EACS
European
AIDS
Clinical
Society

Pr Christine Katlama

Maladies Infectieuses et Tropicales
APHP Hôpital Pitié-Salpêtrière
Paris, France

Switching Suppressive Therapy 2015

- HIV suppression is the rule with effective safe well tolerated ART
- Survival largely improved
- Better ARV drugs
- Simplified treatment
- Transmission reduced

- No cure No vaccine
- Life long therapy
- Persistent inflammation/ activation
- Drug toxicity
- Comorbidities; aging
- Cost and implementation

VIH: a success story of research yet not quite achieved

ART is a life long therapy thoughout decades of life

ART has to be adjusted to different life events

Outline

- Why switching a suppressive therapy therapy ?
- Which drug to switch ?
- How to switch ?
- Future switch strategies in suppressed patients

Antiretroviral drugs : 2015

NRTI	NNRTI	Protease Inhibitors	Integrase Inhibitors	CCR5 Inhibitors
TDF TDF/FTC ABC ABC/3TC 3TC/FTC	Nevirapine Efavirenz[6] Rilpivirine Etravirine	Lopinavir Atazanavir Darunavir	Raltegravir Elvitegravir Dolutegravir	Maraviroc

Single tablet regimen

TDF/FTC/EFV : Atripla
TDF/FTC/RPV : Eviplera
TDF/FTC/EVG/c : Stribild
ABC/3TC/DTG : Triumecq

- Despite increased potency and robustness of ARV
- Standard ART is still a triple drug approach

→ Need for innovation

Why should we change a suppressive ART ?

Reasons to switch ART

- Simplification
- Tolerability

  Prevention of toxicity
- Context

  aging comorbidities

  bone , kidney, CV risk

  pregnancy
- Resistance

  eliminating resistant drug
- Reduce drug burden

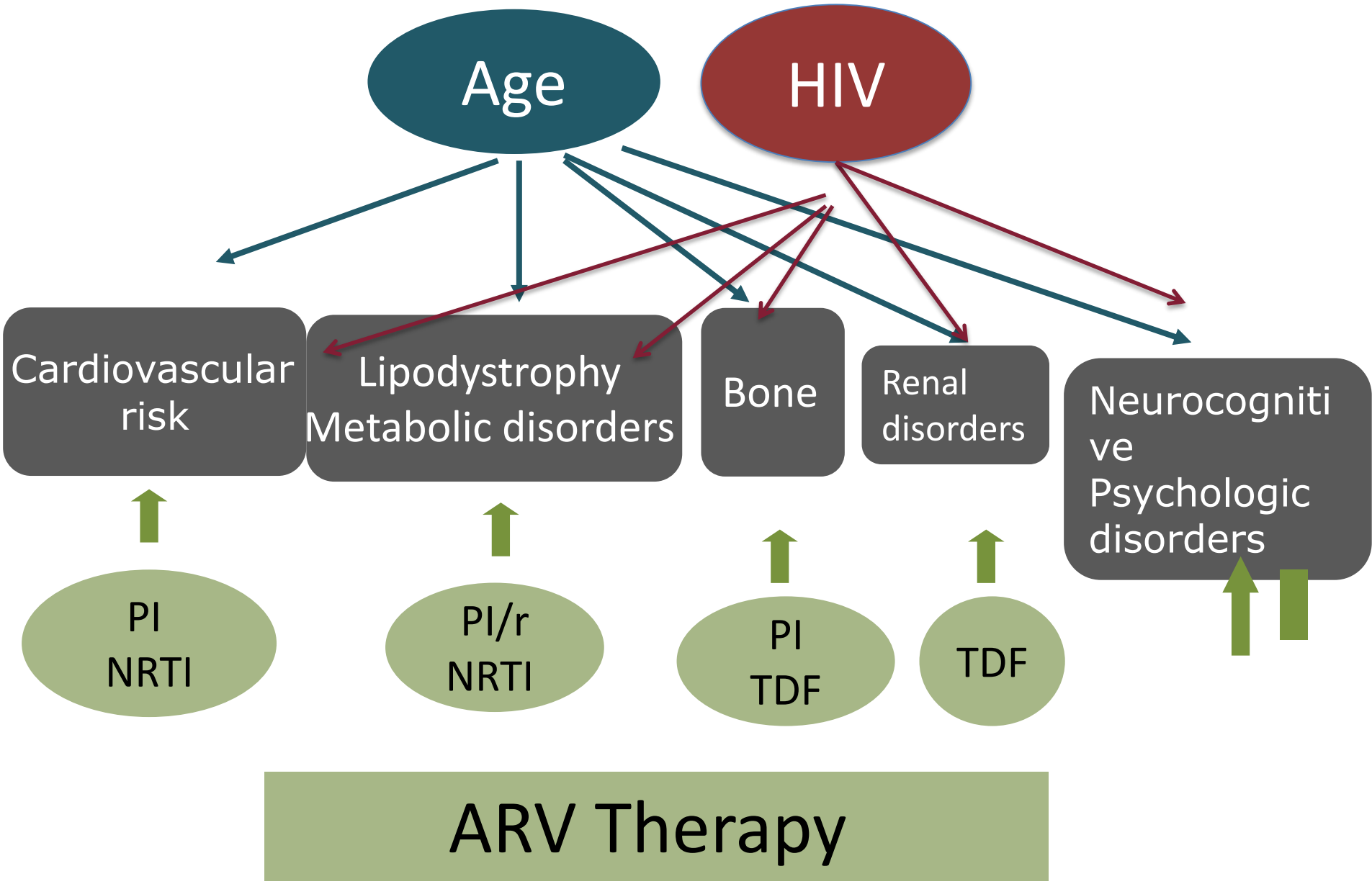
  Preserve option

  adjust ART to HIV disease

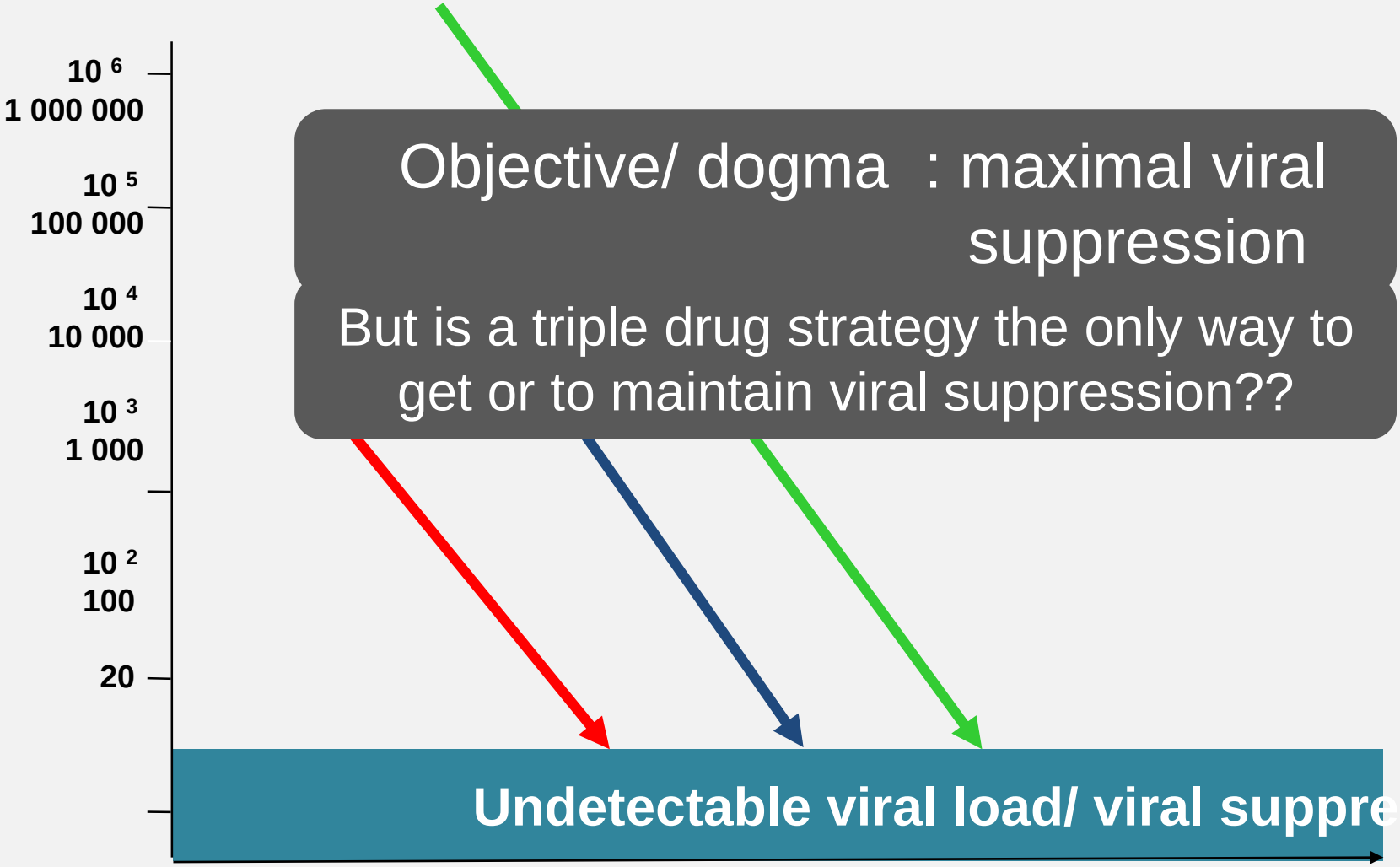
Reasons for stress to change a suppressive ART

- New drug : new toxicity?
- Unmask archived resistance
- Drug drug interactions
- FDC usually 3-4 drugs combo
- Cost

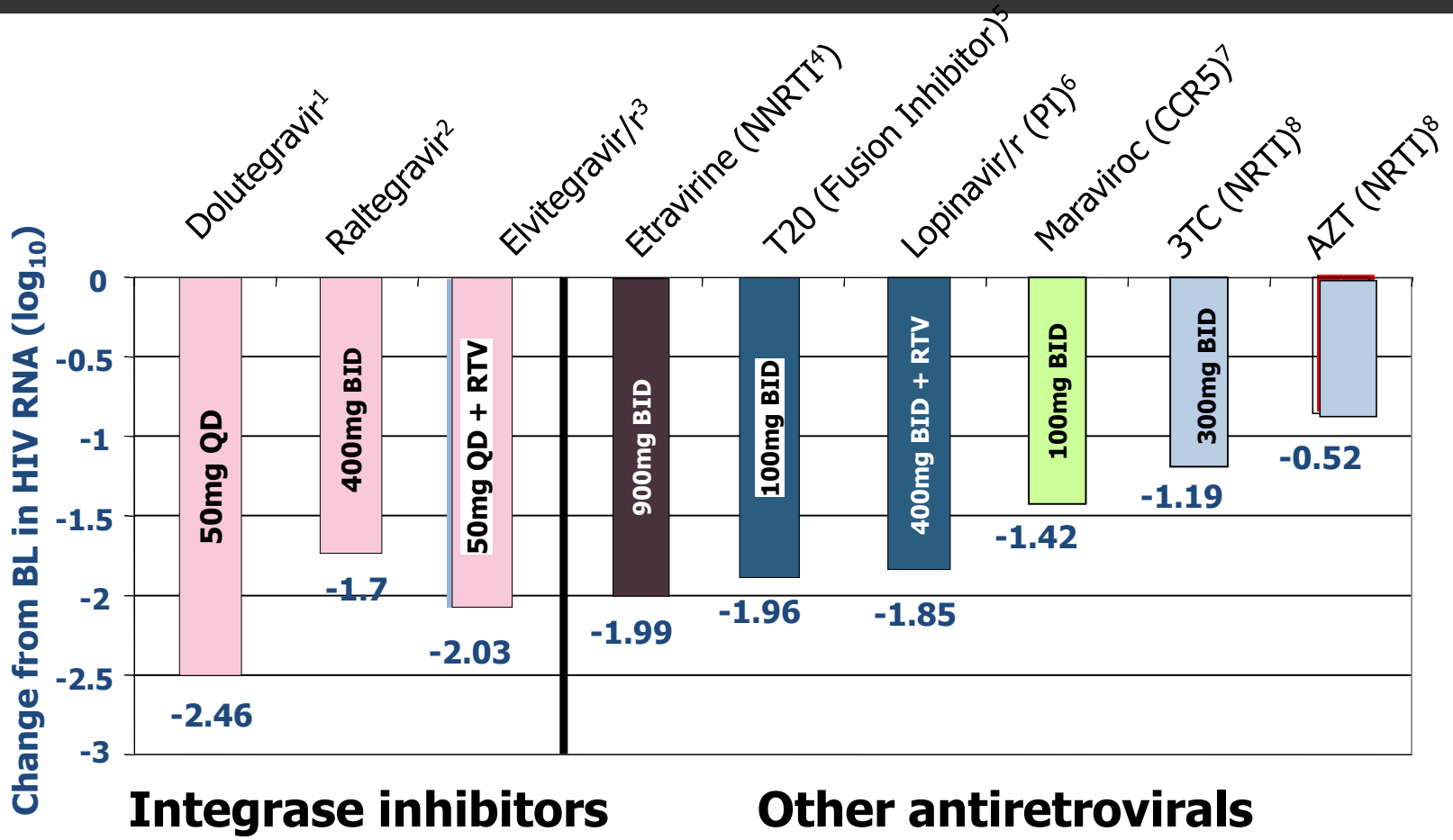
Interactions of age , HIV , ARV drugs



Goal of Antiretroviral Therapy



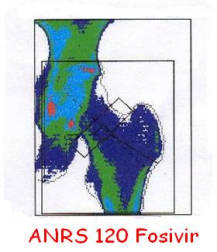
Antiretroviral potency have increased over time



1. Lalezari J. 5th IAS 2009, Cape Town, abstract TUAB105.
2. DeJesus E. J Acquir Immune Defic Syndr 2006 ; 43:1-5.
3. Markowitz et al. JAIDS Volume 43(5) 15 December 2006 pp 509-515.
4. Sankatsing et al. AIDS 2003, 17:2623–2627.
5. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
6. Murphy RL. AIDS 2001;15:F1-F9.
7. Fätkenheuer G et al. Nat Med 2005 Nov; 11:1170-1172.
8. Eron JJ, N Engl J Med 1995, 333:1662-1669.

Nucleosides analogues may not be optimal in patients with long history of NRTI containing regimen

- Aging patients often cumulates a long past history of non suppressive ART regimen with NRTI and thymidine analogues
- Even though TDF/ABC has replaced D4T or AZT , persists in a much lesser extent a degree of mitochondrial toxicity
- Mitochondrial toxicity , a feature of NRTI , limits cell oxygenation



Risk at 10 years of major osteoporotic fracture in HIV infected male

	40-50 ans	50-60 ans	60-70 ans
Screening Fosivir ANRS 120	2.9 IQR 2.4-3.3 n=52	3.0 IQR=2.8-4.0 n=30	4.7 IQR=4.1-6.3 n=14
General Population		1.5	2.9

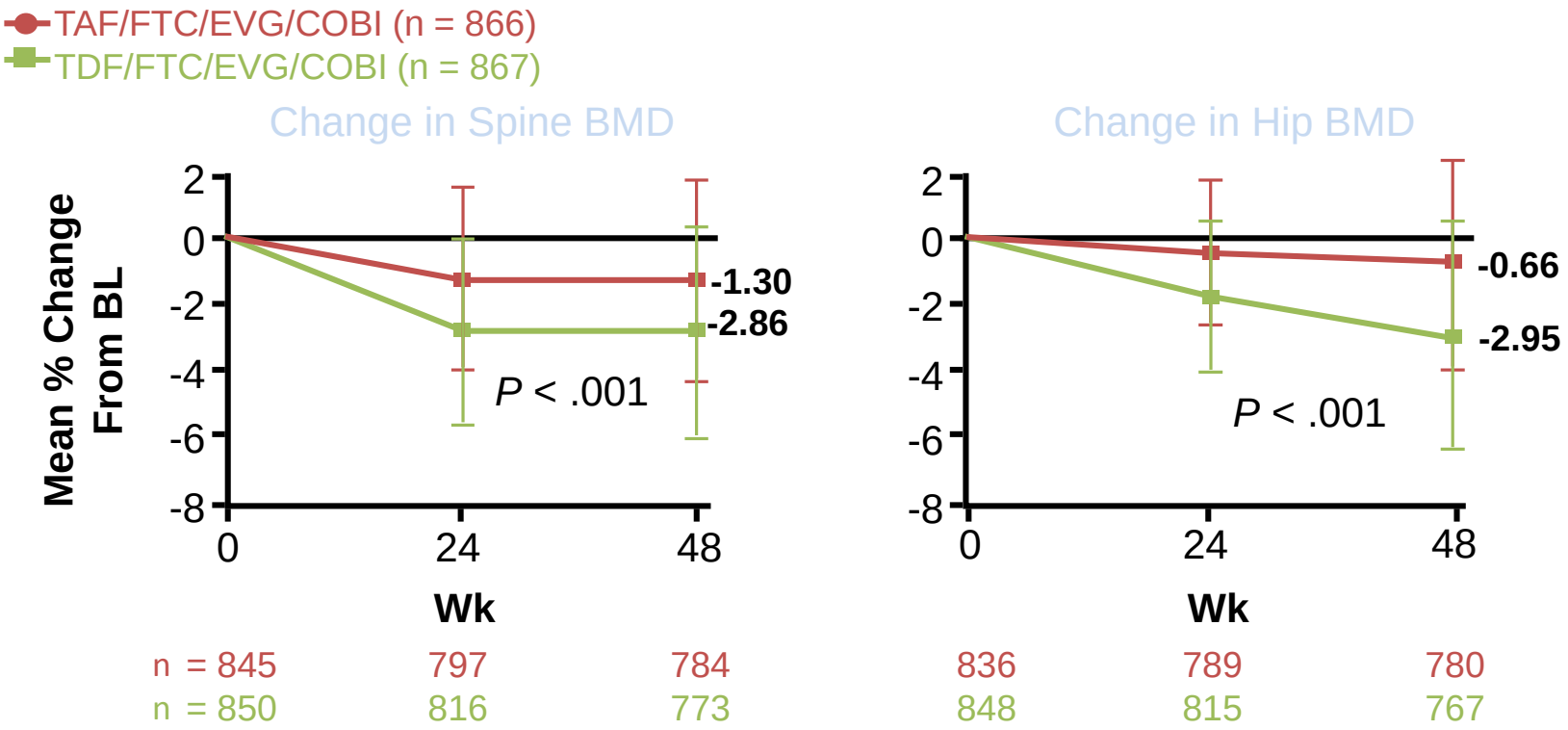
Factors associated to a low bone mineral density :

- Aging, low BMI
- PI, Tenofovir
- Low nadir CD4

Mary-Krause M et al, J clin Dens, 2012
Couris CM et al, Osteoporos Int, 2012

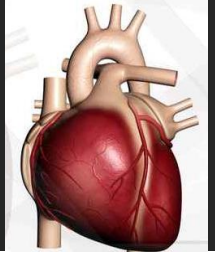
TAF vs TDF Studies in naïve patients 104/111: Smaller decline in hip and spine BMD with TAF

- **Significantly smaller decline in hip and spine BMD with TAF**



Higher lipid levels with TAF, but TC:HDL-C ratio same as TDF[1]

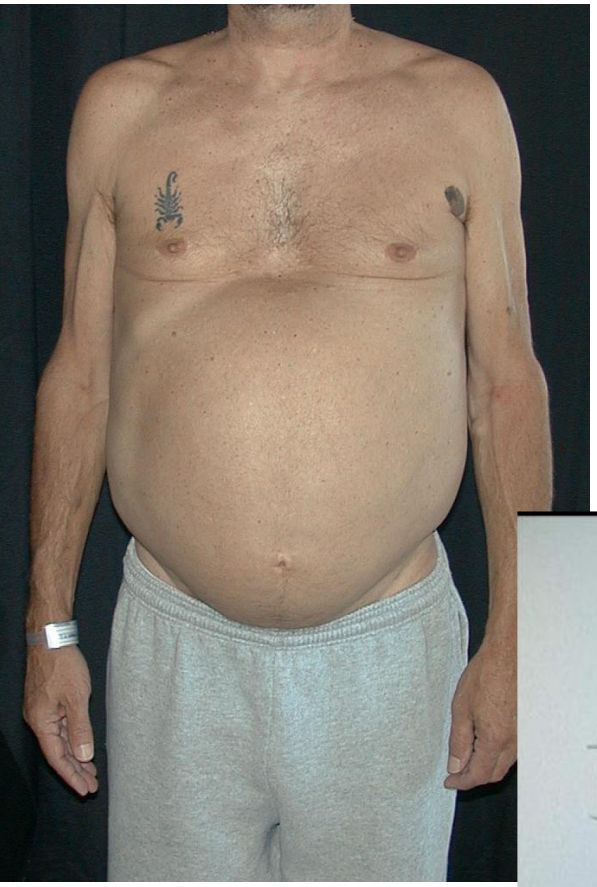
Sax P, et al. CROI 2015. Abstract 143. Reproduced with permission.

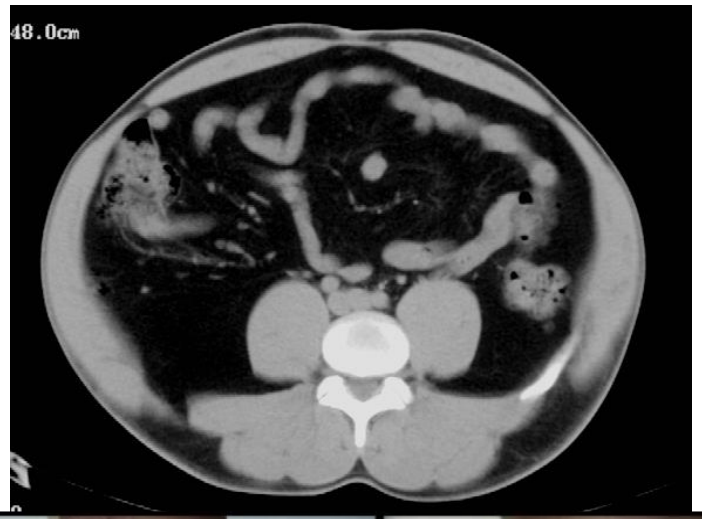


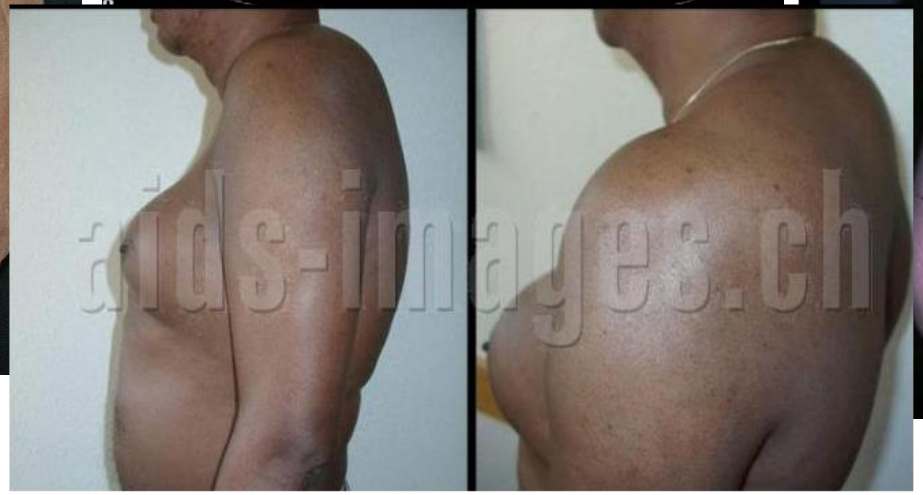
PIs increase cardio-vascular risk *independantly of the lipids effect*

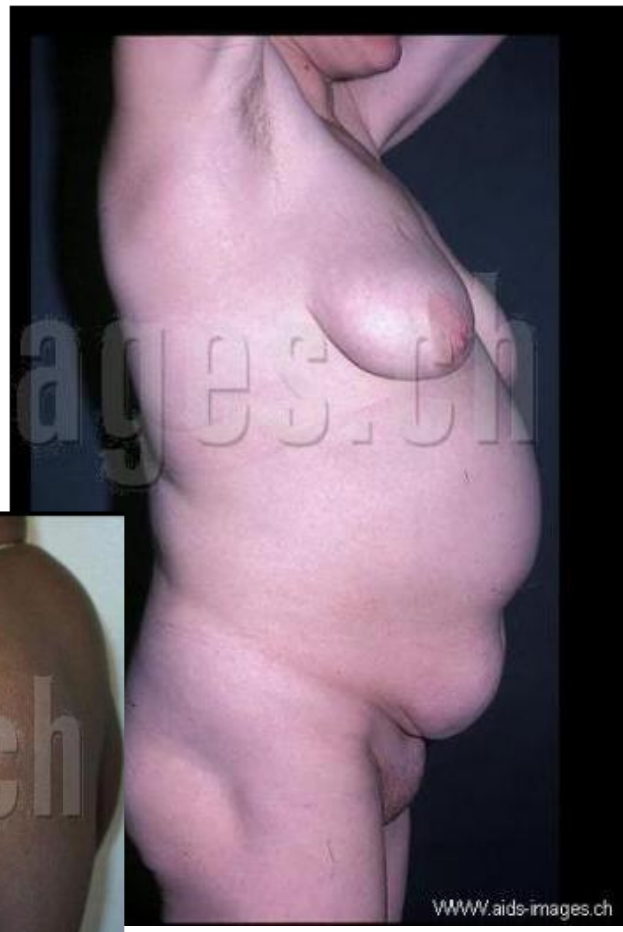
Study	Risk
D:A:D NEJM 2007	1,16 (1,10-1,23) per year of exposition
FHDH ANRS CO4 Arch Int Med 2010,	1,15 (1,06-1,26) per year of exposition
Veterans NEJM 2003	1,23 (0,8-1,9) (16 mois d'exposition médiane) ->1,17 per year of exposition

Lipodystrophy increases inflammation and metabolic disorders





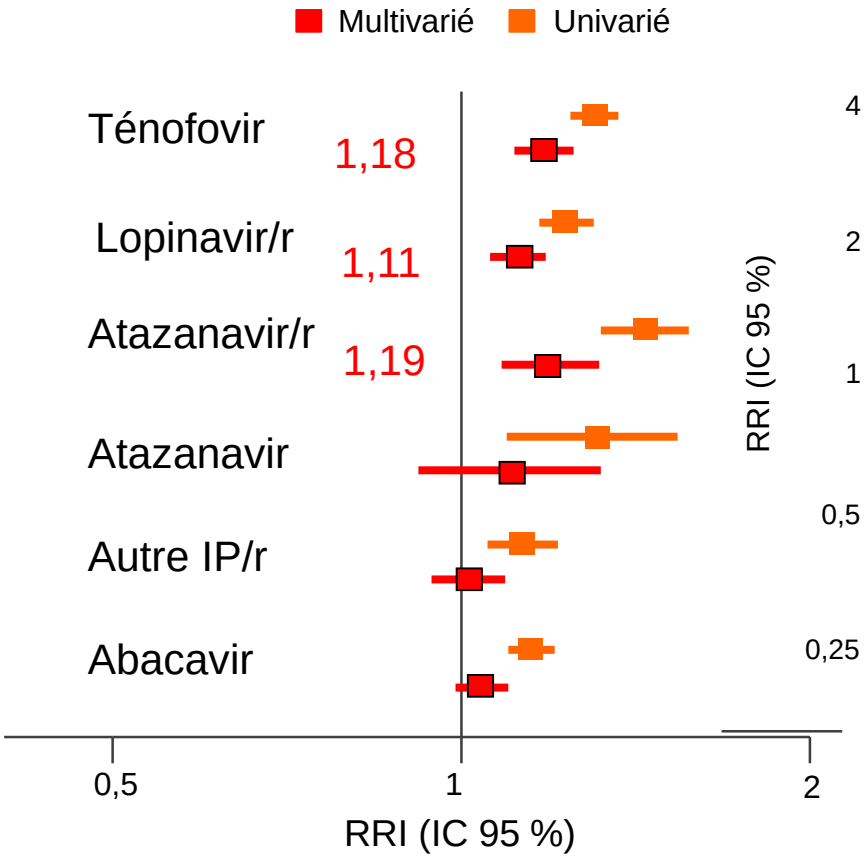


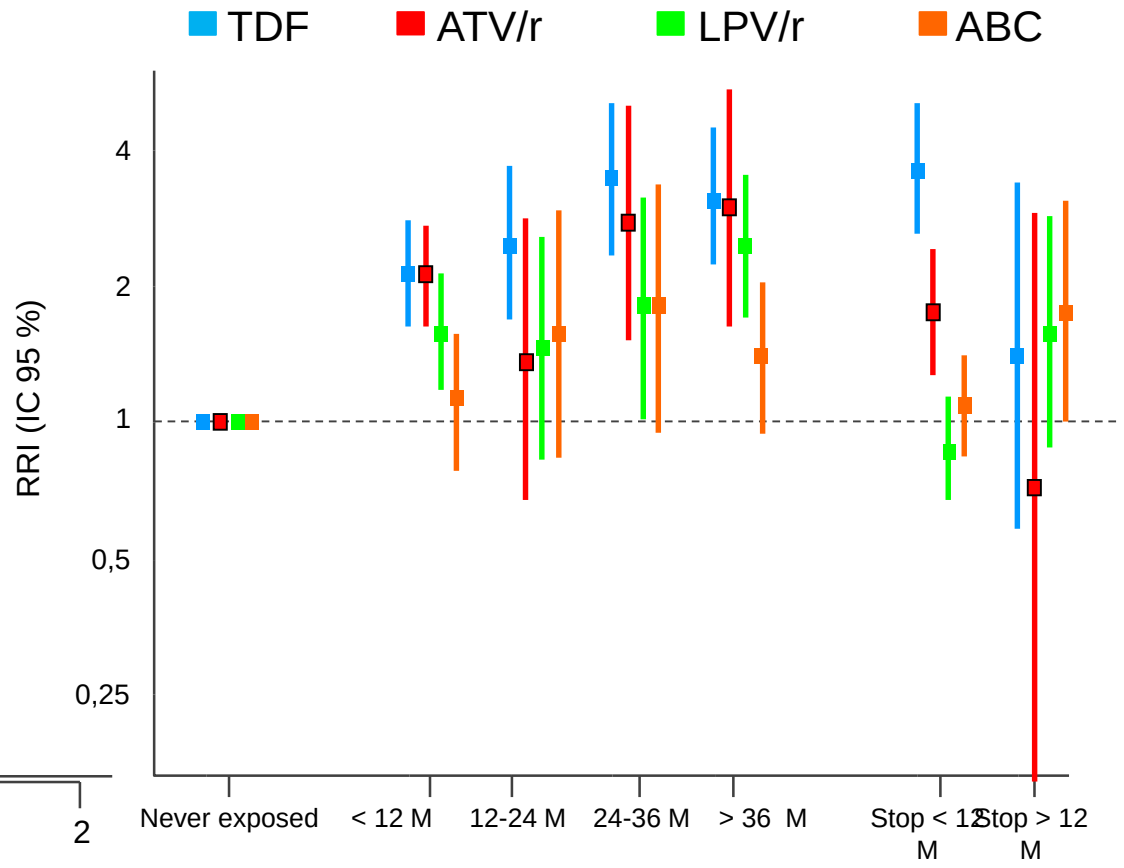


DAD : ARV exposure and renal function

22 603 patients

Passage d'un DFG > 90 à ≤ 70 ml/min

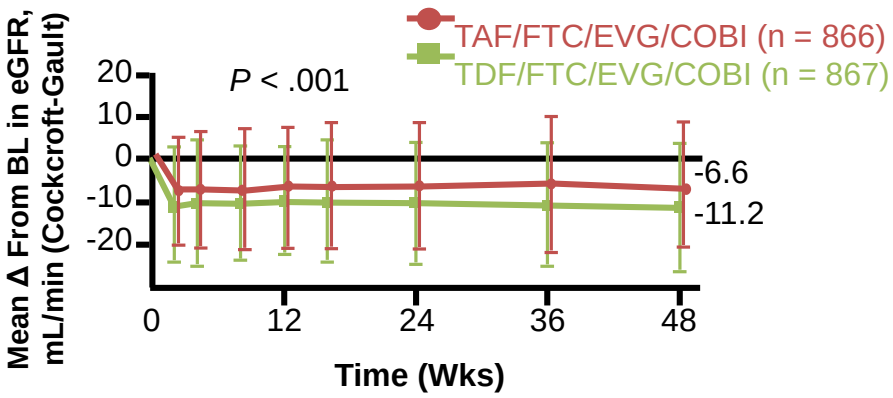




Ryom L, CROI 2012, Abs. 865

Renal Markers With TAF and TDF at Wk 48

Smaller decreases in eGFR with TAF[1]



Smaller changes in proteinuria with TAF[1]

Median % Change From BL in Urine Protein:Creatinine Ratio

Marker	TAF (n = 866)	TDF (n = 867)	*P* Value
Protein	-3	+20	< .001
Albumin	-5	+7	< .001
Retinol-binding protein	+9	+51	< .001
β_2-microglobulin	-32	+24	< .001

- In separate single-arm trial of virologically suppressed pts with eGFR 30-69 mL/min switched to open-label TAF/FTC/EVG/COBI[2]
  - 65% on TDF at BL
- At Wk 48 after switch:
  - 92% maintained virologic suppression
  - No change in eGFR
  - Reduction in proteinuria and markers of renal tubular function
  - Improvement in hip and spine BMD

mission. 2. Pozniak A, et al. CROI 2015. Abstract 795.

Antiretroviral drugs : 2015

NRTI	NNRTI	Protease Inhibitors	Integrase Inhibitors	CCR5 Inhibitors
~~TDF~~ TDF/FTC ABC ABC/3TC 3TC/FTC	Nevirapine Efavirenz[6] Rilpivirine Etravirine	~~Lopinavir~~ ~~Atazanavir~~ ~~Darunavir~~	Raltegravir Elvitegravir Dolutegravir	Maraviroc

FDC

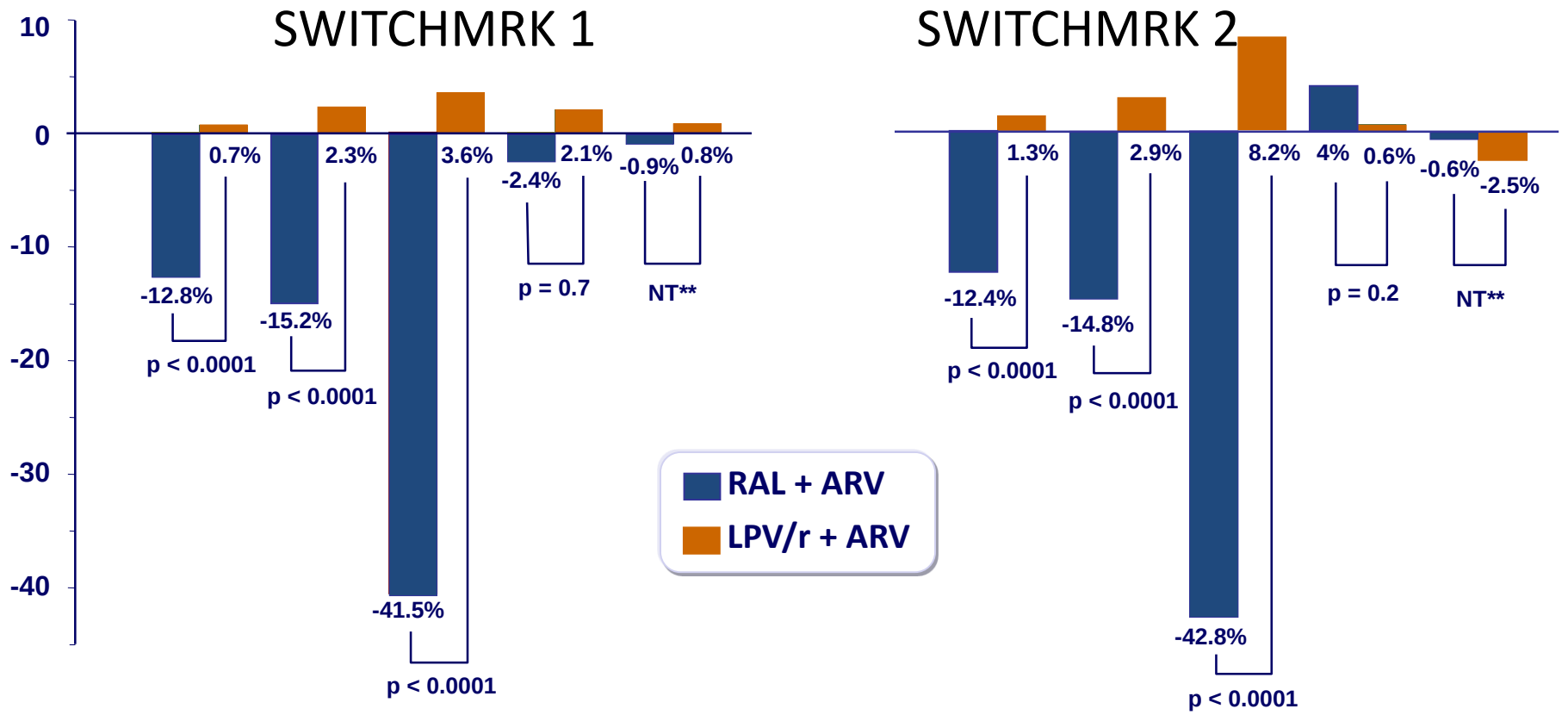
TDF/FTC/EFV : Atripla
TDF/FTC/RPV :Eviplera
TDF/FTC/EVG/c : Stribild
ABC/3TC/DTG : Triumeq

- Despite simplicity and better tolerability ART through guidelines remains a triple drug approach
- Need for innovation

Integrase Inhibitors : a key role in ART and particularly in aging population

- Fast antiviral Efficacy
- Simplicity
- Limited drug interactions : no DDI with raltegravir
- No metabolic disorders
- No fat tissue distribution
- No renal disorders : RAL; mild inc creat : DTG EVG

SWITCHMRK Study: Switch to RAL vs LPV/r changes in fasting lipids from baseline to W12



Mean (mmol/L)	Total cholesterol		Non HDL-C		Triglycerides*		LDL-C		HDL-C	
Baseline	5.6	5.3	4.3	4.1	2.1	1.8	3	2.7	1.3	1.2
W12	4.8	5.3	3.6	4.1	1.3	1.9	2.8	2.7	1.2	1.2

	Total cholesterol		Non HDL-C		Triglycerides*		LDL-C		HDL-C	
Baseline	5.6	5.5	4.3	4.2	2.4	2.5	2.7	2.7	1.2	1.2
W12	4.7	5.5	3.6	4.3	1.4	2.7	2.7	2.7	1.2	1.2

* median changes for triglycerides
** not tested

SWITCHMRK

Eron JJ, Lancet 2010;375:396-407

SPIRAL

AIDS 2010, **24**:000–000

Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study

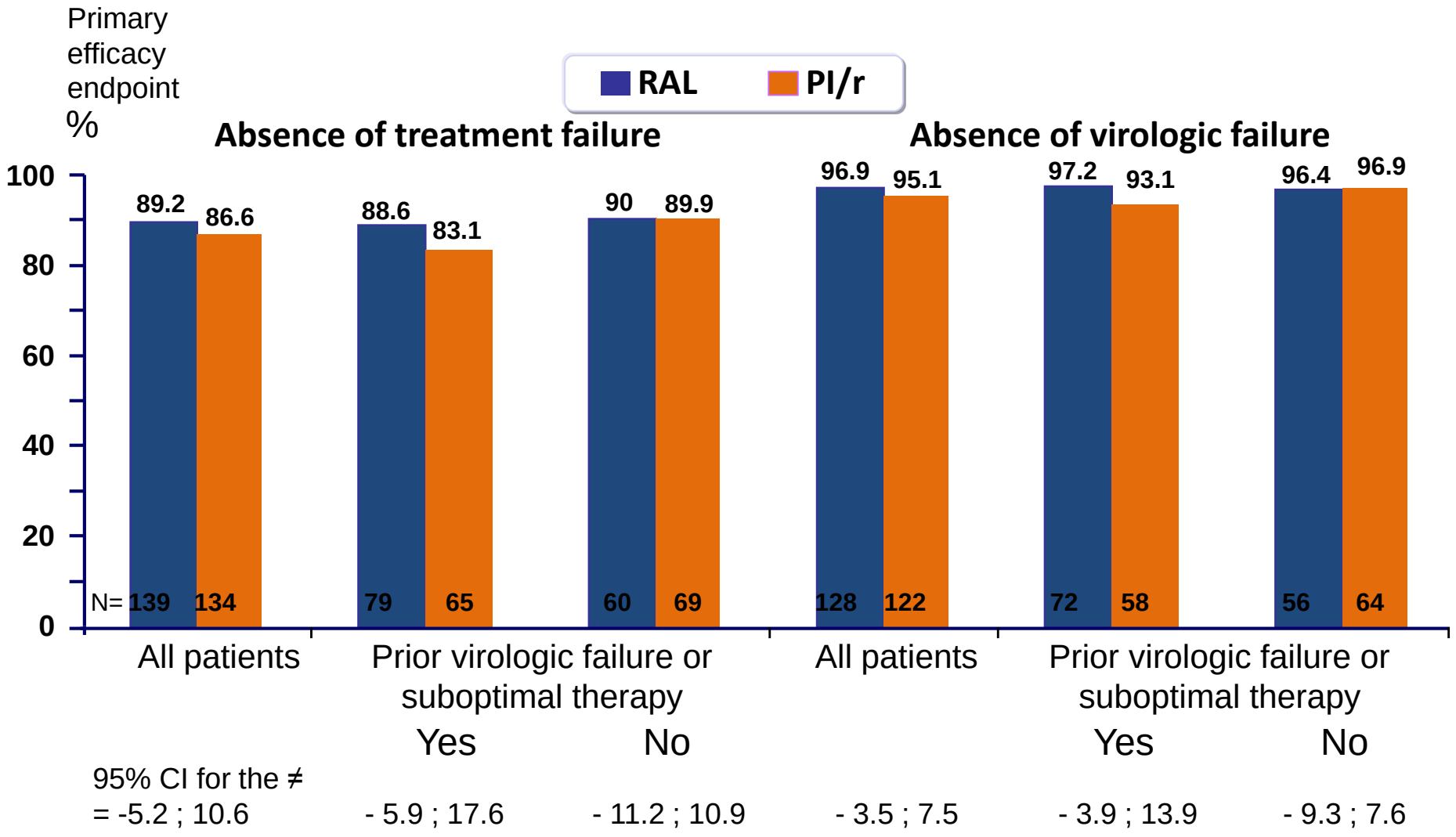
Esteban Martinez[a,*], María Larrousse[a,*], Josep M. Llibre[b], Felix Gutierrez[c], Maria Saumoy[d], Antonio Antela[e], Hernando Knobel[f], Javier Murillas[g], Juan Berenguer[h], Judit Pich[a], Ignacio Pérez[a], José M. Gatell[a], for the SPIRAL Study Group

2NRT+PI regimen VL <50 cp

Switch to raltegravir

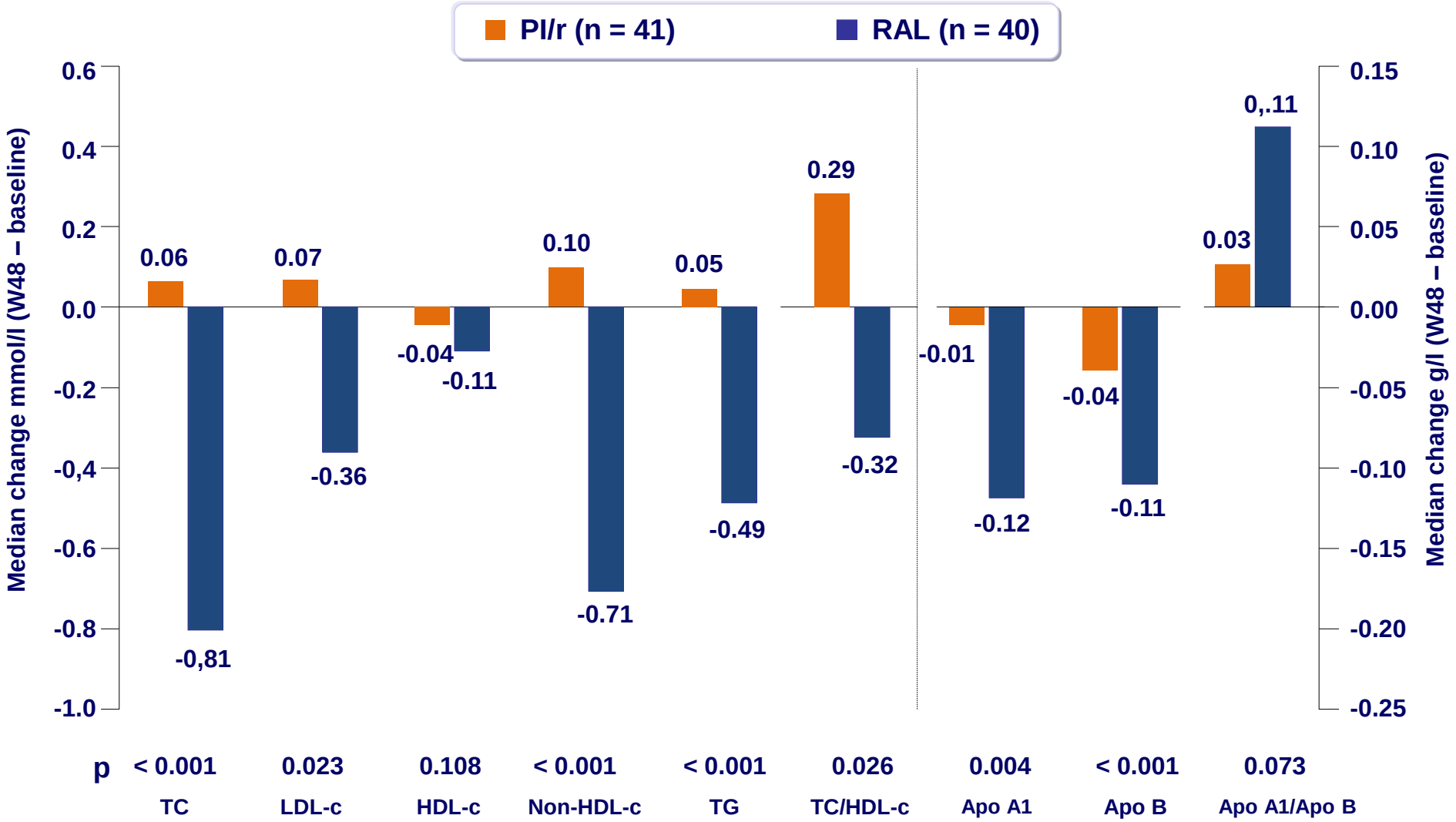
Maintain PI

SPIRAL comparative study : Switch PI/r to RAL in suppressed patients



Martinez E, AIDS 2010;24:1697-1707

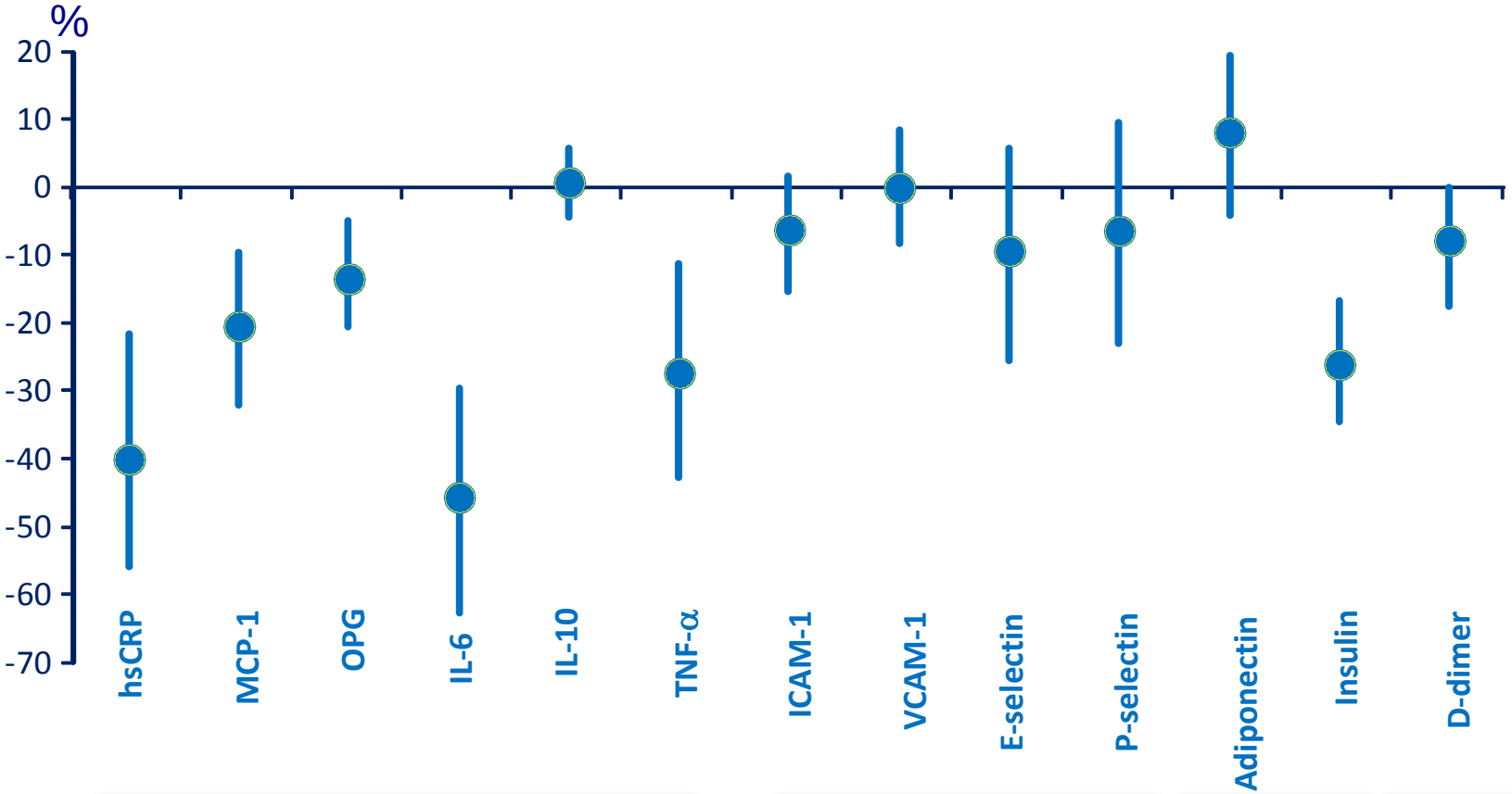
SPIRAL-MET: Switching PI to RAL
Decrease in lipids



Saumoy M, Atherosclerosis

SPIRAL Study: Switching PI/r to RAL
Decrease in cardiovascular biomarkers

Cardiovascular biomarkers: median (95% CI) difference of percent change from baseline to W48, RAL (N = 119) minus PI/r (N = 114)



Martinez E, AIDS 2012;26:2315-26

SPIRAL Study: Switching PI/r to RAL
Correlations between Δ biomarkers and Δ lipids

	Δ Triglycerides	Δ Total cholesterol	Δ LDL cholesterol	Δ HDL cholesterol
Δ hsCRP	-	-	0.2415 (p=0.0016)	-
Δ MCP-1	-	0.1608 (p=0.032)	0.1608 (p=0.032)	0.1807 (p=0.0202)
Δ Insulin	0.2842 (p=0.0001)	- 0.2125 (p=0.004)	-	-

Data expressed Spearman's rho (p)

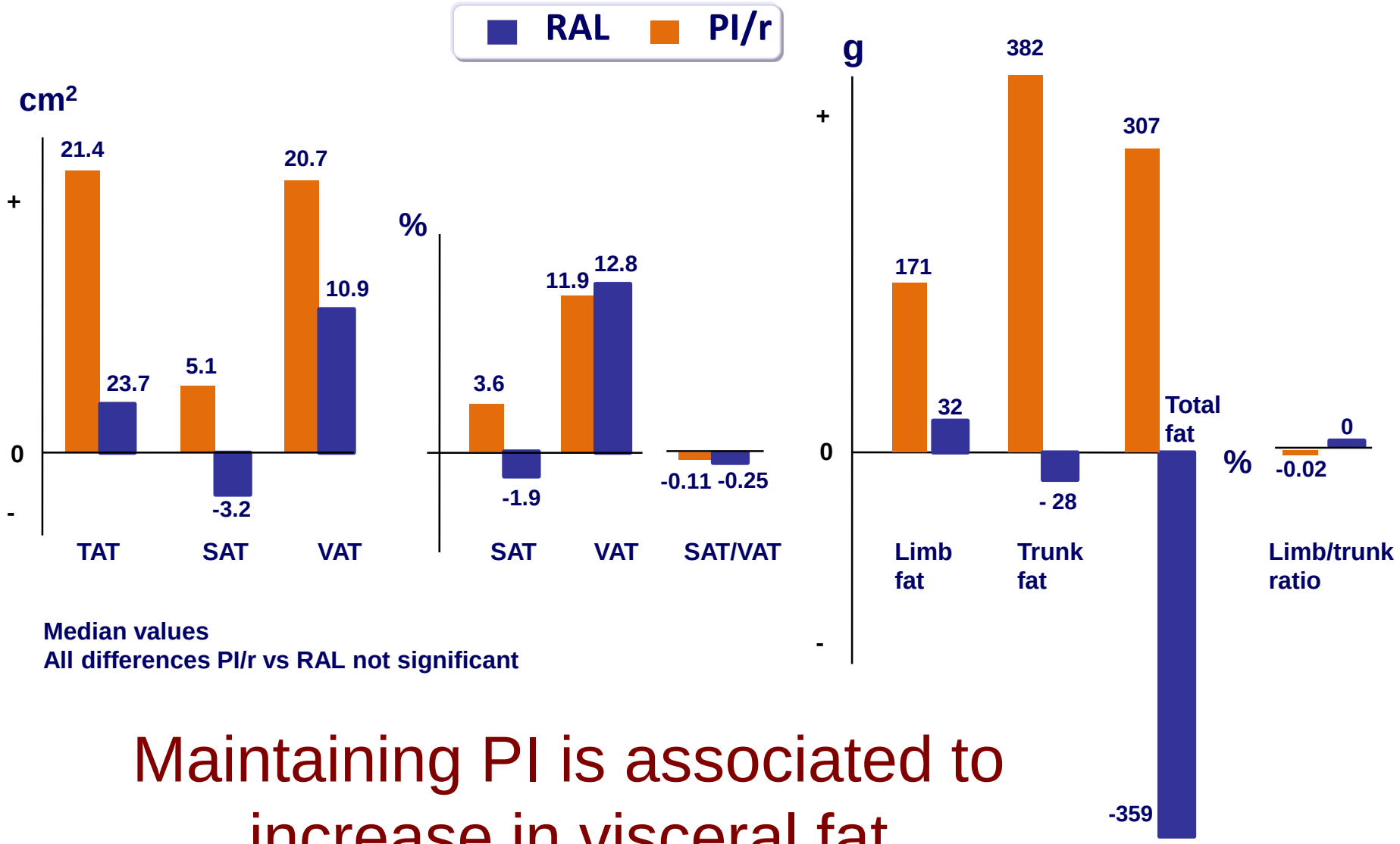
No correlations between Δ OPG, Δ IL-6, Δ IL-10, Δ TNF-alpha, Δ ICAM-1, Δ VCAM-1, Δ E-selectin, Δ P-selectin, Δ Adiponectin, Δ D-dimer and any changes in lipids

Switching from PI/r to RAL led

- not only to significant changes in plasma lipids
- but also to significant changes in several cardiovascular biomarkers associated with inflammation, insulin resistance and hypercoagulability

Martinez E, AIDS 2012;26:2315-26

SPIRAL Study: Switch PI/r to RAL
SPIRAL-LIP substudy (body composition)



Median values
All differences PI/r vs RAL not significant

Maintaining PI is associated to increase in visceral fat

Curran A, AIDS 2012;64:475-481

Switch therapy for toxicity

- **Metabolic disorder /risk** :

discontinue drugs with potential metabolic toxicities PI /EFV replace drugs with no or limited toxicity :

- integrase inhibitor INI : RAL/ DTG; EVG
- NNRTI other than EFV : NVP/ RPV/ ETV

- **Bone disorder /risk**

- discontinue TDF; replace with TAF / consider PI

- **Renal disorder :**

- discontinue TDF; consider TAF
- INI : RAL/DTG

Rules before switching therapy 1

- Explain

  - why you want to switch regimen; there must be a potential benefit

  - the possibility of going back to prior Rx in case of intolerance to new regimen in a situation of viral control , it is possible

- Check for the complete patient ART history ++++

  may be as long as 20 years ; get information on

  - preART VL and CD4

  - prior resistance testing and viral load past history

Rules before switching therapy 2

- To select a new regimen consider which drug is doing what

  ex : viral suppression on 2 NRTI+PI may be due majoritarily to PI ..

- Avoid a situation of functionnal monotherapy

  be careful with STR where the 3° agent is a drug with low genetic barrier to resistance (NNRTI or INI)

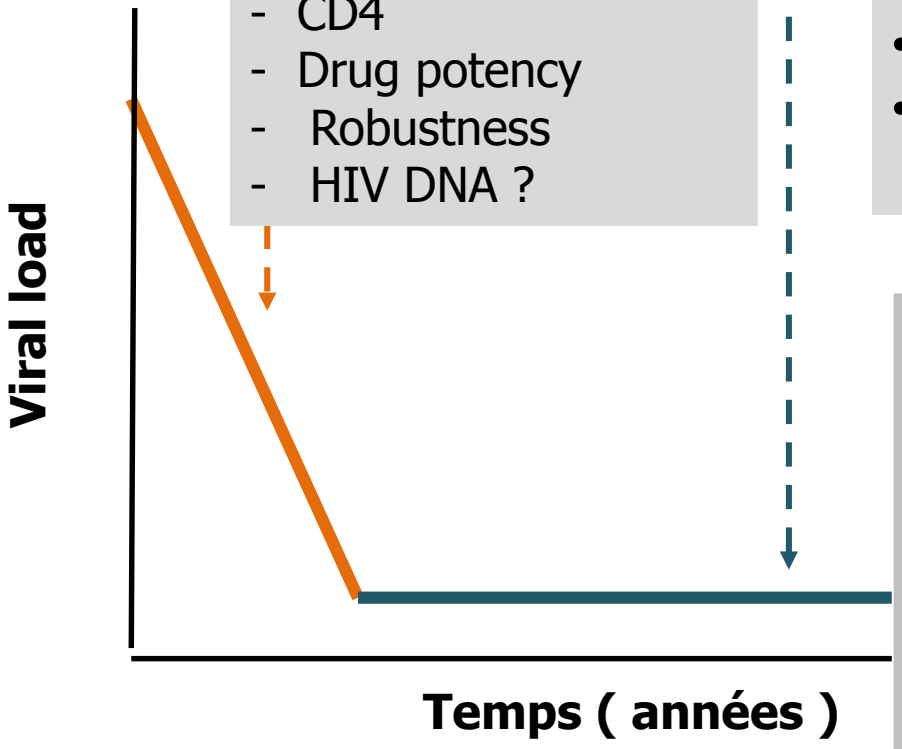
- Check for VL at W4 W12..*some failures may be slow to appear*

Can we control viral load with a non triple therapy ?

Induction

1996 HAART Triple therapy : a revolution

Nb drugs depends of
- HIV RNA
- CD4
- Drug potency
- Robustness
- HIV DNA ?



2015

- More potent
- More robust drugs
- Earlier ART with lower HIV RNA and higher CD4

Which strategies ?

- to maintain viral suppression
- with immune profile and low inflammation I
- with low reservoir
- Which predictive markers of success ?

Towards a lighter suppressive ART

Monotherapy

Dual therapies

Dose reduction

Intermittent ART

Towards a lighter suppressive ART

Monotherapy
PI

Dual therapies
PI/3TC
RAL/ETV
DTG/RPV
DTG/3TC

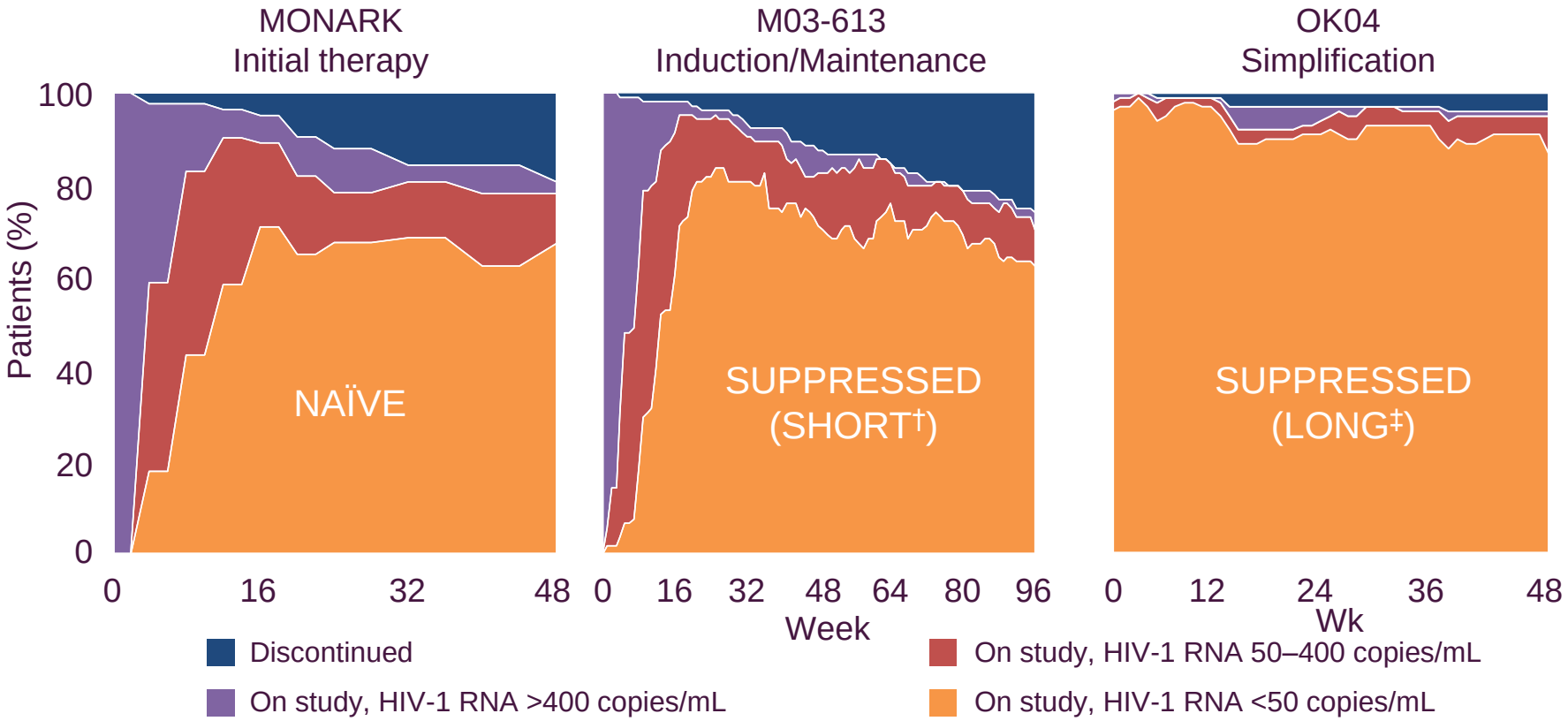
Dose reduction
ATV , DRV , EFV

Intermittent ART
Study 4D ANRS

Towards a lighter suppressive ART

Monotherapy

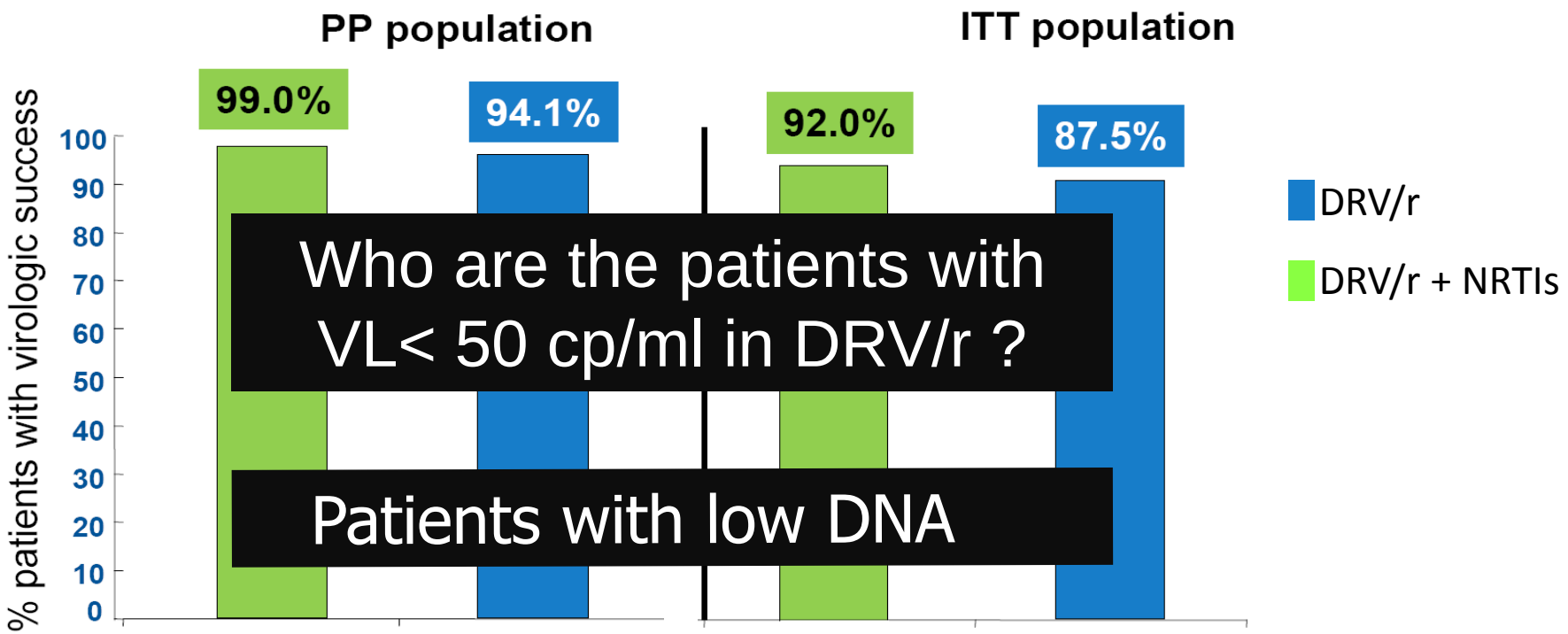
PI/r monotherapy
Monotherapy with LPV/r*[1]



*Boosted PI monotherapy is an off-label approach.
†Short-term suppression: ≤24 weeks;[2] ‡Long-term suppression: >6 months.[3]

Adapted from 1. Arribas JR, EACS 2009, Cologne, Germany. Oral Presentation; 2. Cameron WD, et al. J Infect Dis. 2008;198:2234–40; 3. Arribas JR, et al. JAIDS 2005;40:280–7.

MONOI Darunavir monotherapy in patients with suppressed viremia



Response	Difference (Lower limit CI)
Rx success (PP, n=204))	- 4.9% (- 9%)
Rx success (ITT, n=225)	- 4.5% (-11%)

MONET: Primary Efficacy Analysis: HIV RNA <50 copies/mL at Week 48

Per Protocol analysis (PP)
Primary analysis

-1.6%; lower limit 95%CI: -10.1%

Intent to Treat analysis (ITT)

-1%; lower limit 95%CI: -9.9%

HIV RNA <50 by Week 48 (%)

100
90
80
70
60
50
40
30
20
10
0

87.8%
86.2%
85.3%
84.3%

HIV DNA predictive of viral rebound

DRV/r + 2NRTI (PP) N=123
DRV/r mono (PP) N=123
DRV/r + 2NRTI (ITT) N=129
DRV/r mono (ITT) N=127

J. Arribas et al, AIDS 2010

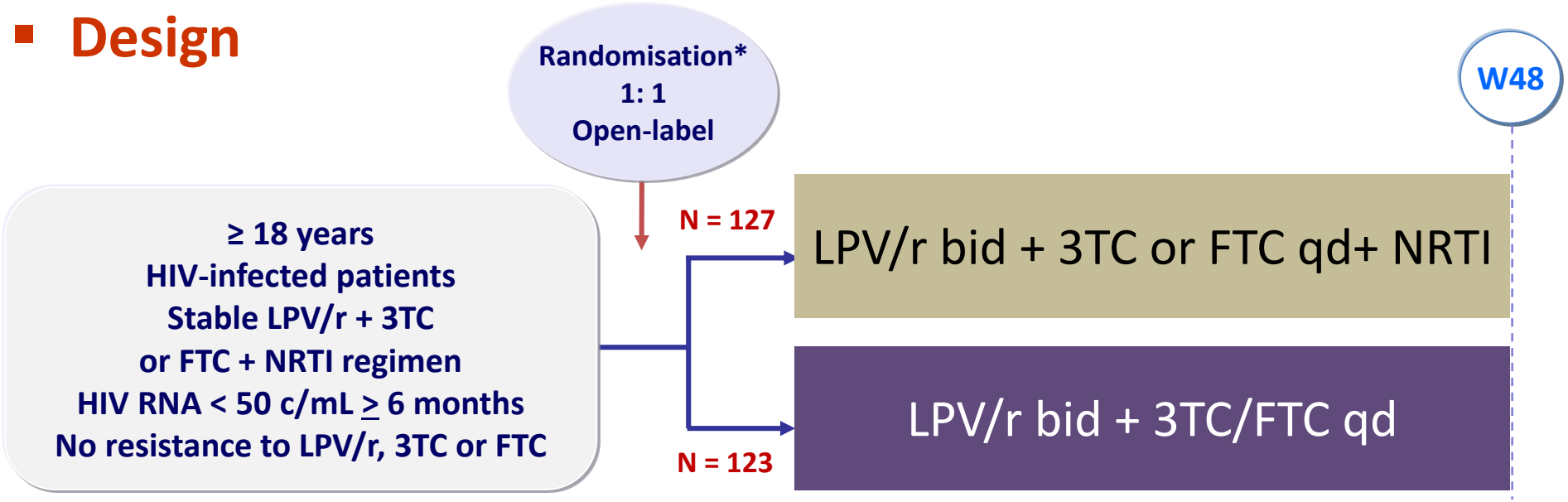
Towards a lighter suppressive ART

Dual therapies

- OLE : LPV/3TC
- SALT: ATV/FTC
- RAL/ETV

OLE Study: Switch to LPV/r + 3TC/FTC

Design



* Randomisation was stratified on time to HIV suppression (< or > 1 year) and nadir CD4 cell count (< or > 100/µl)

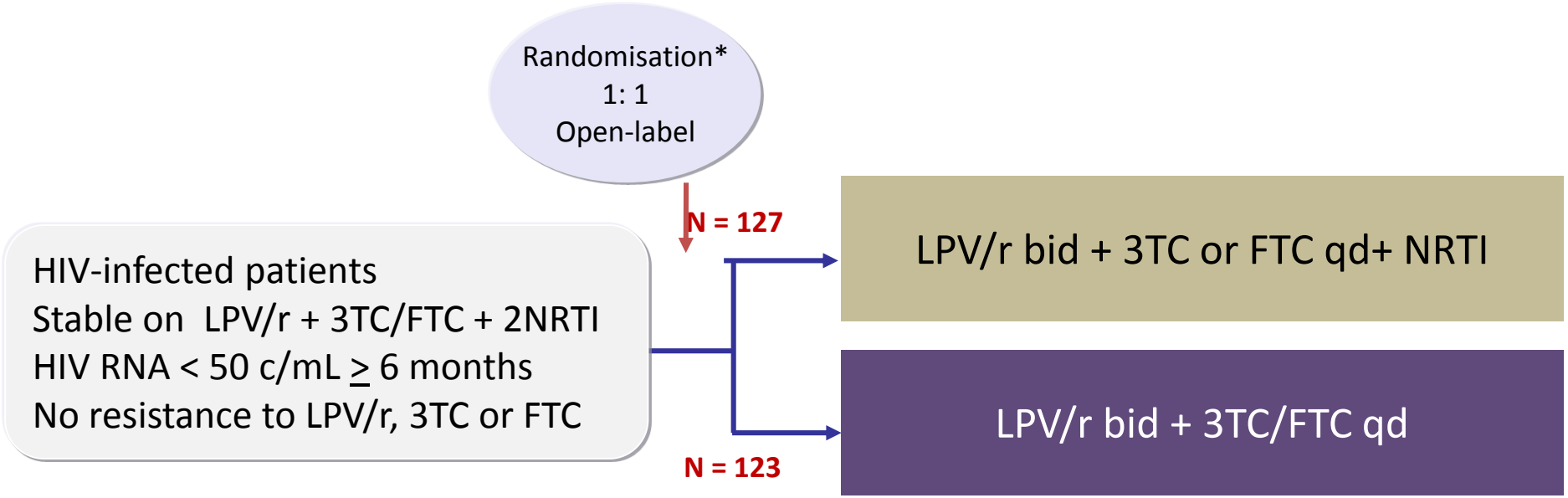
Objective

- Primary Endpoint : proportion without treatment failure at W48 (ITT)
  - Treatment failure : 2 consecutive HIV RNA ≥ 50 c/mL, death, new AIDS event, loss to follow-up, or change or permanent discontinuation of any antiretroviral drug
  - Non-inferiority of dual therapy, upper limit of the 2-sided 95% CI for the difference = 12%, 80% power

OLE

Arribas JR. Lancet Infect Dis 2015;2015;15:785-92

OLE Study: Switch to LPV/r + 3TC/FTC



Primary Endpoint : proportion without treatment failure at W48 (ITT) NI CI : 12%

Population

median age : 45 years CD4 nadir : 175 /mm3

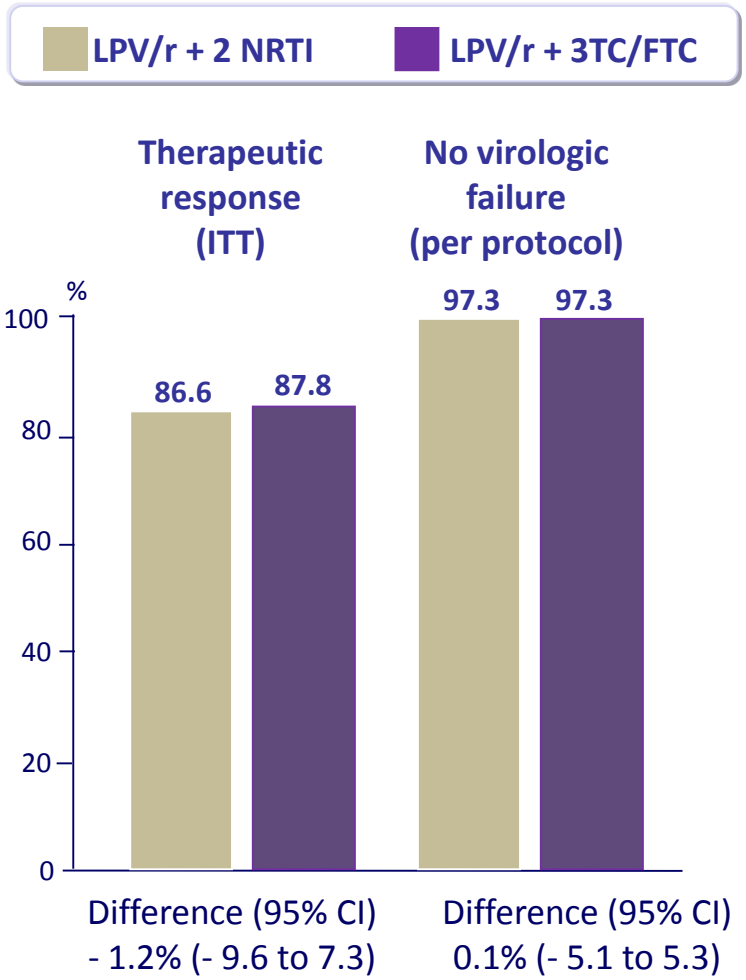
duration of viral suppression : 50 months

OLE

Arribas JR. Lancet Infect Dis 2015;2015;15:785-92

OLE Study: Switch to LPV/r + 3TC/FTC
Efficacy results at W48

HIV RNA < 50 c/mL (ITT)



Confirmed virologic failure

	LPV/r + 2 NRTI	LPV/r + 3TC/FTC
N	3	3
Analyzed for resistance	2	2
Emergence of resistance	-	1 (K103N + M184V)

Number of viral blips similar in both arms (N = 12)

Causes of therapeutic failure

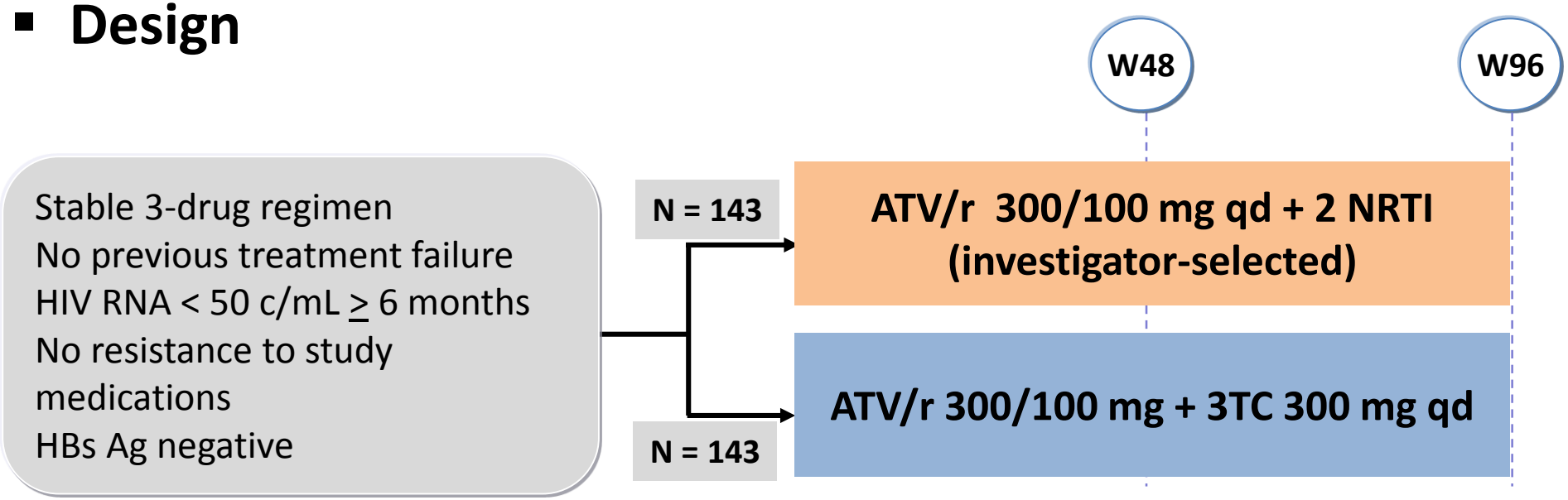
	LPV/r + 2 NRTI	LPV/r + 3TC/FTC
Adverse event	3%	1%
Virologic failure	2%	2%
Lost to follow-up	2%	3%
Other	6%	6%

OLE

Arribas JR. Lancet Infect Dis 2015;2015;15:785-92

SALT Study: switch to ATV/r + 3TC

- **Design**



* Randomisation was stratified on active HCV infection and previous treatment (NNRTI, PI/r, CCR5 antagonist, integrase inhibitor)

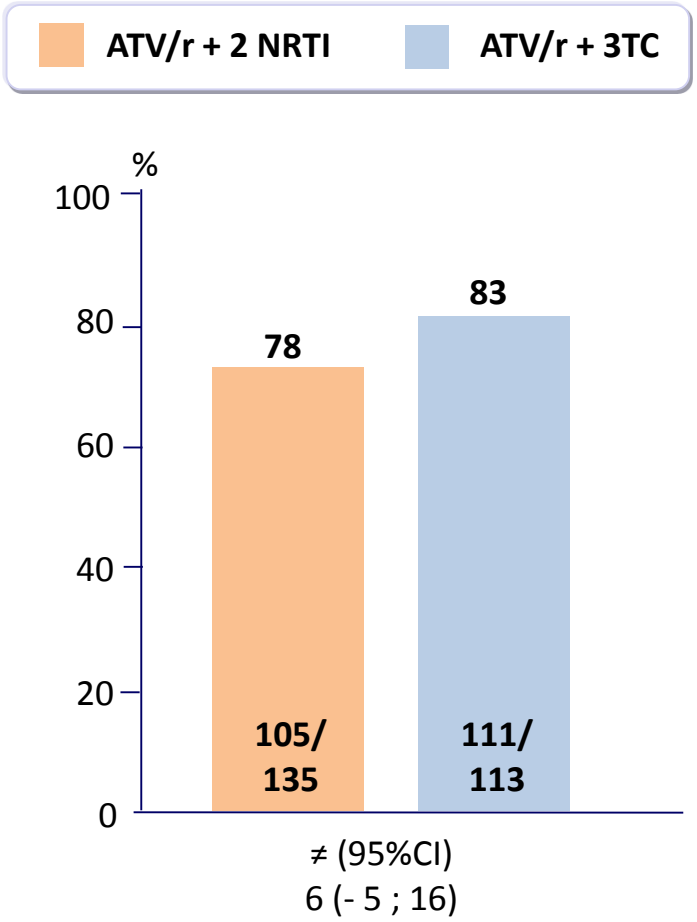
- **Objective**
  - Primary Endpoint : proportion with treatment success at W48
    - Treatment failure : treatment discontinuation or modification for any cause or confirmed virologic rebound (2 consecutive HIV RNA > 50 c/mL)
    - Non-inferiority of ATV/r + 3TC (per protocol) ; lower limit of the 95% CI for the difference = -12%

SALT

Perez-Molina JA. Lancet Infect Dis 2015;15:775-84

SALT Study: switch to ATV/r + 3TC

HIV RNA < 50 c/mL at W48 (Per protocol, TLOVR)



Confirmed virologic rebound

	ATV/r + 2 NRTI	ATV/r + 3TC
N	4	5
Emergence of resistance mutations	1 (M184V)	0

Safety

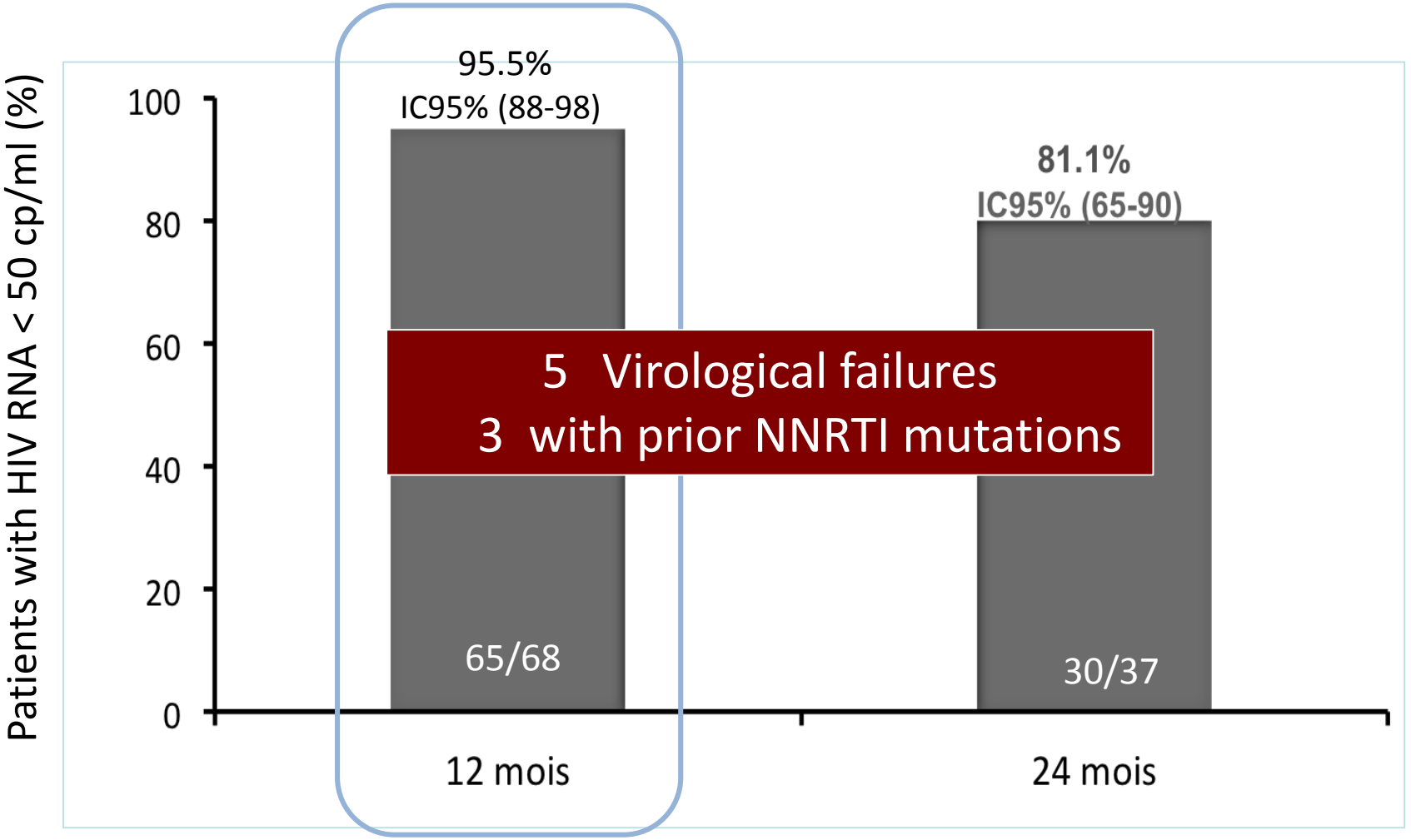
	ATV/r + 2 NRTI N = 141	ATV/r + 3TC N = 140
AEs leading to discontinuation	10 (7.2%)	3 (2.2%)
Grade 3-4 AEs	78 (55%)	77 (55%)
Hyperbilirubinemia	71	72
Icterus	2	0
Liver function test	2	2
Hyperlipidemia	2	3
Thrombocytopenia	1	2
Severe adverse events (none related to study medication)	8	6

SALT

Perez-Molina JA. Lancet Infect Dis 2015;15:775-84

Cohort Pitie- salpetriere Switch dual RAL/ETR

Virological success (per protocole)



L'analyse per protocole exclue les patients ayant arrêté pour des raisons autres que l'échec virologique

Switch RAL/ETR

Virological failures W48

	Replication under NNRTI (>200 copies/mL)	Exposure RAL	Cumulative resistance prior to switch retrospective (INNTI&II)
1	Yes	No	-
2	No	No	V179I
3	Yes	No	K103N, Y181C

	CV plasmatique					CV contrôle	Resistance profile at failure
	D0	M1	M3	M6	M12		
1	37	-	69			51	V72I
2	<20	<20	-	90		38	-
3	<40	-	-	2653	7679	7679	P225H, Y181C, N155H

Efficacy excellent if no prior NNRTI resistance

One INI resistance developed

Calin R AFRAVIH 2014

ETRAL ANRS : Study design

- ANRS study start january 2015
- Identify a treatment strategy without NRTI and PI : RAL/ETR
- Non comparative switch study

- Primary end point : % pts with VS at W48

- HIV1 ; âge ≥ 45
- CV <50 copies/mL depuis au moins 2 ans
- CD4 >200 /mm^3
- Stable ART with PI /r > 6 months
- Integrase inhibitor and etravirine naive
- No NNRTI mutation except for K103N ; full sensitivity to ETR

160 patients

RAL 400 mg BID + ETR 200 mg BID

DXA scan
- bone
- fat tissue

W48 primary end point
% pts with VL< 50 cp/ml

W96 Follow-up

Centers in France (15) Spain (3)

Towards a lighter suppressive ART

Dose reduction
ATV , DRV , EFV

400-mg EFV non inferior to 600-mg EFV with TDF/FTC for initial ART

- Randomized, double-blind, placebo-controlled, noninferiority phase III trial

636 ART-naive
CD4 : 273 /mm^3
HIV-1 RNA : 4.75 log

EFV* 400 mg + Placebo + TDF/FTC n = 324

EFV* 600 mg + TDF/FTC n = 312

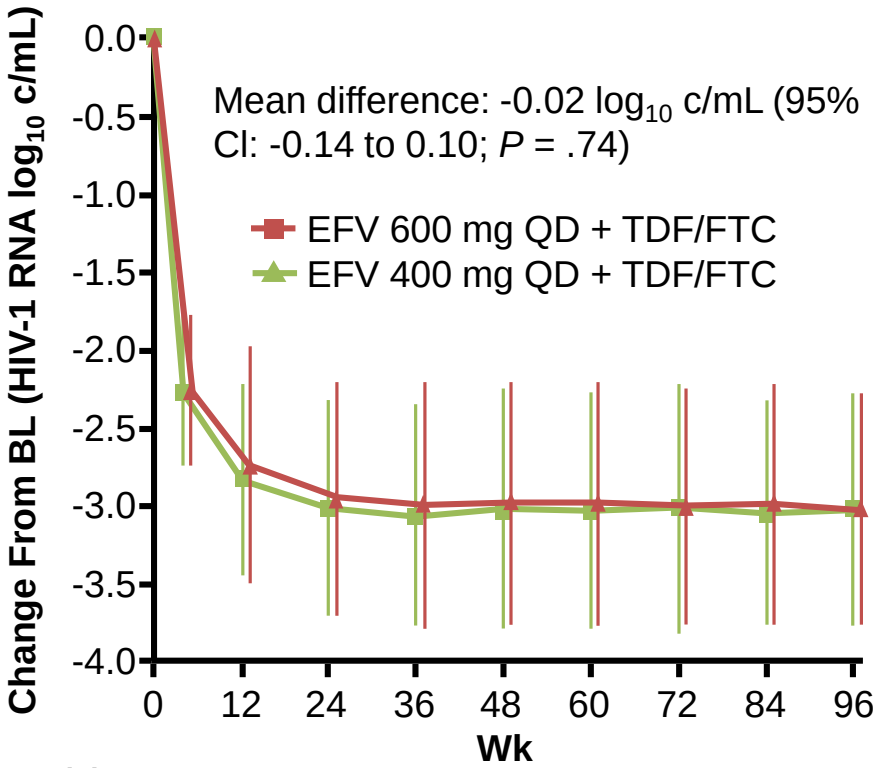
HIV-1 RNA < 200 cp/ml W48		
NC=F	**ITT**	**PP**
90.0 %	94.1 %	98.3 %
85.8 %	92.2 %	97. 4 %

- More drug–related AEs for EFV 600 **47.2%** mg vs EFV 400 mg **36.8%**; *p*=.008
- More discontinuations of EFV 600 mg due to AE vs EFV 400 mg
  1.9% vs 5.8%; *p* = .010

Puls R, et al. IAS 2013. Abstract WELBB01.

*EFV administered as 200-mg tablets.

ENCORE 1: EFV 400 mg QD Noninferior to 600 mg QD Through 96 Wks



Pts at Risk, n

EFV 400 mg	321	316	312	310	312	307	304	300	299
EFV 600 mg	309	302	301	299	295	291	290	289	286

- Mean change in CD4+ cell count from BL greater with 400-mg vs 600-mg EFV (*P* = .03)
- Rate of EFV-related AEs lower with 400-mg vs 600-mg dose: 37.7% vs 47.9% (*P* = .01)
- Trend toward lower rate of discontinuation for EFV-related AEs with 400-mg vs 600-mg dose: 8.3% vs 15.5% (*P* = .07)
- Frequency of treatment emergent NNRTI resistance similar in both arms

Carey D, et al. Glasgow HIV 2014. Abstract O421. Reproduced with permission.

Maintaining viral suppression with alternative strategies
Clinical studies ongoing

Dual Therapies

RAL/ETR
DTG/RPV

DTG/3TC

Dose reduction

DRV/r 400 mg
ATV/r 200 mg

Intermittent ART

4 jours off
Study 4D

Need for clinical studies in different patients populations

Long acting drugs
UneA major opportunity in treatment and prevention

Rilpivirine LA

- Nanosuspension NNRTI
- Monthly IM Injections

GSK744 LAP

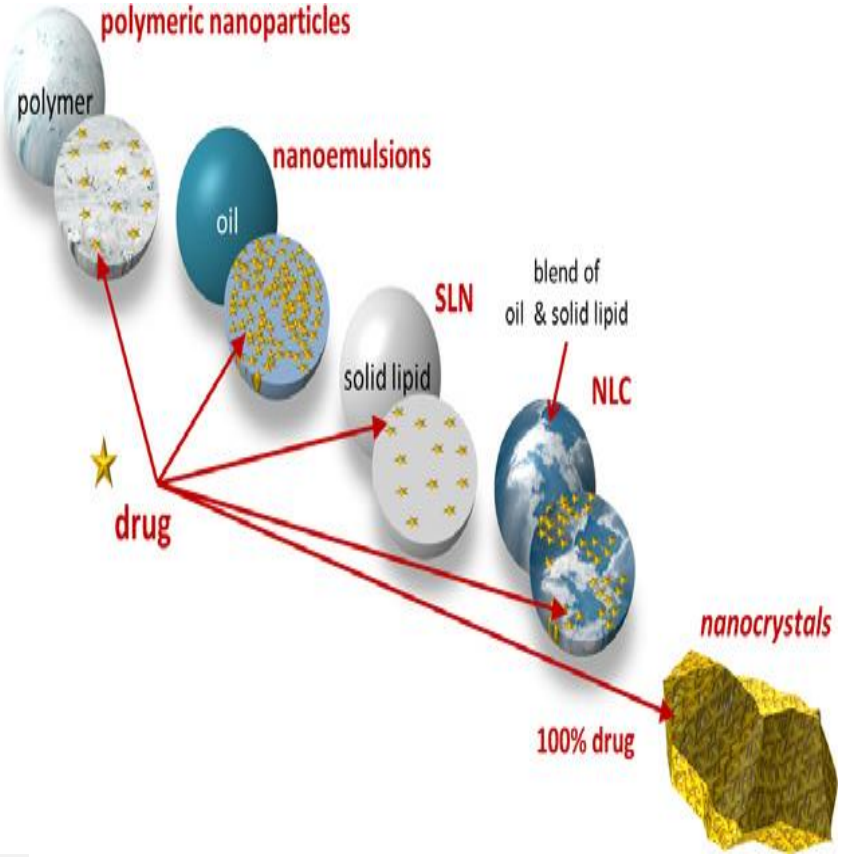
- Nanosuspension inhibiteur intégrase
- IM/SC Monthly / every 3 mo
- 200-1200 mg tested

GSK 744 oral study Latte)

10 20 30 60 mg + TDF/FTC

Efficacy > 90%

No difference between doses



Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Cabotegravir and Rilpivirine as Two-Drug Oral Maintenance Therapy: LATTE Week 96 results

Figure 1. LATTE Study Design

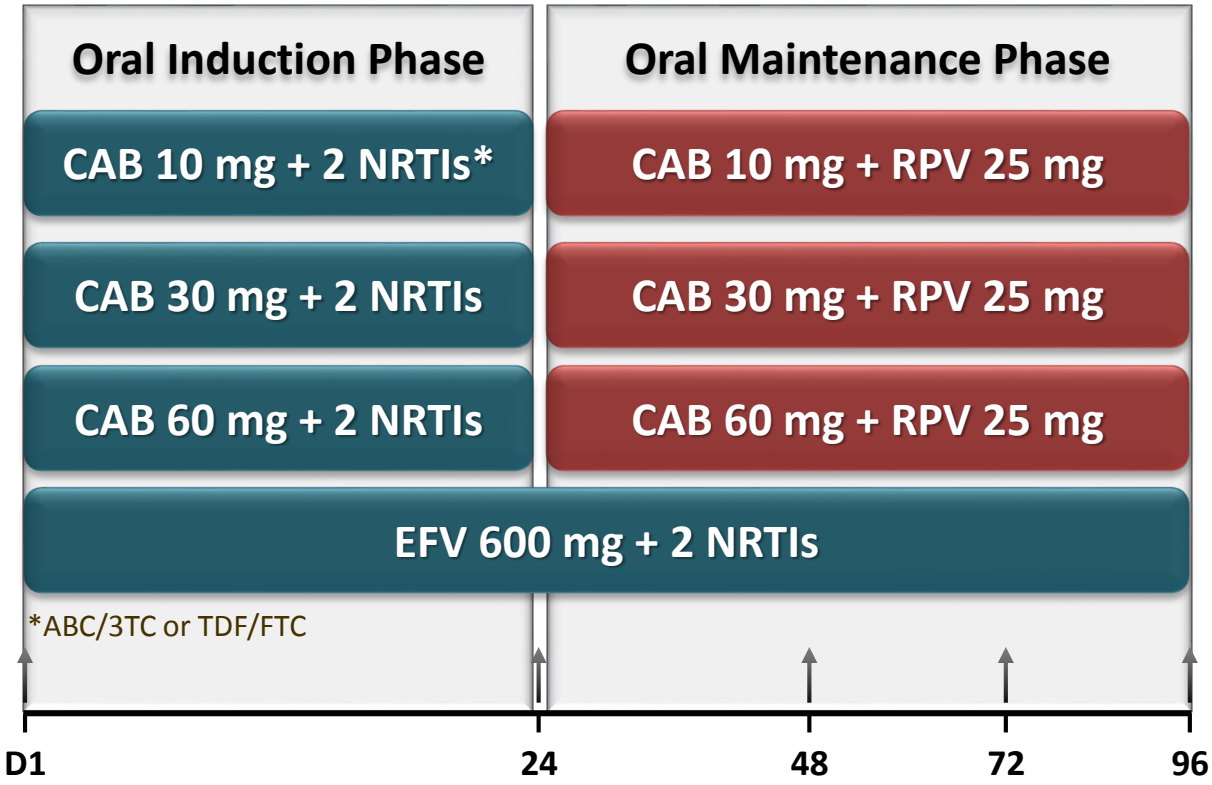
HIV ART-naïve

HIV-1 RNA ≥1000 c/mL

CD4 ≥ 200 cells/mm^3

1:1:1:1

Randomization Stratified by VL and NRTI

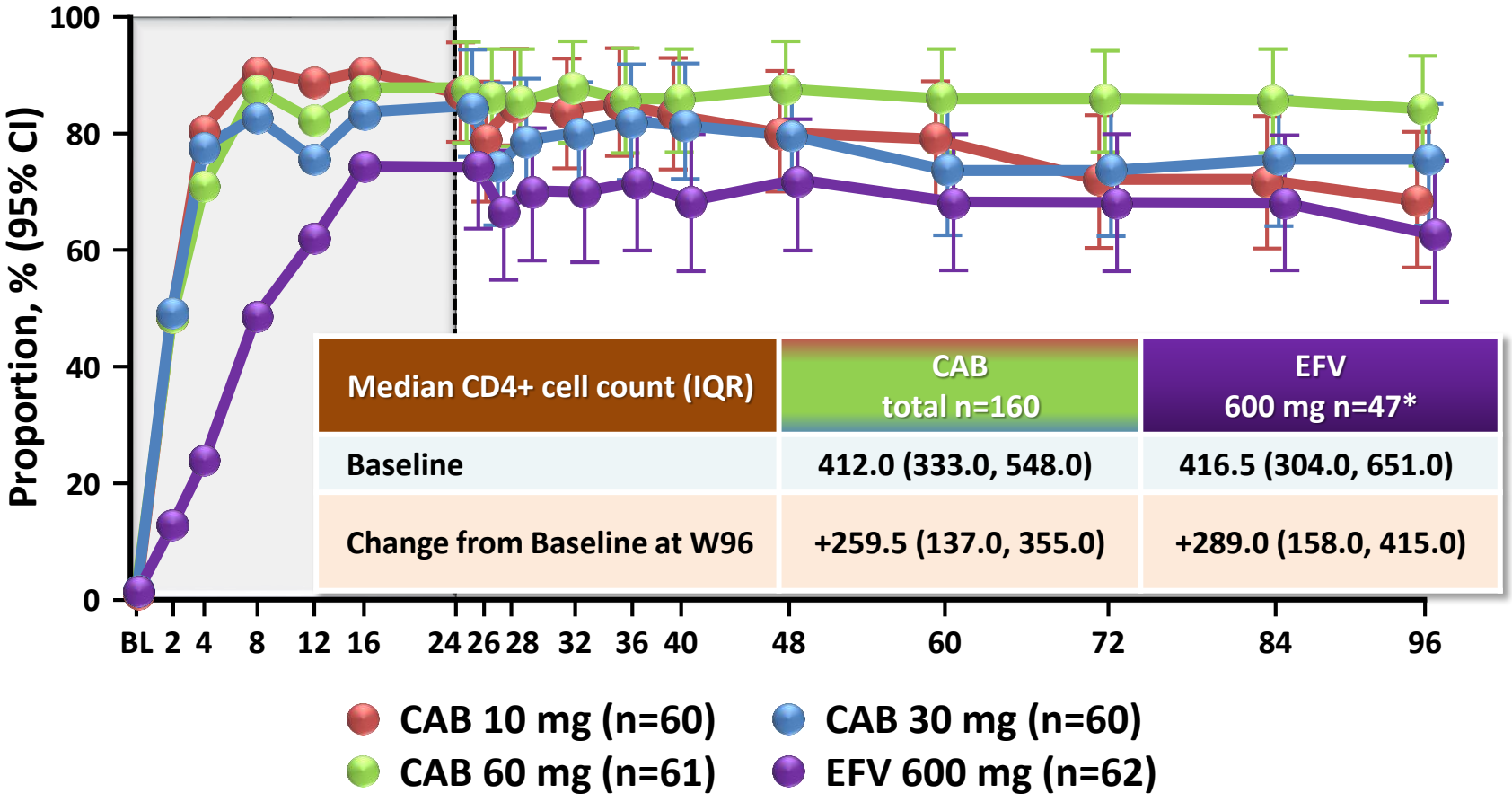


Following Week 96, subjects on the CAB arms transition into the Open-Label Phase. Subjects on the EFV arm are withdrawn from the study at Week 96.

Margolis A *et al*, Abstract 554LB, CROI Seattle 2015

Cabotegravir and Rilpivirine as Two-Drug Oral Maintenance Therapy: LATTE Week 96 results

Figure 2. Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)



Median CD4+ cell count (IQR)	CAB total n=160	EFV 600 mg n=47*
Baseline	412.0 (333.0, 548.0)	416.5 (304.0, 651.0)
Change from Baseline at W96	+259.5 (137.0, 355.0)	+289.0 (158.0, 415.0)

Margolis A et al, Abstract 554LB, CROI Seattle 2015

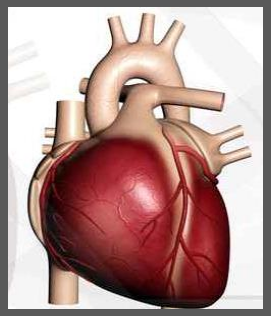
Long life management of ART

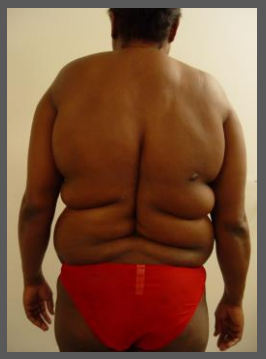
HIV

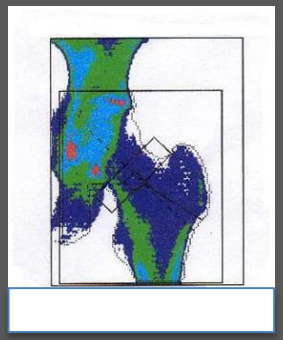
ART

Aging

Co-morbidities







Early ART

Minimal ART

Healthy aging
- balanced diet
- exercice
- prevention

Need for individualized therapy in Long-term virological suppression