TDF/FTC
  - ATV/COBI + TDF/FTC
  - DTG/ABC/3TC (?)
- **Likelihood of pregnancy**
  - ATV/r + TDF/FTC
- **HCV coinfection**
  - RAL + TDF/FTC
  - DTG/ABC/3TC (or TDF/FTC)

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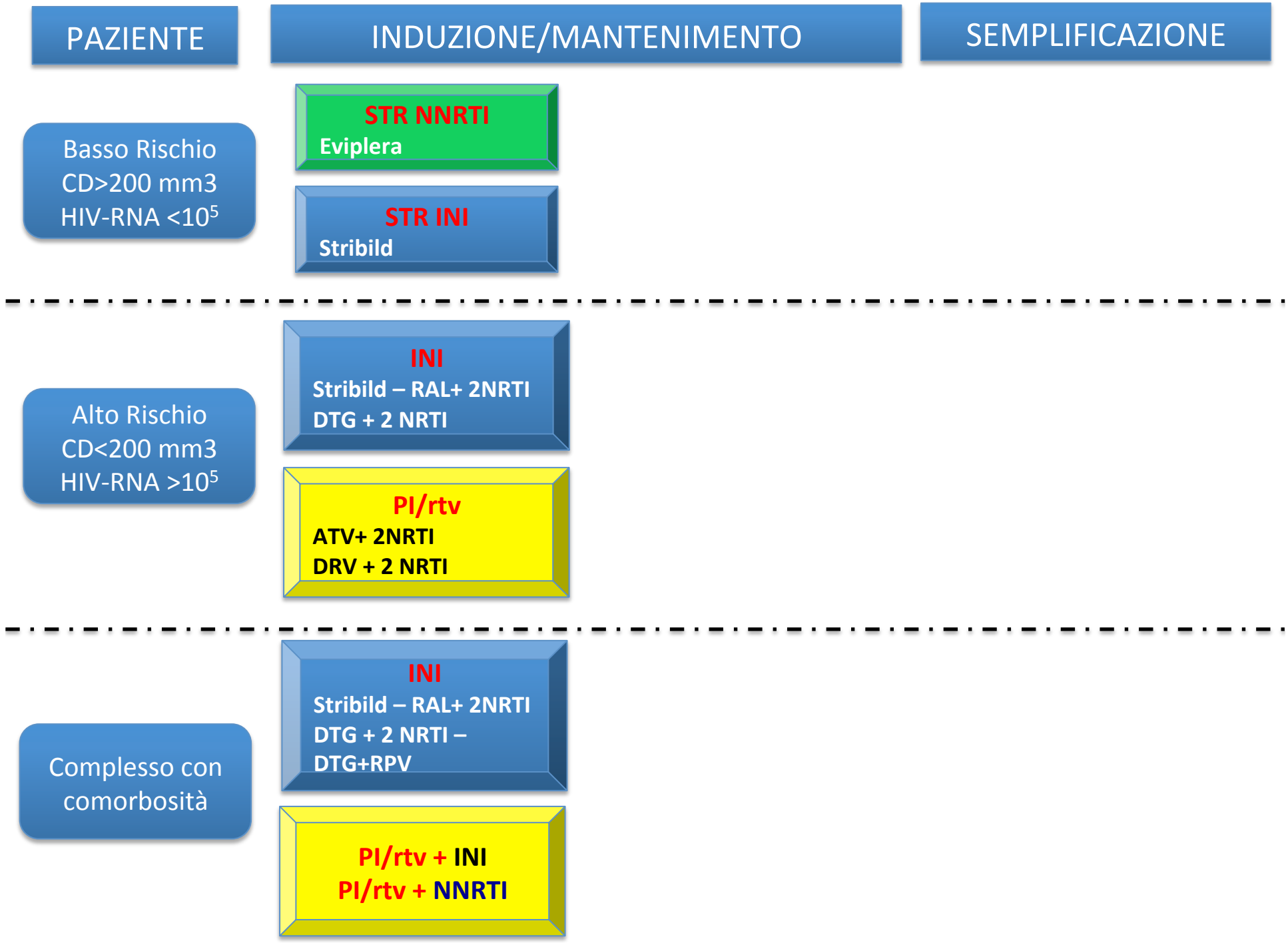
PAZIENTE
INDUZIONE/MANTENIMENTO
SEMPLIFICAZIONE
Basso Rischio
CD>200 mm3
HIV-RNA <10^5
STR NNRTI
Eviplera
STR INI
Stribild
Alto Rischio
CD<200 mm3
HIV-RNA >10^5
INI
Stribild – RAL+ 2NRTI
DTG + 2 NRTI
PI/rtv
ATV+ 2NRTI
DRV + 2 NRTI
Complesso con comorbosità
INI
Stribild – RAL+ 2NRTI
DTG + 2 NRTI –
DTG+RPV
PI/rtv + INI
PI/rtv + NNRTI


PAZIENTE
INDUZIONE/MANTENIMENTO
SEMPLIFICAZIONE
Basso Rischio
CD>200 mm3
HIV-RNA <10^5
STR NNRTI
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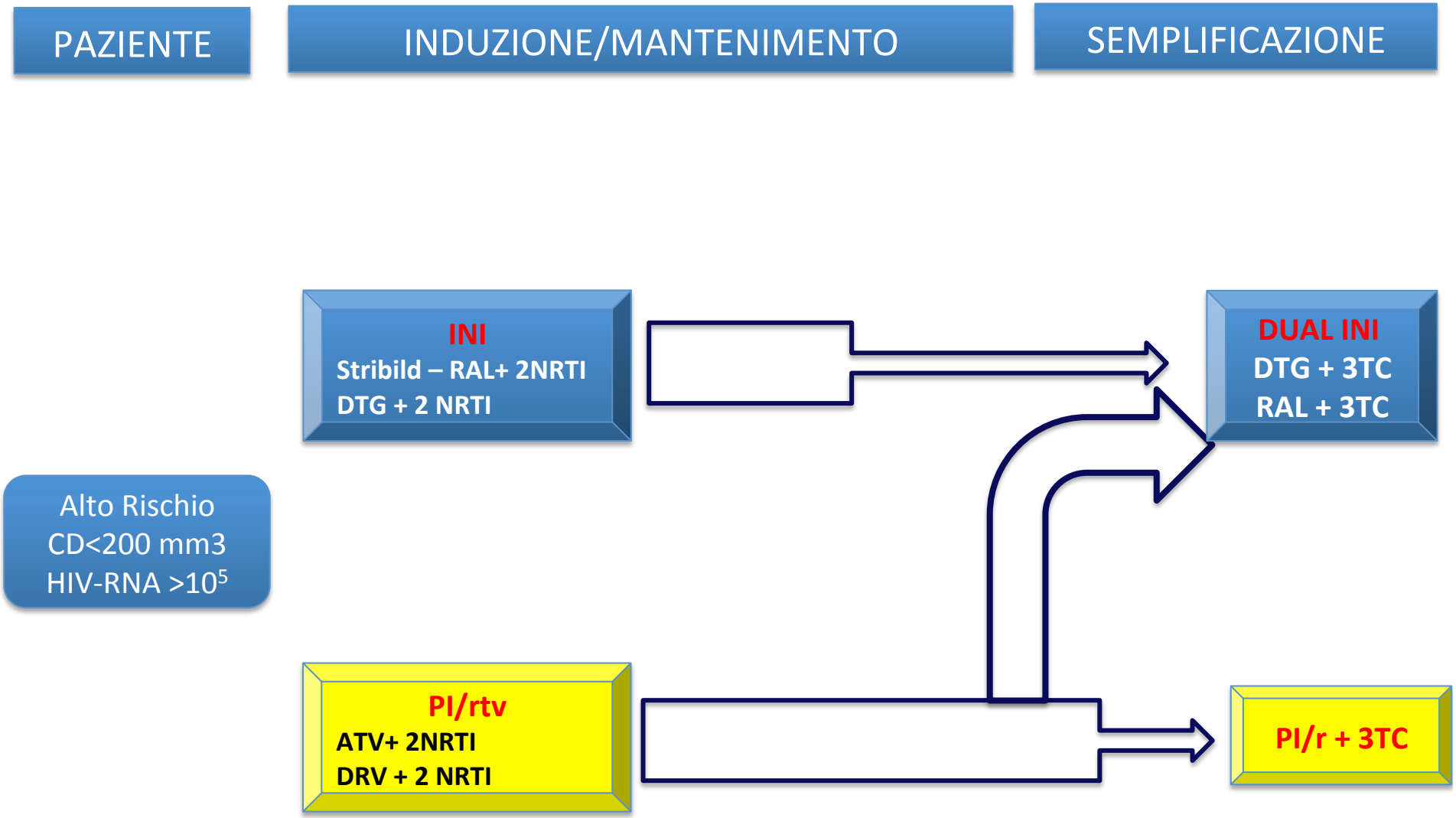
STR INI
Stribild
DUAL INI
RAL+3TC – DTG+3TC
PI/r + 3TC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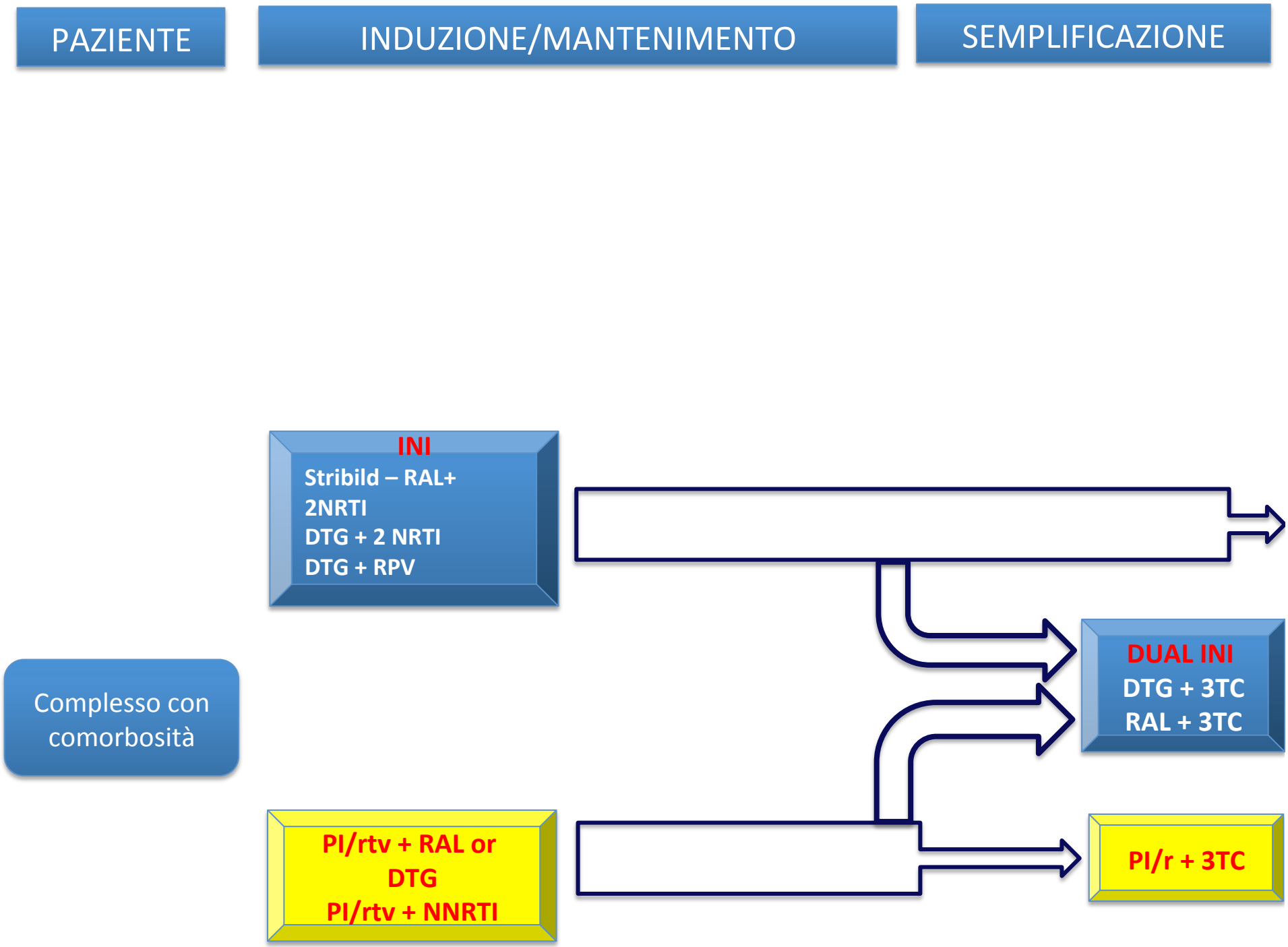
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Complesso con comorbosità
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Stribild – RAL+
2NRTI
DTG + 2 NRTI
DTG + RPV
PI/rtv + RAL or
DTG
PI/rtv + NNRTI
DUAL INI
DTG + 3TC
RAL + 3TC
PI/r + 3TC

Seminario Nadir 2015 - Iniziativa resa possibile grazie al supporto di ViiV Healthcare

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