EACS
European
AIDS
Clinical
Society

Switching Suppressive Therapy

EACS Summer course 2016

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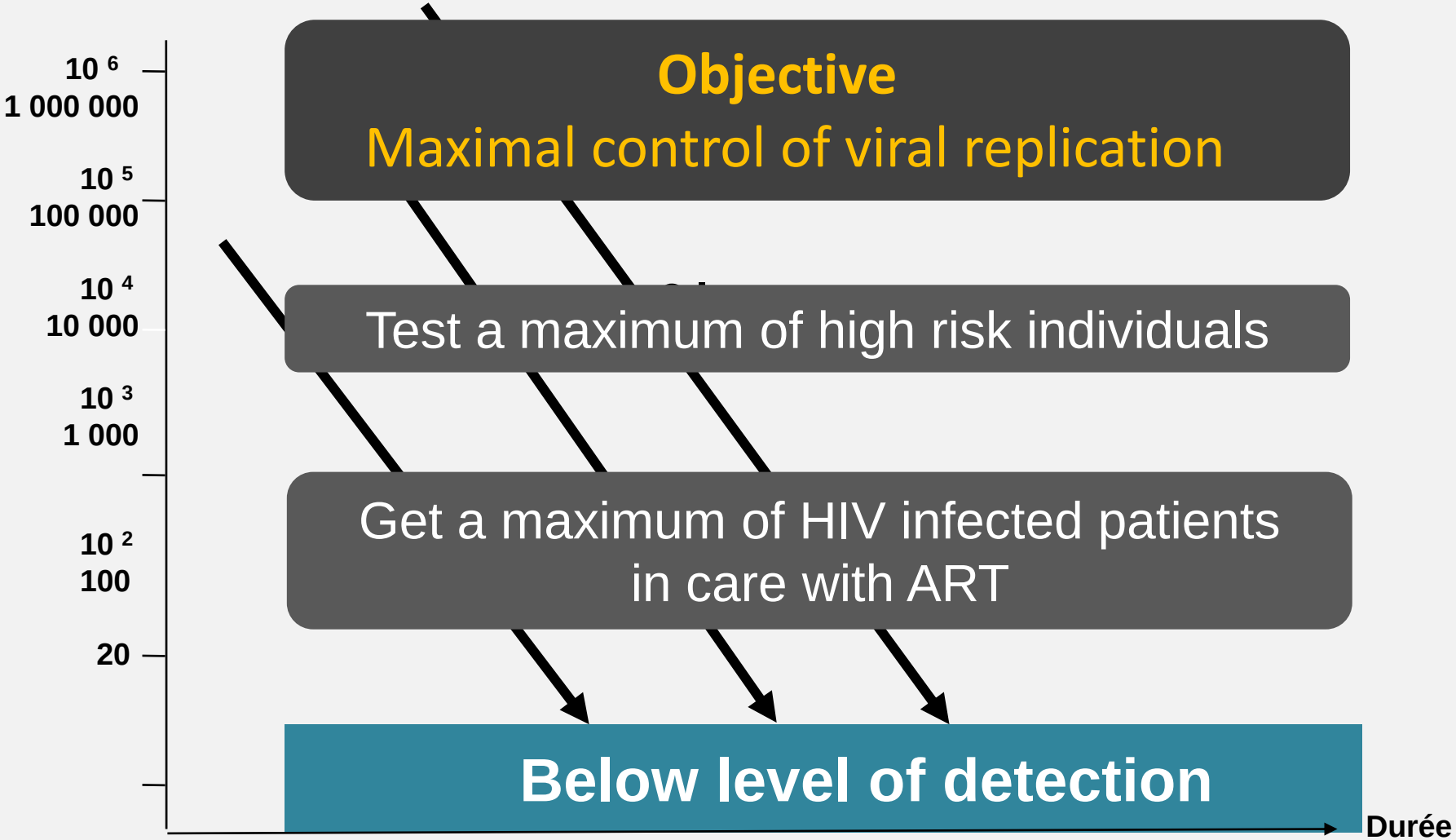
- HIV has to be suppressed all life long as the best option to prevent deleterious effects of HIV replication and prevent sexual transmission
- ART has to be maintained long life
- ART has to be maximally tolerated ; robust and affordable

- Long term toxicity of ART
- Comorbidities Aging
- Life long therapy without missing periods is a challenge for any individual
- cost and implementation
-

HIV Therapy : one of the biggest challenge in medicine

Antiretroviral Therapy Goals



ART is a life long therapy thoughout decades of life

ART has to be adjusted to different life events

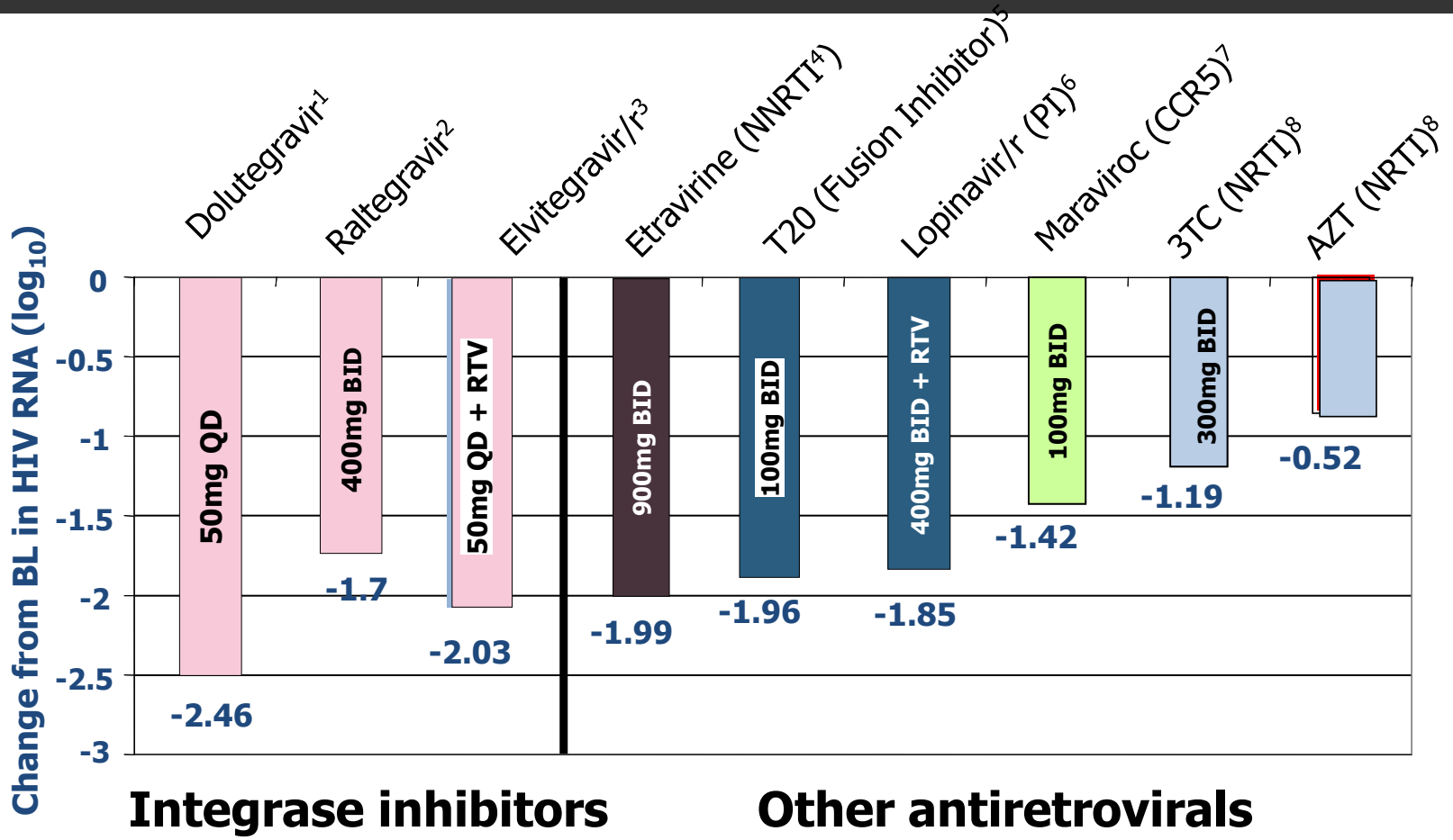
Antiretroviral Drugs : 2016

NRTI	NNRTI	Protease Inhibitors	Integrase Inhibitors	CCR5 Inhibitors
TDF TAF TDF or TAF /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[R] 1
TDF/FTC/RPV : Eviplera[R]
TDF/FTC/EVG/c : Stribild[R]
TAF/FTC/EVG/c Genvoya[R]
ABC/3TC/DTG : Triumeq [R]

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.

Adjust ART to each individual

Treatment at any stage of HIV infection

- More heterogeneity in patients (CD4 and VL)
- Longer duration of ART

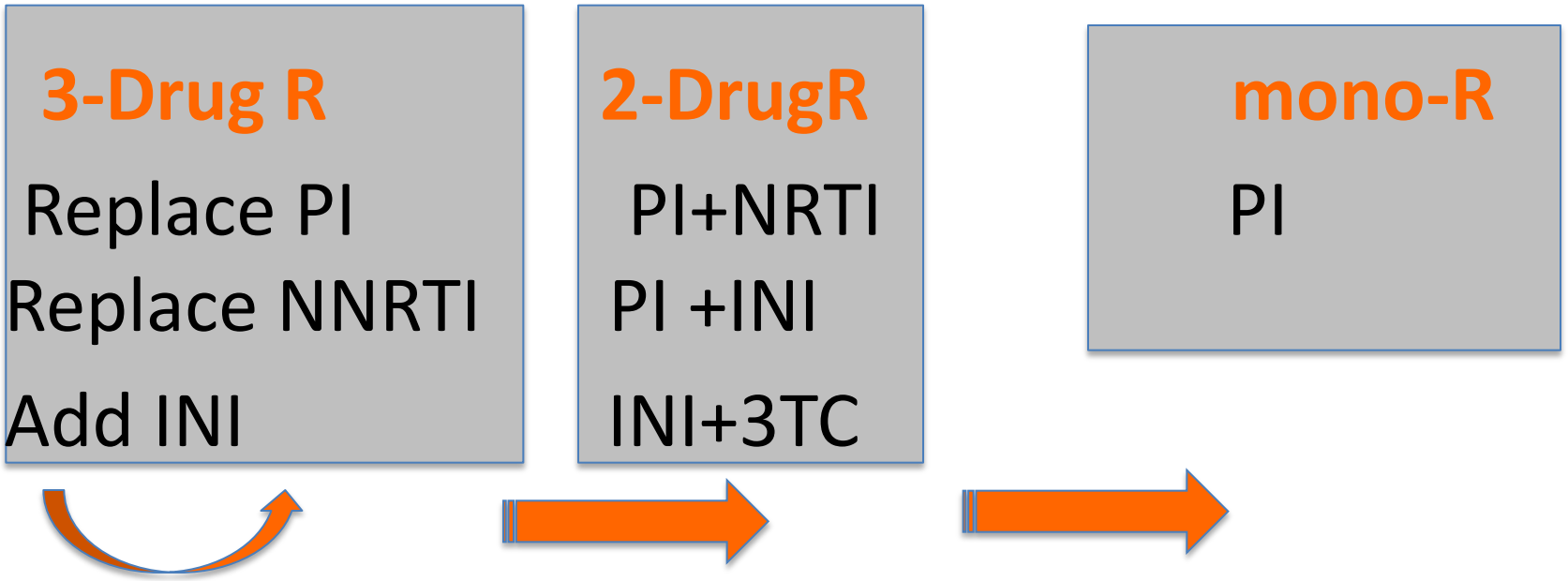
- **Age**
- **Status CD4 /CV**
- **Life style**
- **Comorbidities**
- **Access to care**

Outline

- Why switching a suppressive therapy therapy ?
- How to switch ?
- Switch strategies
- Strategies to reduce drug burden

Switching : Options

Switch : Modification of a suppressive regimen
Simplification =/ drug reduction



ARV Reduction : Check for sensitivity of remaining drugs

Why changing a suppressive ART ?

Reasons to switch ART

Toxicity / Tolerability

toxicity management

Context

- aging comorbidities
- bone , kidney, CV risk
- pregnancy

Reduce drug burden

- remove resistant drugs
- adjust ART to HIV disease

Reasons for switch "anxiety "

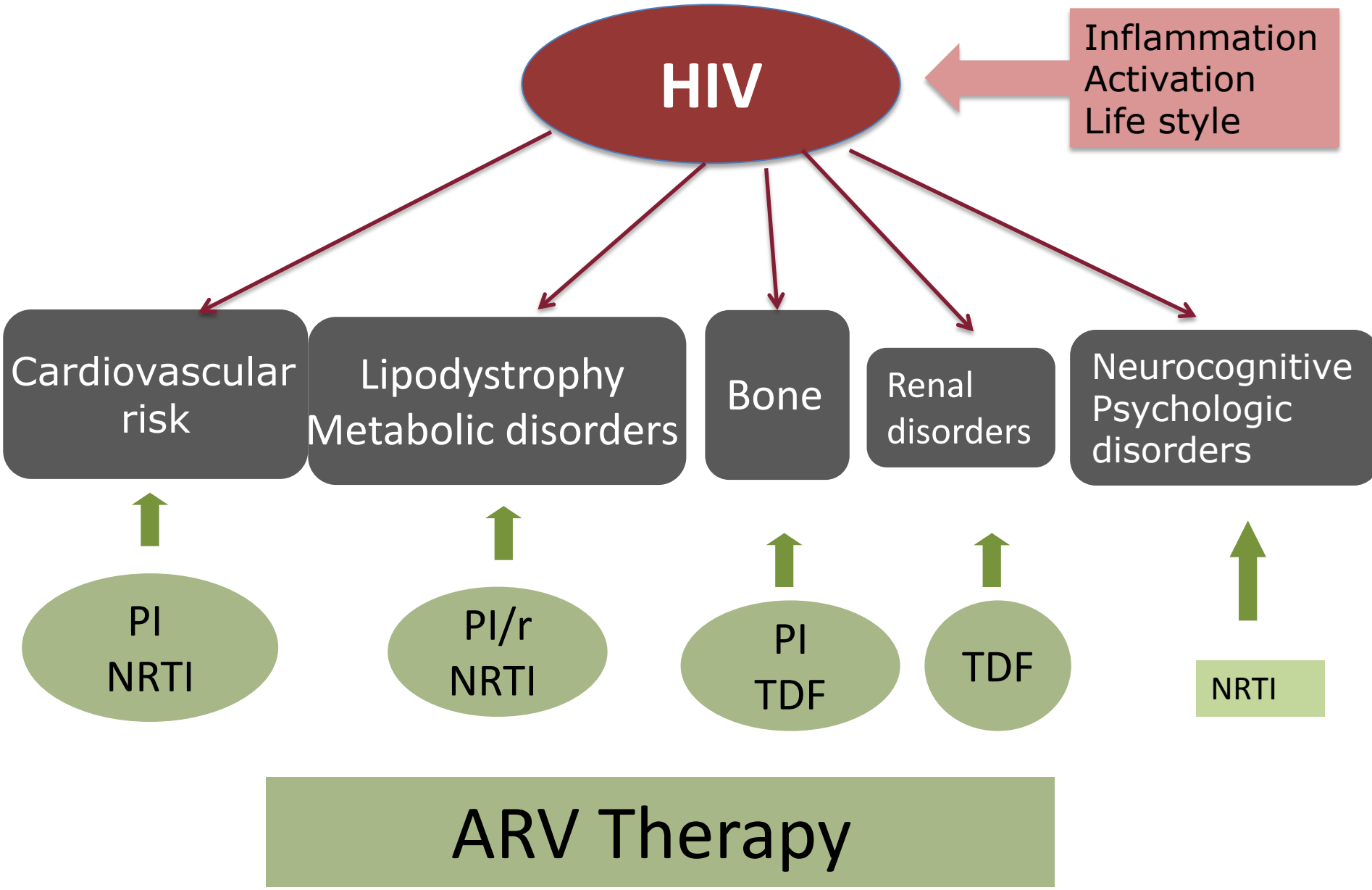
Issues to be considered before switching

- New drug : new toxicity?
- Unmask archived resistance
- Drug drug interactions
- Leaving a STR

Outline

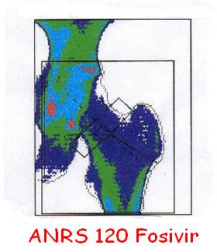
- Why switching a suppressive therapy therapy ?
- Which drug to switch ?
- How to switch ?
- Future switch strategies in suppressed patients

Interactions of HIV and ARV drugs



Nucleosides analogues may not be optimal in aging 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 intakes
- 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



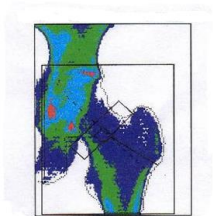
Risk at 10 years of major osteoporotic fracture in HIV infected male

	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



EuroSIDA: Impact of TDF Exposure on Risk of Fractures in HIV-Infected Pts

- Prospective analysis of 11,820 HIV-infected pts
- Followed from baseline (Jan 2004) to last visit or death to assess for fractures, femoral osteonecrosis

TDF Exposure	Any Fracture IRR (95% CI)		Osteoporotic Fracture* IRR (95% CI)
	Univariate	Multivariate†	Multivariate†
Ever used vs never used	1.71‡ (1.42-2.06)	**1.40‡ (1.15-1.70)**	1.10 (0.76-1.58)
On TDF vs not on TDF	1.38‡ (1.16-1.64)	**1.25‡ (1.15-1.70)**	1.12 (0.79-1.60)
Cumulative TDF exposure/5 yrs	1.28‡ (1.13-1.50)	1.08 (0.94-1.25)	0.99 (0.69-1.43)

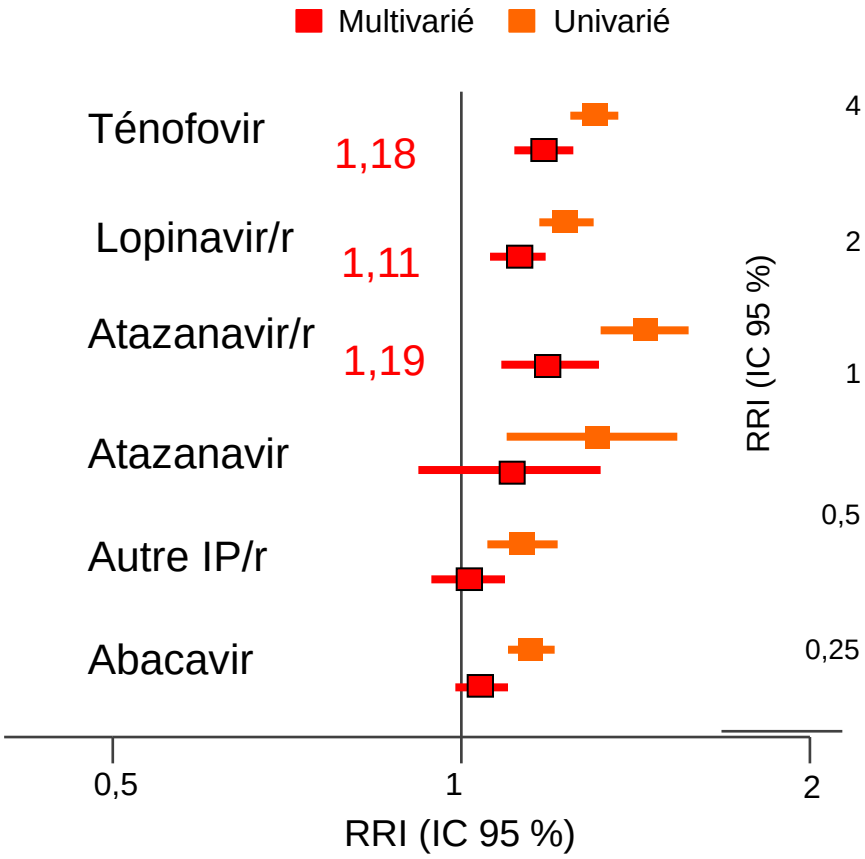
*Fracture of the spine, arm, wrist, or hip. †Adjusted for demographics, HIV-specific variables, and comorbidities. ‡$P < .05$

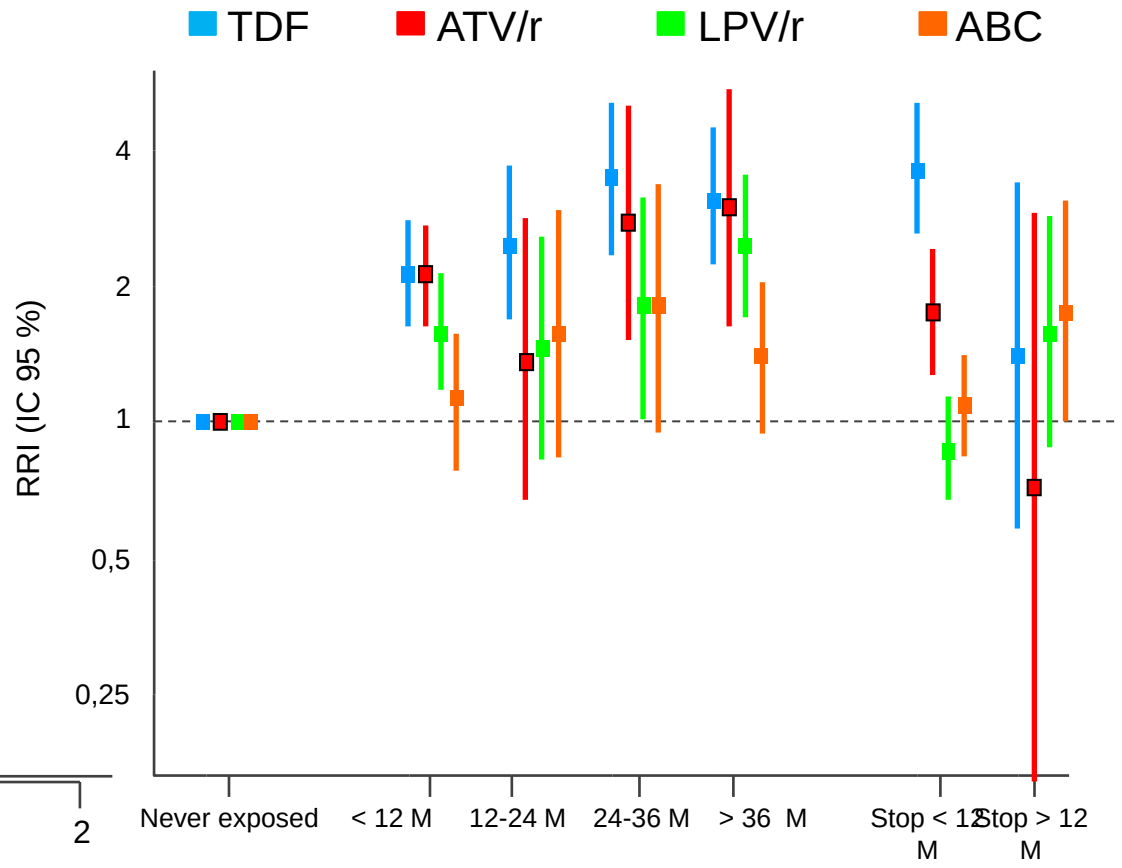
Borges AH, et al. CROI 2016. Abstract 46.

DAD : ARV exposure and renal function

22 603 patients

Passage d'un DFG > 90 à ≤ 70 ml/min



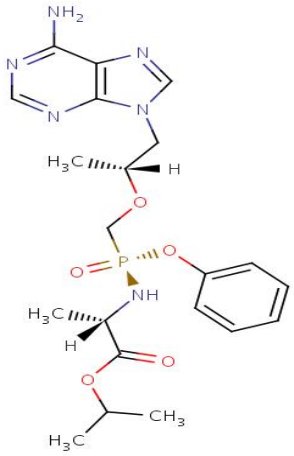


Ryom L, CROI 2012, Abs. 865

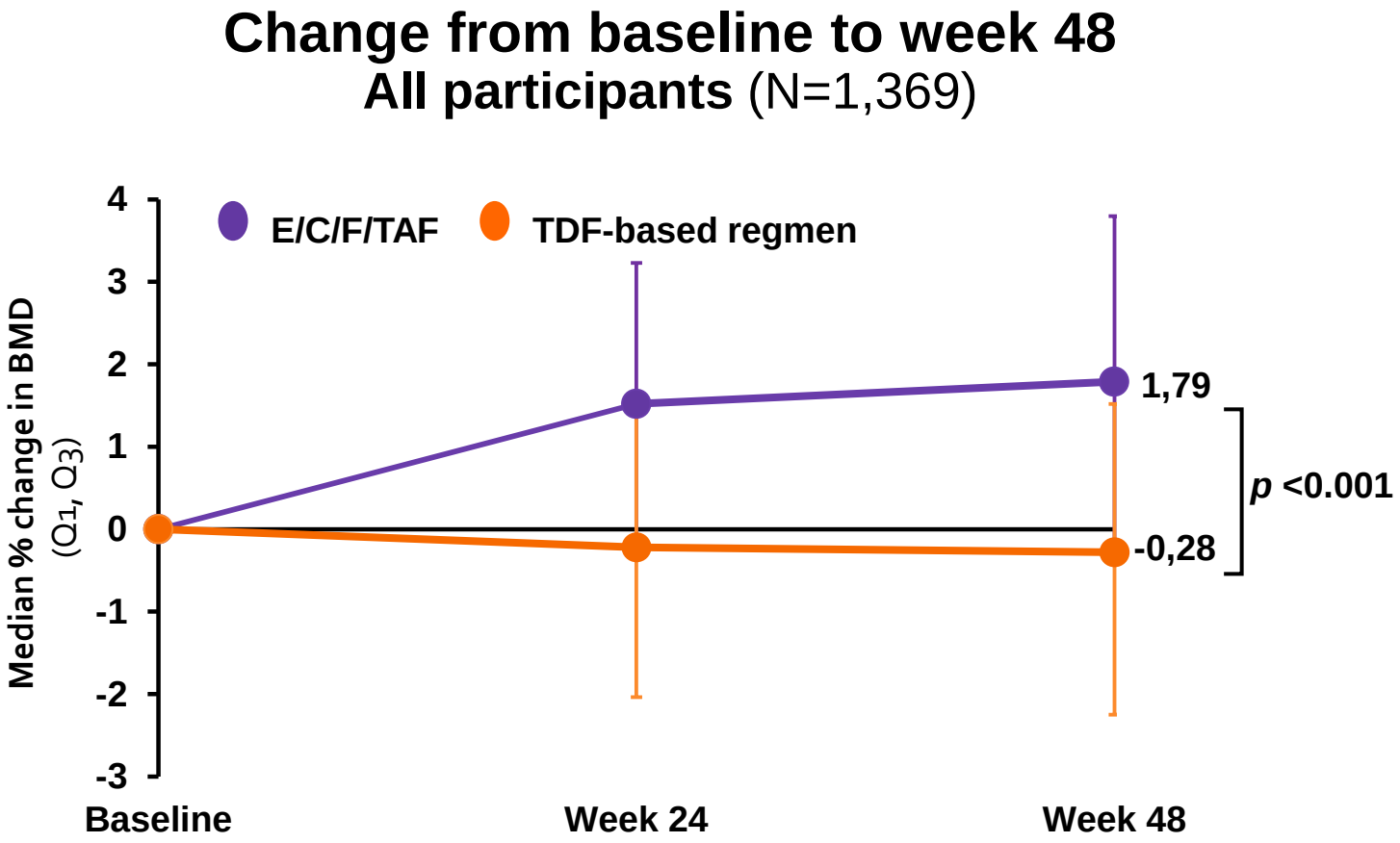
Tenofovir Alafenamide Fumarate (TAF) a new version of an old drug

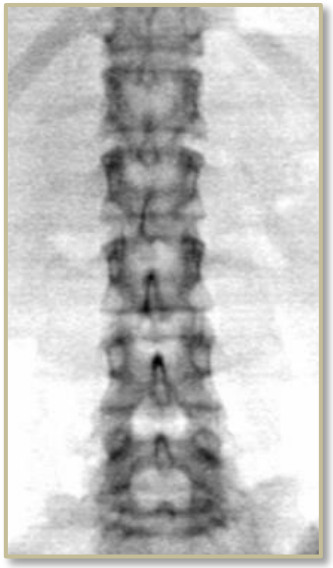
- Prodrogue NRTI, converted in active tenofovir diphosphate
- Différent du tenofovir disoproxil fumarate o[illegible] Viread®
  - More activ[illegible] vs 1.0 log VL
  - [illegible] plus actif
  - High intracellular concentration ++
  - Bettter tolerated kidney and bones
  - Co-formulation possible
  - Dosage : 10 mg par jour

TAF will progressively replace TDF



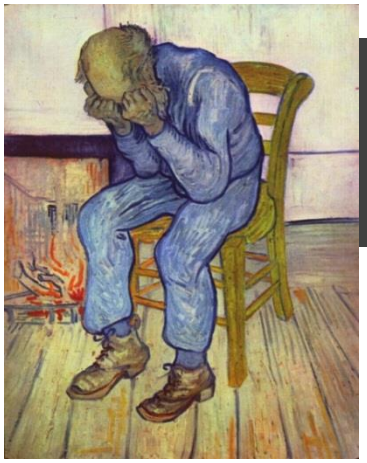
Switching From a TDF regimen to a TAF Regimen
Spine BMD scan results



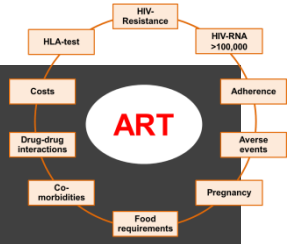


- 2% increase at W48 was observed significant regardless of prior treatment regimen

Mills A, et al. IAS 2015. Vancouver, CA; #TUAB0102



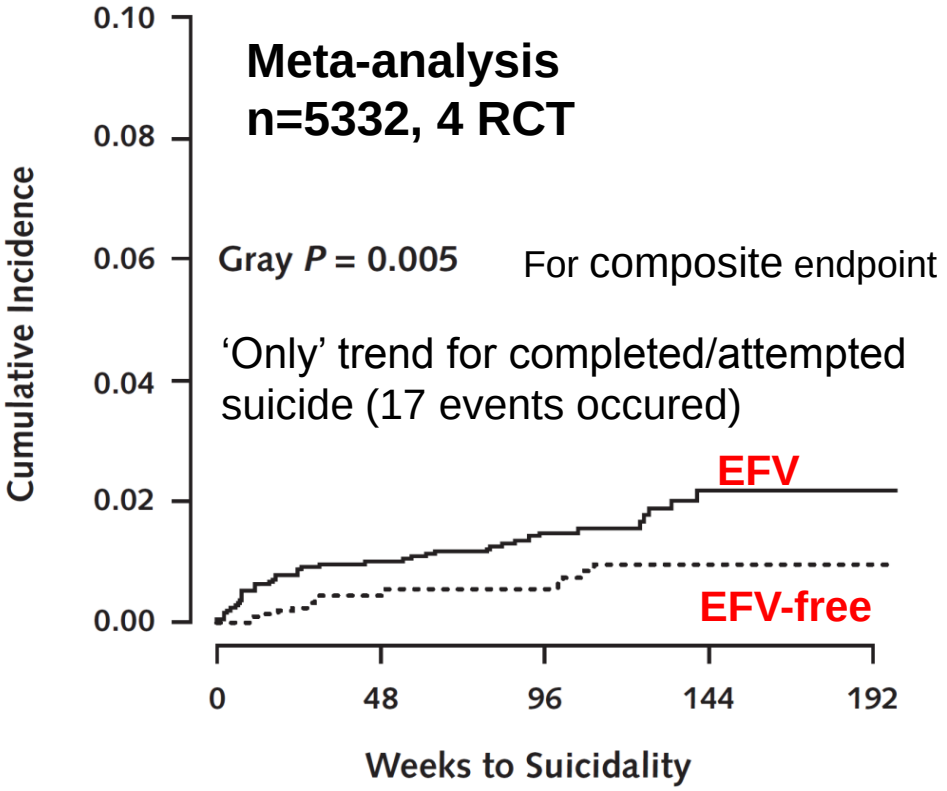
CNS - Depression



- Efavirenz (6%)

2x higher risk for suicidality

- Rilpivirine (8%)
- Elvitegravir/c (5%)
- Raltegravir (6%)
- Atazanavir/r (2%)



But Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study

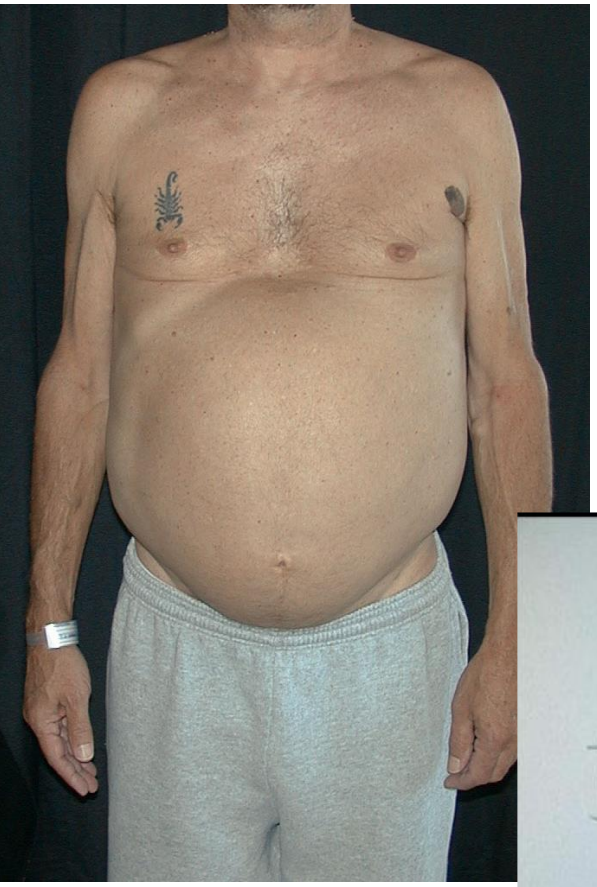
C. Smith; L. Ryom; A. d'Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

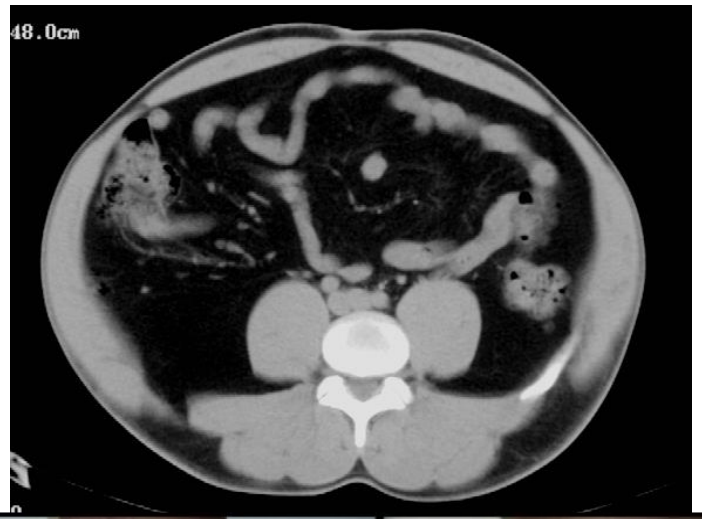
Cohen et al., Lancet 2011; Molina et al, Lancet 2011; Elion et al., JAIDS 2013; Mollan et al, Ann Intern Med 2014

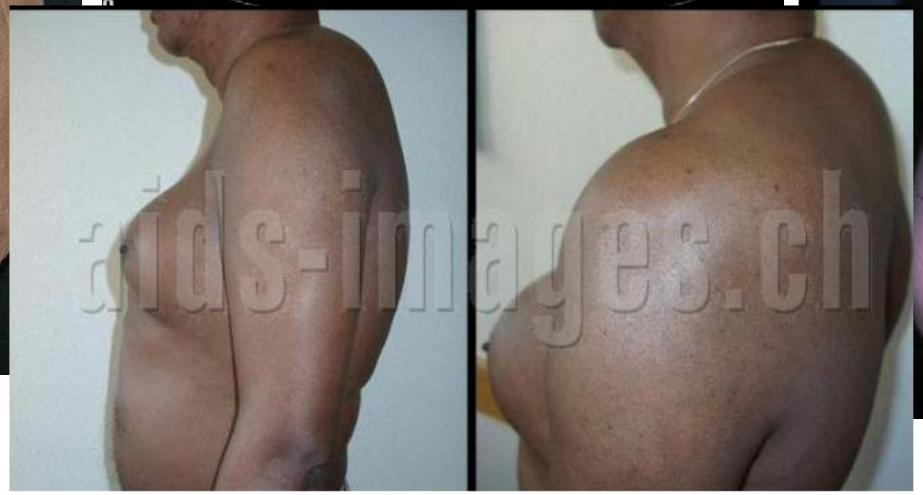
Protease inhibitors PI increase cardio-vascular risk

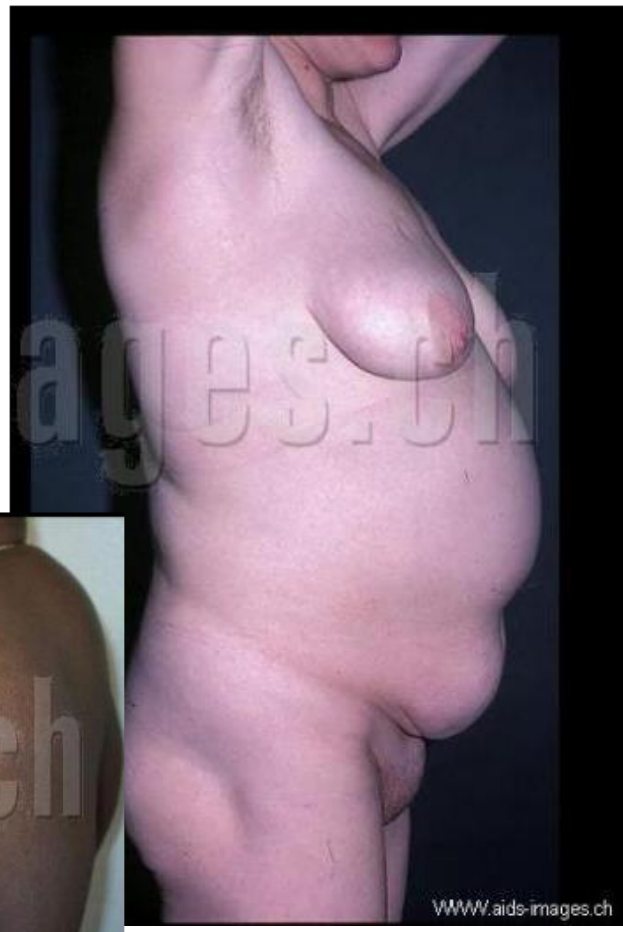
Study	Risk
D:A:D NEJM 2007	1,16 (1,10-1,23) per year of exposition
FHDH ANRS CO4 Arch Int Med 2010,	1,15 (1,06-1,26) per year of exposition
Veterans NEJM 2003	1,23 (0,8-1,9) (16 mois d'exposition médiane) ->1,17 per year of exposition

Lipodystrophy increases inflammation and metabolic disorders









ART and Effects on Lipids

TDF

RAL
DTG

RPV

ABC

EFV

ATV/r or ATV/cobi
DRV/r or DRV/cobi
EVG/cobi

How to switch ?

ART Switching Management 1

- **1 Explain**

- *why you propose a switch; there must be a potential benefit (sparing drug)*

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

- **2 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*

ART Switching Management 2

- **3 Select** a new regimen and **Avoid** a situation of functional monotherapy

  - consider which drug is doing what

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

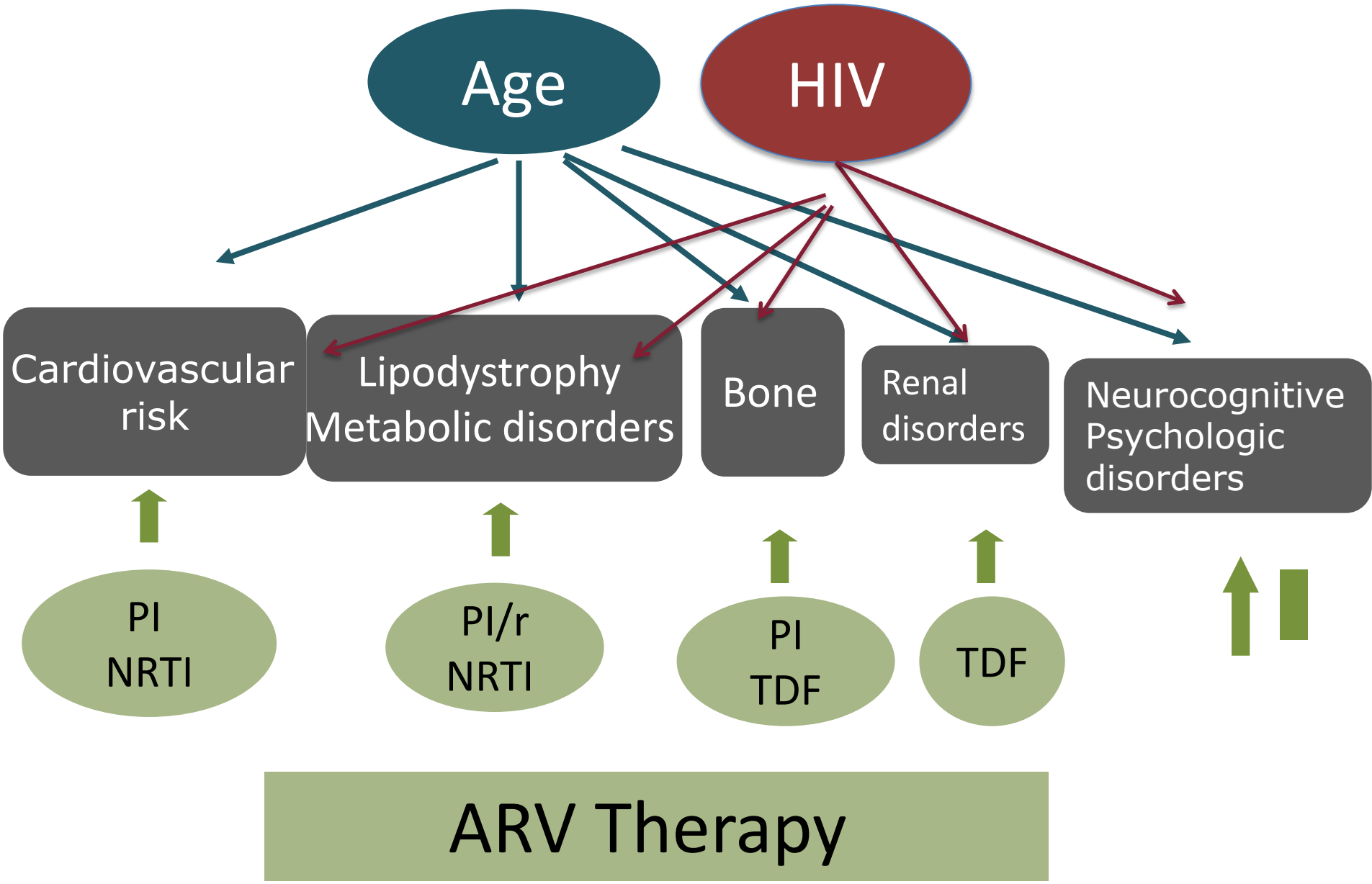
- **4 Check** drug drug interactions

  - *between antiretroviral drugs*
  - *with ARV and comedications*

- **5 Control** maintenance of viral suppression at W4 W12..

  some failures may be slow to appear

Interactions of age , HIV , ARV drugs



Aging HIV infected patients : a key increasing population worldwide

CONTEXT

- **Long term past ART** :
  NRTI : legs and buttock lipoatrophy from Thymidines
  PI : cumulative lipohypertrophy ; metabolic
  NNRTI : psycho – effects
- **Ageing comorbidities**
  - heart bone muscle
  - mild loss / disturbances in memeory
- **Decreased renal function**
  Drug accumulation
- **Poly-comedications**
- more Drug drug intercation

ADAPT ART

- Avoid NRTI
- Avoid PI
- Avoid boosted drugs
  (Drug Drug interactions)
  Polcardio vascular drugs
  psycho drugs
- Preference to simple regimen (forget)
- Low drug dosage might be appropriate (monitoring plasma concentration)

PROMOTE Healthy style life

Integrase Inhibitors : a key role in ART and particularly in long term treated 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

SPIRAL

Switch PI/r to RAL in suppressed patients

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

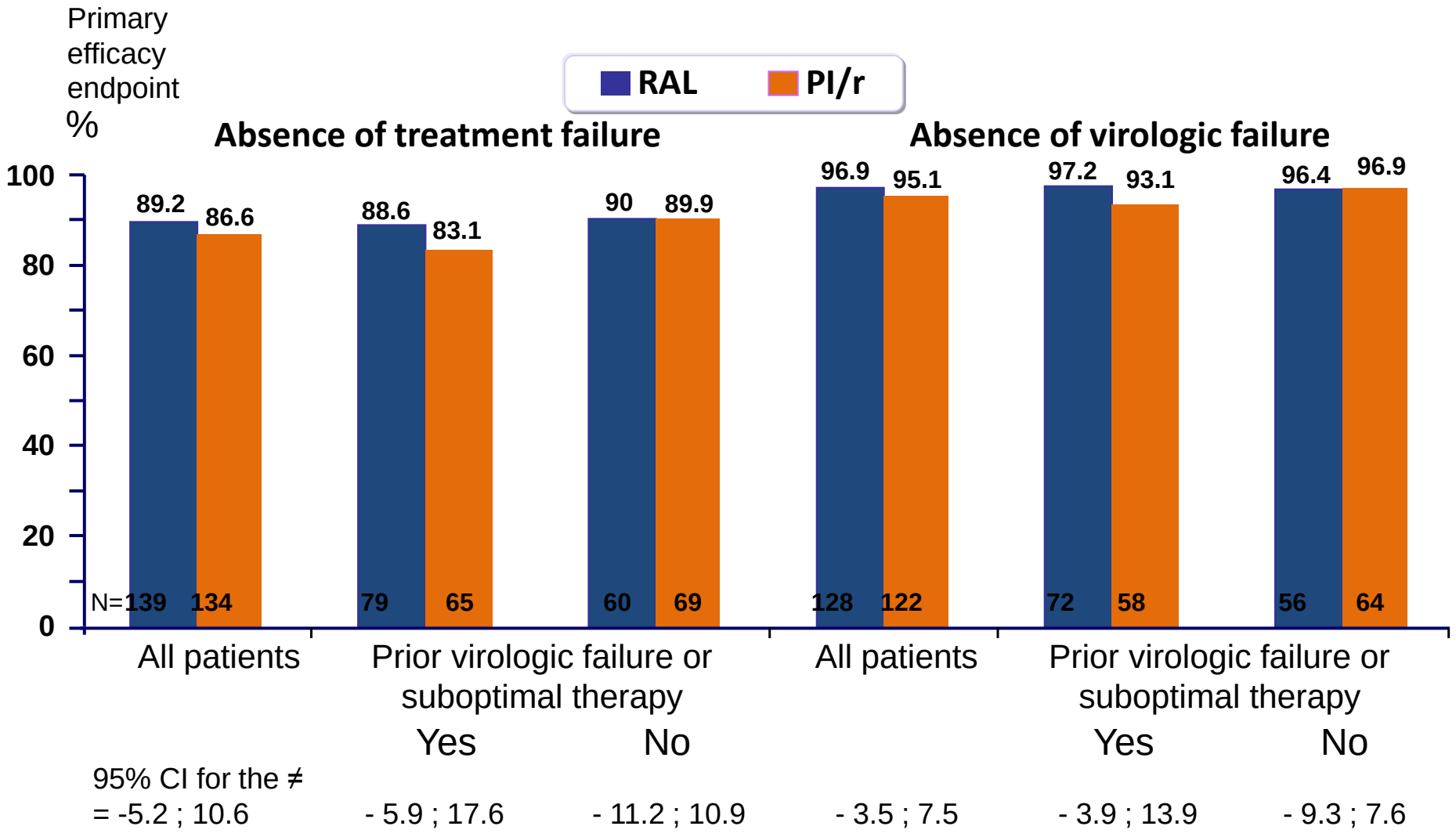
2NRT+PI regimen VL <50 cp

Switch to raltegravir

Maintain PI

SPIRAL

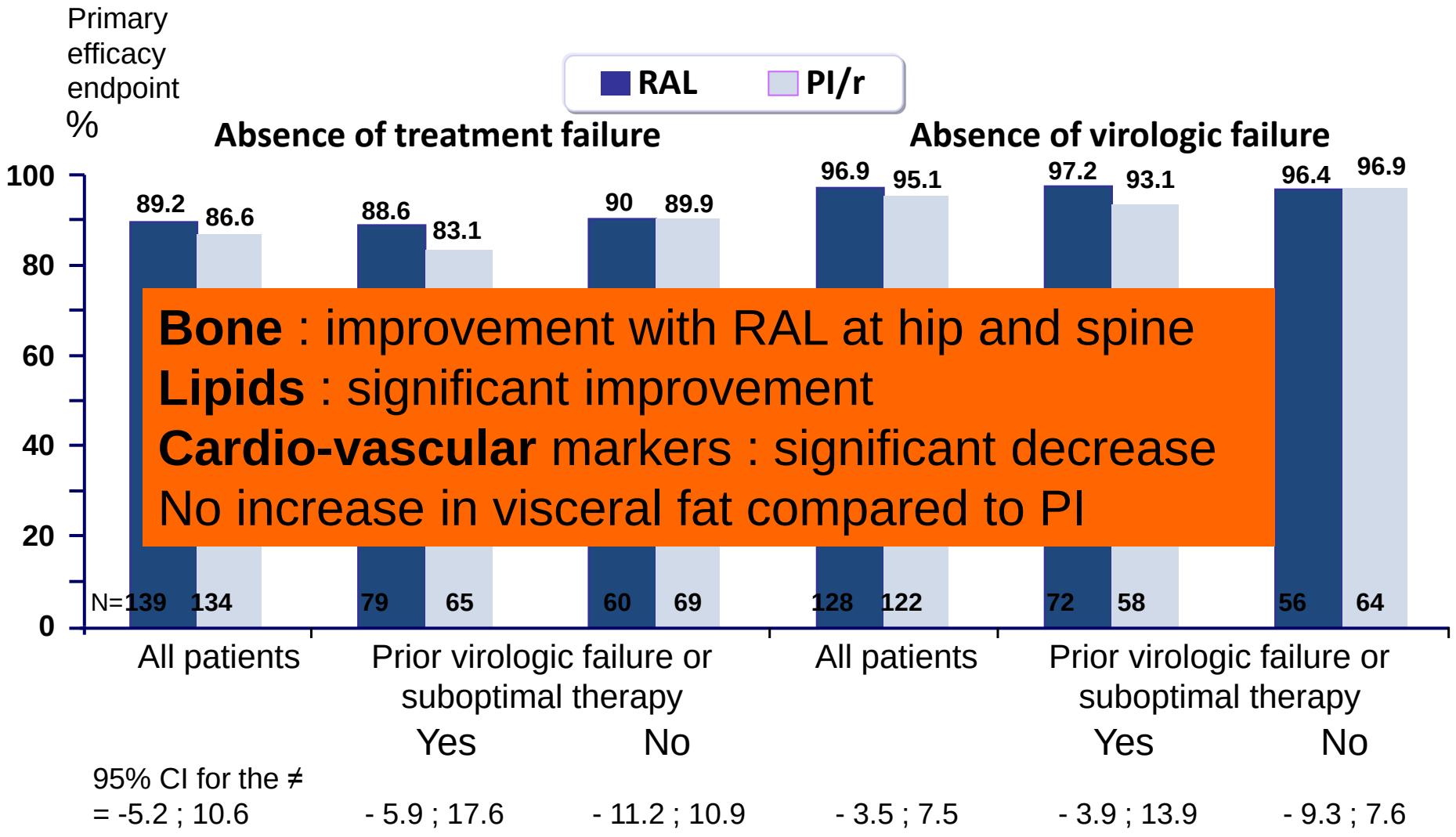
Switch PI/r to RAL in suppressed patients



Martinez E, AIDS 2010;24:1697-1707

SPIRAL

Switch PI/r to RAL in suppressed patients



Bone : improvement with RAL at hip and spine
Lipids : significant improvement
Cardio-vascular markers : significant decrease
No increase in visceral fat compared to PI

Martinez E, AIDS 2010;24:1697-1707

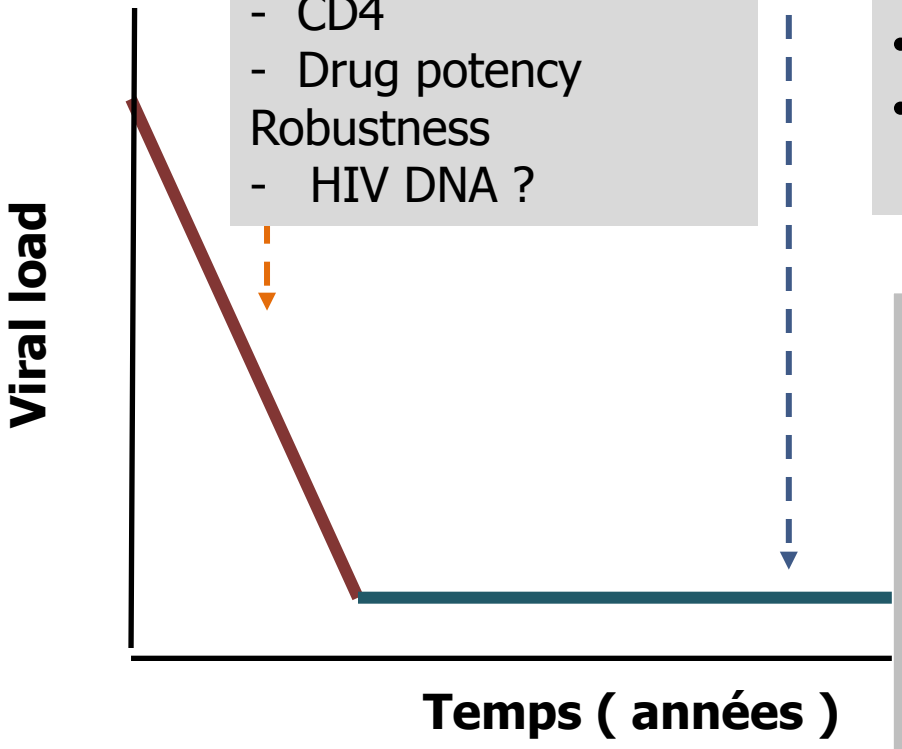
New concepts in Antiretroviral therapy
Individualization of therapy

Induction

1996 HAART Triple therapy : a revolution

Nb drugs depends of
- HIV RNA
- CD4
- Drug potency

Robustness
- HIV DNA ?



2016

- 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 ?

Reasons to individualize ART

- Reduce drug burden
- Prevent / reduce long term toxicity
- Spare drug capital
  Adapt ART to CD4 and plasma VL and to reservoirs ?
- Cost reduction

Towards a lighter suppressive ART

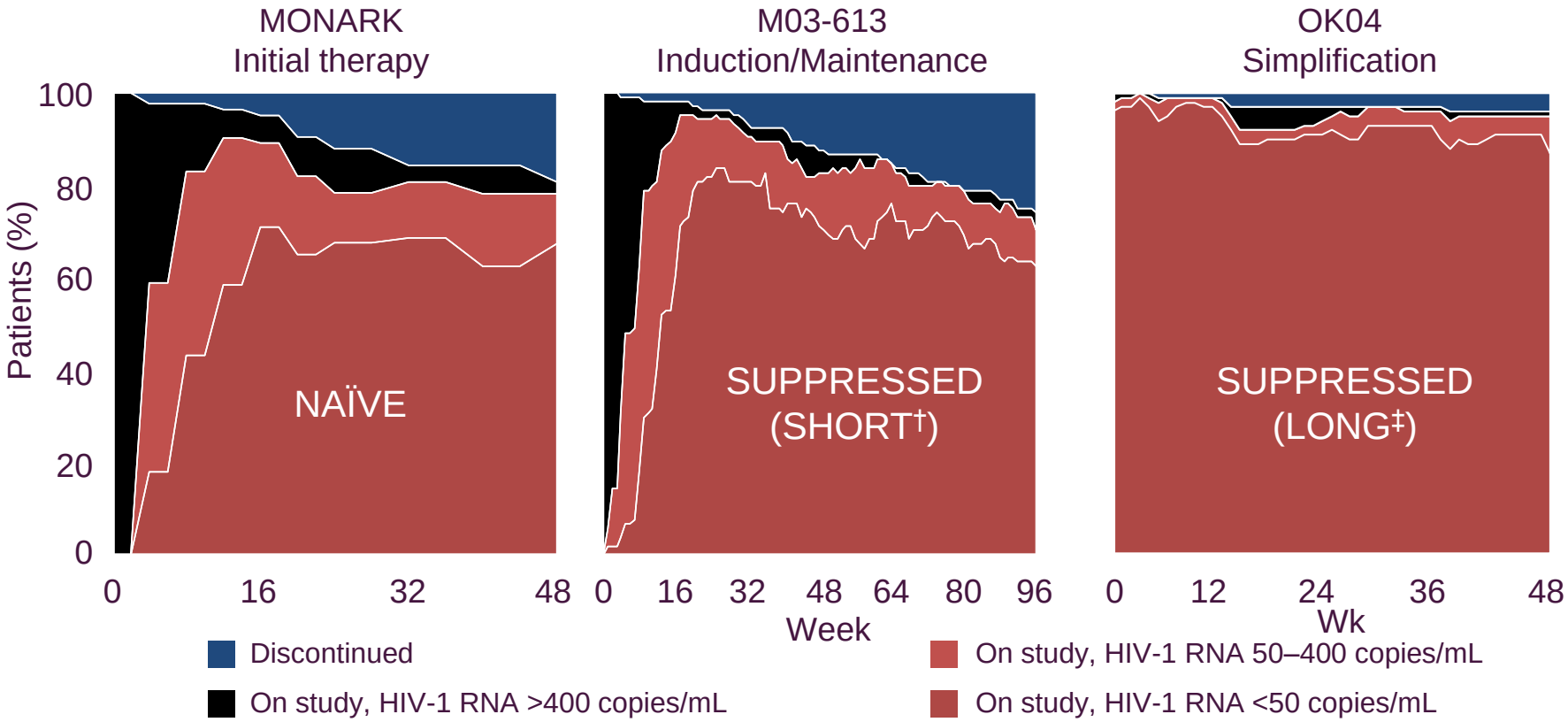
Monotherapy

Dual therapies

Dose reduction

Intermittent ART

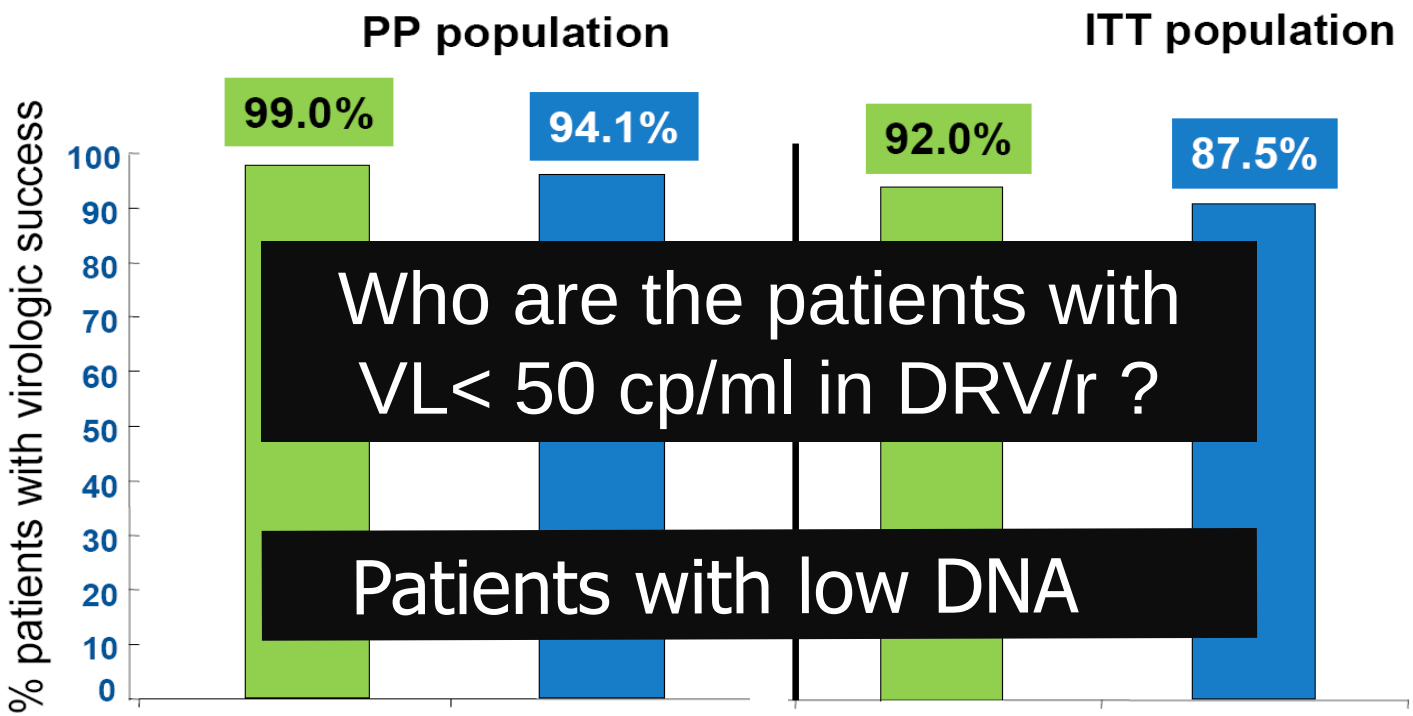
PI/r monotherapy
Monotherapy with LPV/r*[1]



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

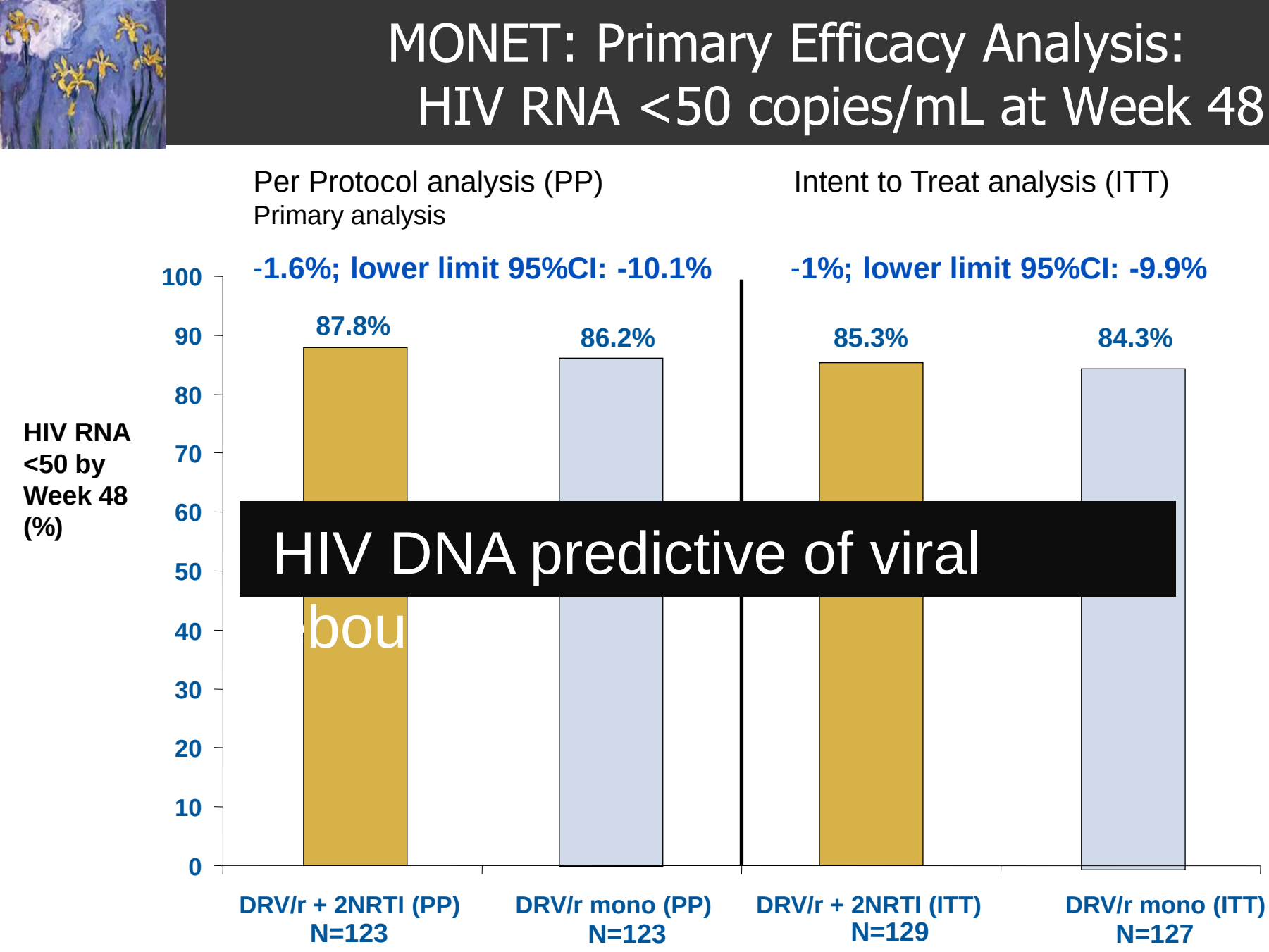
Adapted from 1. Arribas JR, EACS 2009, Cologne, Germany. Oral Presentation; 2. Cameron WD, et al. J Infect Dis. 2008;198:2234–40; 3. Arribas JR, et al. JAIDS 2005;40:280–7.

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



J. Arribas et al, AIDS 2010

Evolution of Integrase Mutations in 2 Dolutegravir Monotherapy Switch Studies

- All 4 pts with virologic failure had history of INSTI use before switch; 1 pt had previous raltegravir failure but no INSTI resistance

HIV-1 RNA at VF, c/mL	INSTI Resistance by Timepoint (Detection Source)			
	Day 0	Wk 4	Wk 12/13	Wk 24
155[1]	-	None (DNA)	-	118R (DNA)
469[2]			R: EVG RAL	-
291[2]	None (DNA)	-	-	155H (RNA) R: EVG RAL
2220[2]	None (DNA)	None (RNA)	None (DNA)	E138K / G140A, Q148R (RNA) R: DTG EVG RAL

1. Rojas J, et al. EACS 2015. Abstract 1108. 2. Katlama C, et al. EACS 2015. Abstract 714.

Dolutegravir monotherapy in patients with suppressed HIV viremia.

- Dolutegravir : potent INI ; higher genetic brrier to resistance
- Pilot studies on going to evaluate whether dolutegravir can be used in some patients as mono therapy

- Katlama et al 28 pts ; 25 VS maintained ; 3 failures with prior INI exposure

- Martinez et al : 31 pts ; 30 VS ; 1 failure

- Larger studies needed

Towards a lighter suppressive ART

Dual therapies

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

GARDEL: Dual ART LPV/r +3TC

Non inferior to Triple ART in ART naïve patients

GARDEL
GLOBAL ARV DESIGN ENCOMPASSING LOPINAVIR/RITONAVIR AND LAMIVUDINE VS LOPINAVIR/RITONAVIR BASED STANDARD THERAPY

Phase III, randomized, controlled, open-label study
Argentina, Chile, Mexico, Peru, Spain, US.

426 ART- naive pts
VL: 4.87 log
CD4: 320/mm3
No PI resistance

- LPV/r 400/100mg BID + 3TC 150 mg BID n=217
- LPV/r 400/100mg BID + 3TC /FTC + NRTI n=209

HIV-1 RNA < 50 W48	ITT exposed - Snapshot	ITT Snapshot VL> 5 log	Exposed
LPV/r 400/100mg BID + 3TC 150 mg BID n=217	88.3 %	87.2%	95.5%
LPV/r 400/100mg BID + 3TC /FTC + NRTI n=209	83. 7 %	77. 9 %	96.6%

- Grade 2-3 adverse events **more frequent in triple-ART** arm (88 vs 65 events)
- Hyperlipidemia more common in dual-ART arm (23 vs 16 pts)
- Limited resistance (2 with M184V in LPV/3TC)

Cahn P, et al. EACS 2013. Abstract LBPS7/6

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

- Randomized, open-label phase III noninferiority trial
- Primary endpoint: free of VF at Wk 48

Wk 48 primary analysis

239 patients

- HIV+ patients
- HIV-1 RNA < 50 c/mL
- on triple ART with LPV/RTV + 3TC or FTC + NRTI for 6 mos;
- no resistance to LPV/RTV or 3TC or FTC

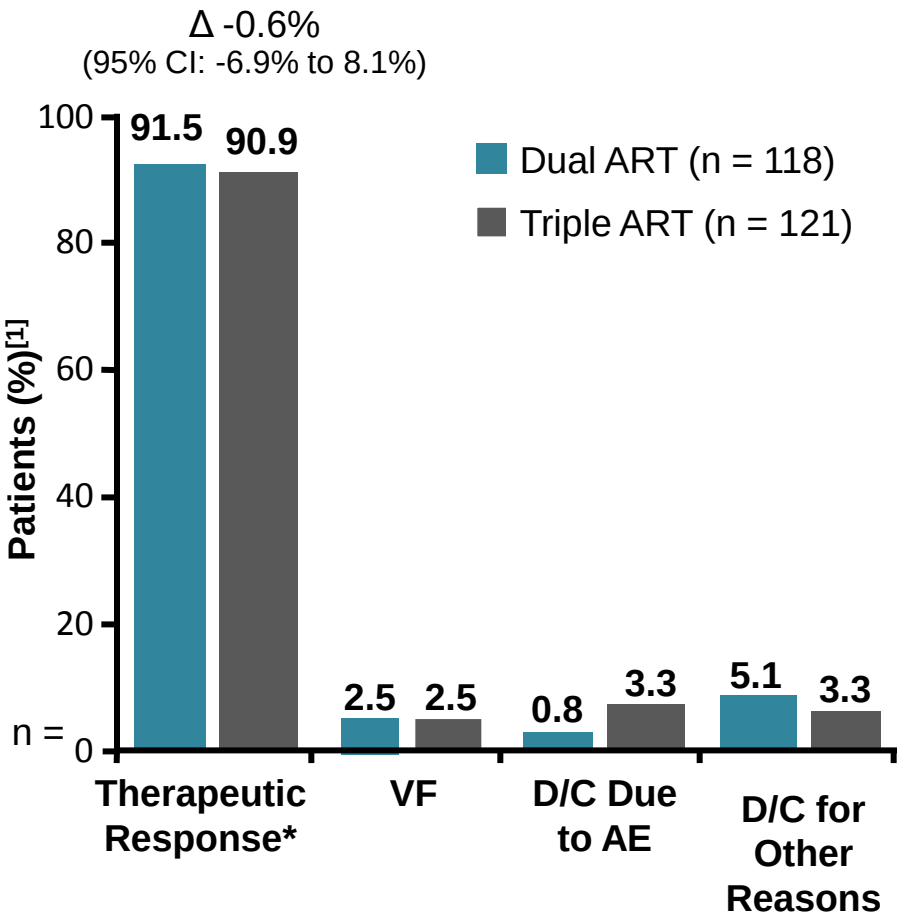
LPV/r 400/100 mg BID
+ 3TC or FTC

LPV/r 400/100 mg BID
+ 3TC or FTC
+NRTI/FTC or 3TC in FDC*

*TDF/FTC: 60%; ABC/3TC: 28%; Other: 12%

Gatell J, et al. AIDS 2014. Abstract LBPE17.

OLE : Switching to LPV/3TC non inferior to triple ART at W 48



- VF in 3 pts in each arm

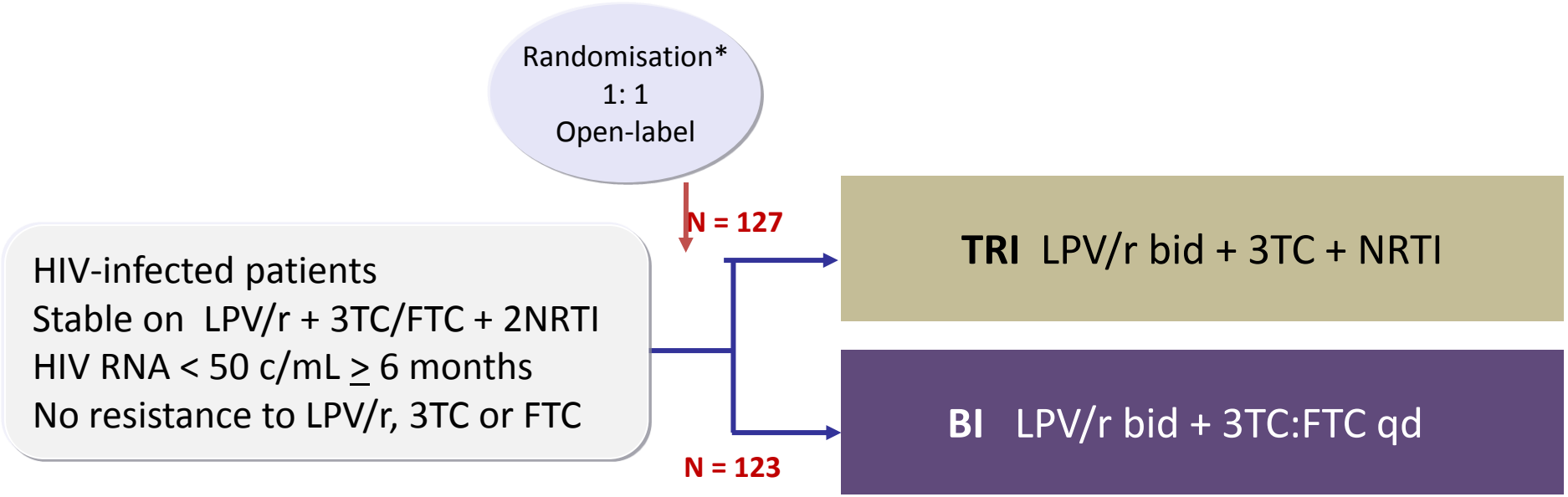
1 pt (dual-ART) tested for resistance; had K103N and M184V

- New grade 3/4 AEs in 9 pts in each arm
- greater increases in TC (*P* = .02), numerically greater increases in TG (*P* = .09) in dual-ART arm
- Numerically greater decreases in creatinine in triple-ART arm
- **SALT** trial of switches in suppressed pts showed switch to ATV/RTV + 3TC noninferior to switch to ATV/RTV + 2 NRTIs[2]

1. Gatell J, et al. AIDS 2014. Abstract LBPE17. Graphic used with permission. 2. Perez-Molina JA, et al. AIDS 2014. Abstract LBPE18.

Dual therapy 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

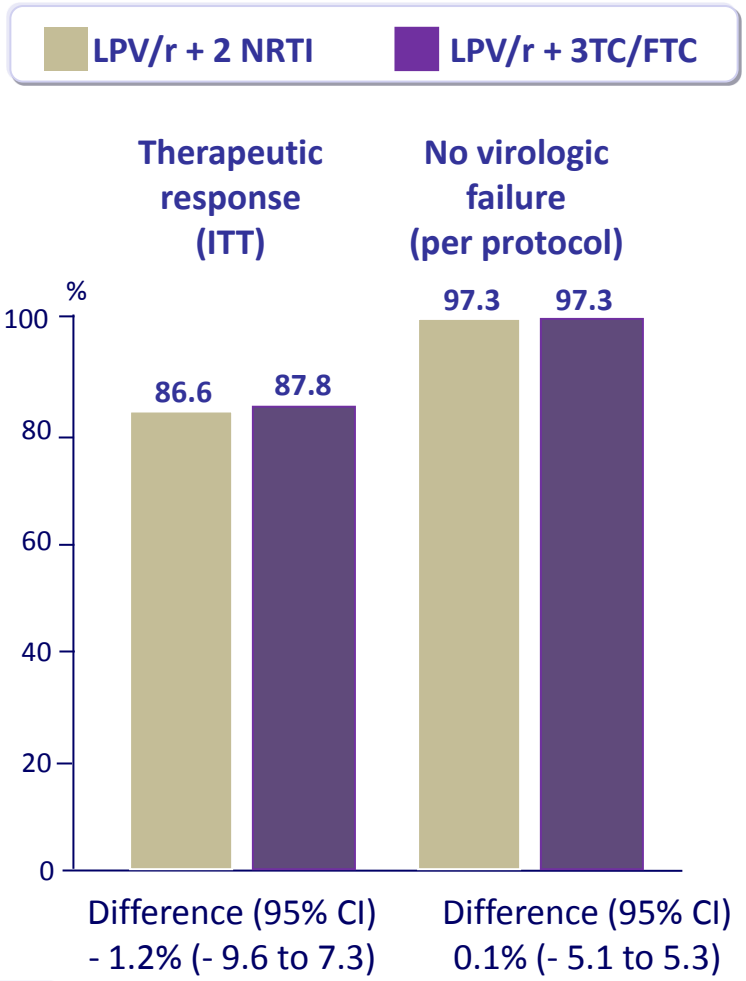
duration of viral suppression : 50 months

OLE

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

Dual therapy **OLE Study** Switching to LPV/3TC non inferior to triple ART at W 48

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

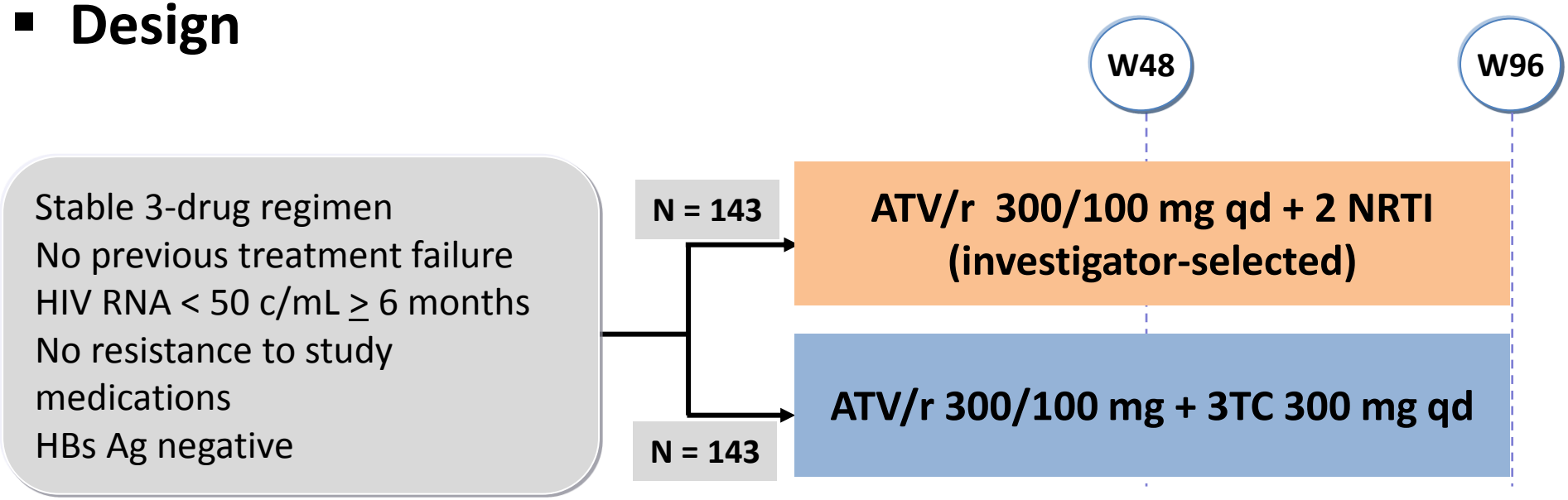
	LPV/r + 2 NRTI	LPV/r + 3TC/FTC
Adverse event	3%	1%
Virologic failure	2%	2%
Lost to follow-up	2%	3%
Other	6%	6%

OLE

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

Dual therapy 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)

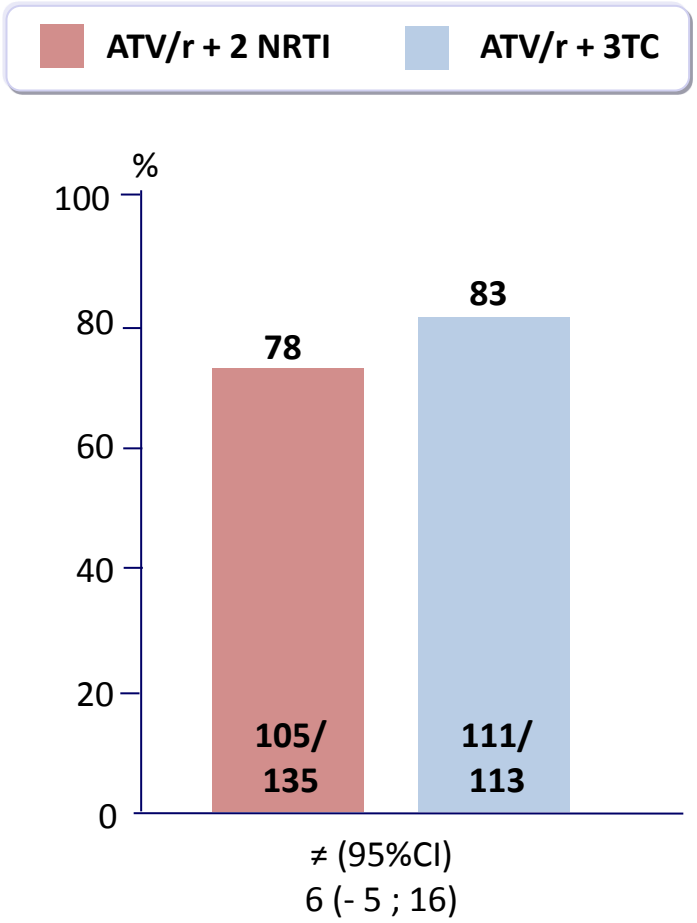
- **Objective**
  - Primary Endpoint : proportion with treatment success at W48
    - Treatment failure : treatment discontinuation or modification for any cause or confirmed virologic rebound (2 consecutive HIV RNA > 50 c/mL)
    - Non-inferiority of ATV/r + 3TC (per protocol) ; lower limit of the 95%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

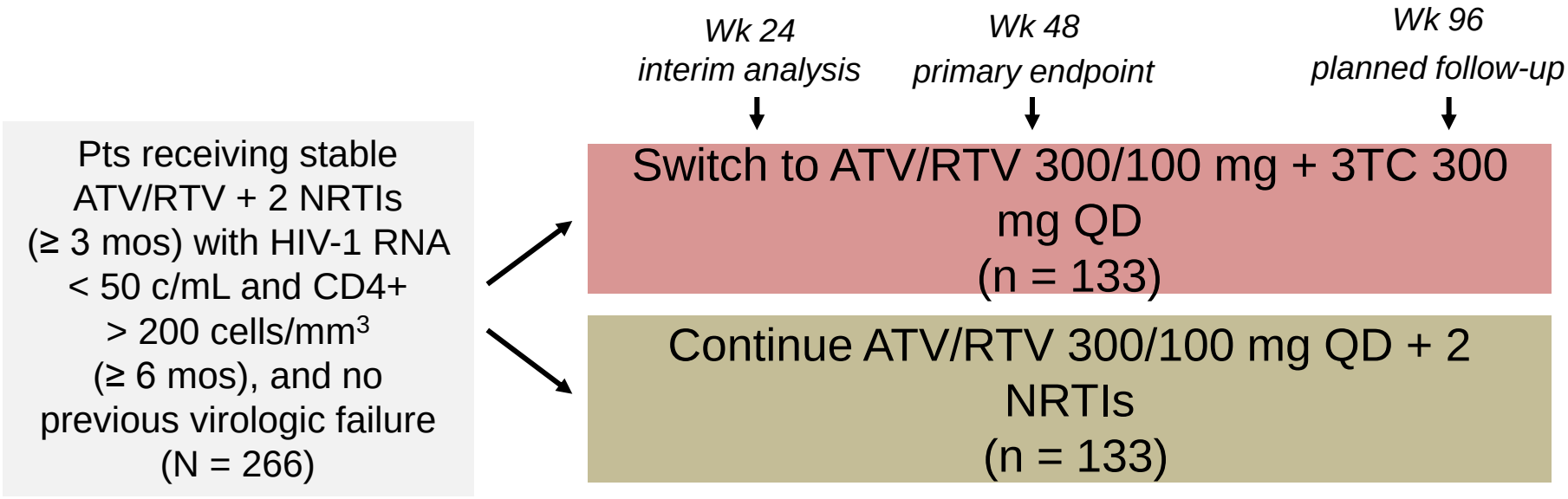
	ATV/r + 2 NRTI N = 141	ATV/r + 3TC N = 140
AEs leading to discontinuation	10 (7.2%)	3 (2.2%)
Severe adverse events (none related to study medication)	8	6

SALT

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

ATLAS-M: Switch From Suppressive ATV/r+ 2 NRTIs to ATV/r + 3TC

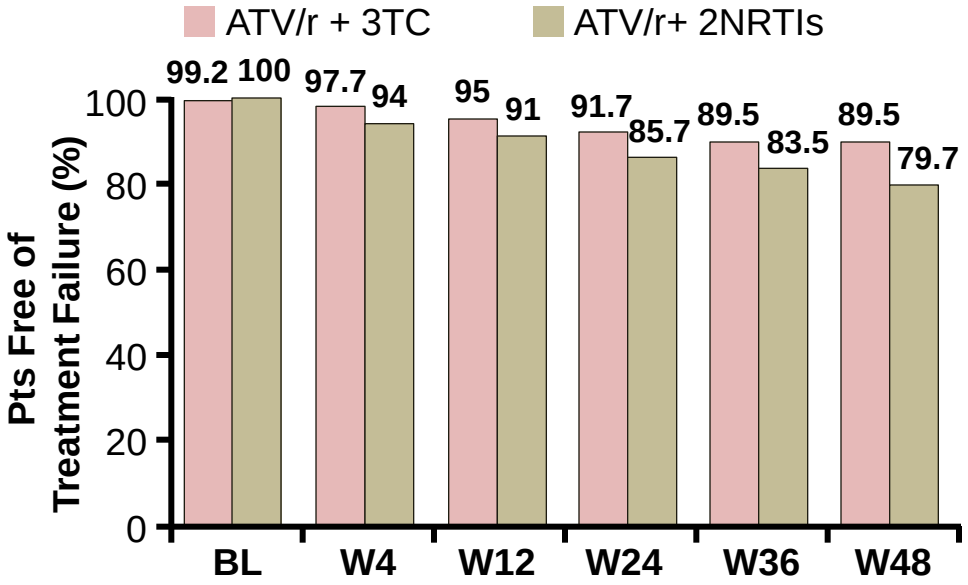
- Randomized, multicenter, open-label phase IV trial
  - Primary endpoint: absence of treatment failure at Wk 48, defined as ART modification for any reason

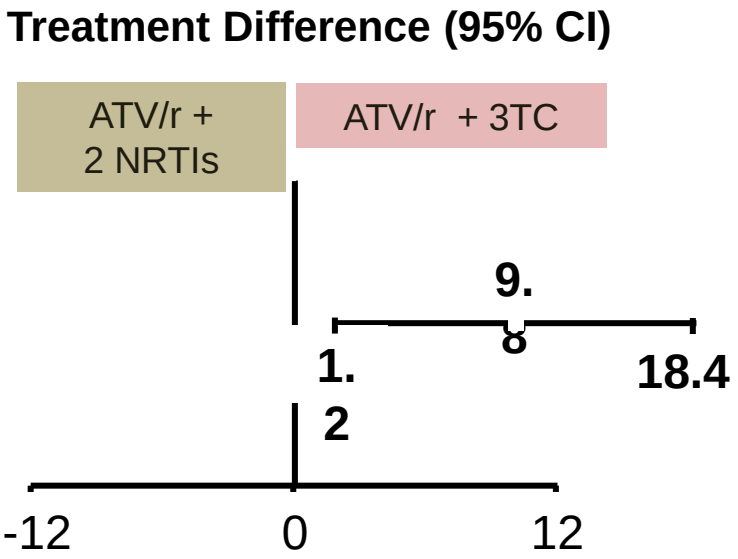


Di Giambenedetto S, et al. EACS 2015. Abstract 867.

ATLAS-M: Switch to ATV/r
Virologic Efficacy Through Wk 48

- Switch to ATV/RTV + 3TC noninferior and superior (post hoc) to continuing ATV/RTV + 2 NRTIs in ITT, S=F analysis





- Significantly greater increases in TC ($P < .01$), LDL ($P < .05$), and HDL ($P < .01$) with ATV/RTV + 3TC vs ATV/RTV + 2 NRTIs at Wk 48
- Mean change in eGFR at Wk 48: +2 mL/min with ATV/RTV + 3TC vs -4 mL/min with ATV/RTV + 2 NRTIs ($P < .001$)

Di Giambenedetto S, et al. EACS 2015. Abstract 867.

Boosted PI Dual Therapy: Phase III or IV Studies

Study	Treatment Setting	N	Regimen	Results
NEAT001[1]	Initial	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF; poor efficacy in pts with high viral loads, low CD4+ cell counts
GARDEL[2]	Initial	426	LPV/RTV + 3TC	Similar efficacy as LPV/RTV + 2 NRTIs
MODERN[3]	Initial	797	DRV/RTV + MVC	**Inferior** efficacy vs DRV/RTV + 2 NRTIs
OLE[4]	Switch	250	LPV/RTV + 3TC	Similar efficacy as continued standard ART
KITE[5]	Switch	60	LPV/RTV + RAL	Small study; encouraging efficacy
SALT[6]	Switch	286	ATV/RTV + 3TC	Similar efficacy as ATV/RTV + 2 NRTIs
ATLAS-M[7]	Switch	266	ATV/RTV + 3TC	Improved efficacy vs ATV/RTV + 2 NRTIs

References in slidenotes.

ETRAL : Schéma de l'étude

- Etude ANRS
  Dé marrage nov 2015
- Identifier une stratégie sans NRT et sans IP : RAL/ETR
- Etude non comparative
- Objectif : succès de la stratégie avec moins de 10 échecs viro / arret RAL/ETR

- Patient infecté par VIH-1, âge ≥ 45 ans
- CV <50 copies/mL depuis au moins 2 ans
- CD4 >200 cellules/mm^3
- Traitement ARV stable incluant un IP/r > 6 mois
- Naïf d'inhibiteur de l'intégrase et de l'étravirine
- Pas de mutation INNTI sauf K103N
- Sensibilité complète à ETR dans géno ADN

160 patients

RAL 400 mg x 2jour + ETR 200 mg x2/jour

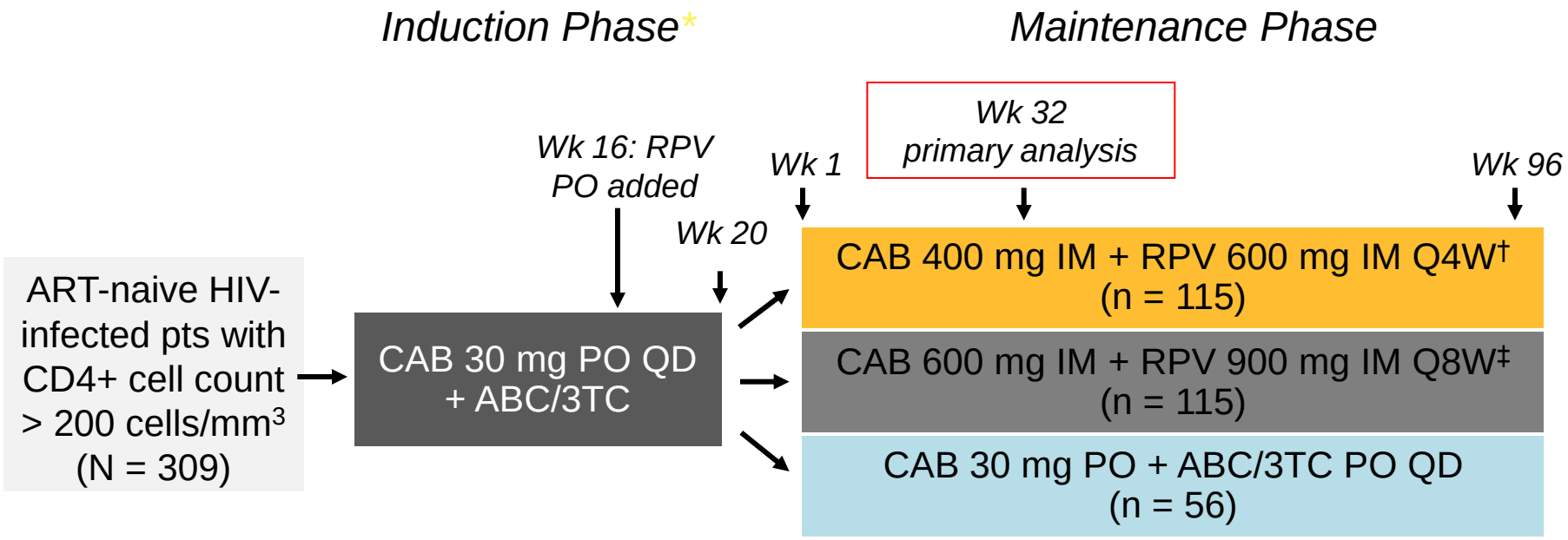
DXA scan
- Os
- Tissu

S48 Critères principal
Succès strategie

S 96 Critères secondaires

LATTE-2: Cabotegravir IM + Rilpivirine IM for long-Acting maintenance ART

- Multicenter, open-label phase IIb study
  - Cabotegravir: integrase inhibitor



6 pts discontinued for AEs or death in induction analysis. *Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. †Loading dose: Day 1, CAB 800 mg + RPV 600 mg. ‡Loading dose: Day 1, CAB 800 mg + RPV 900 mg; Wk 4, CAB 600 mg.

Margolis DA, et al. CROI 2016. Abstract 31LB.

LATTE-2: Cabotegravir IM + Rilpivirine IM for long-Acting maintenance ART

- **Virologic efficacy of Q4W/Q8W IM therapy similar to oral therapy**

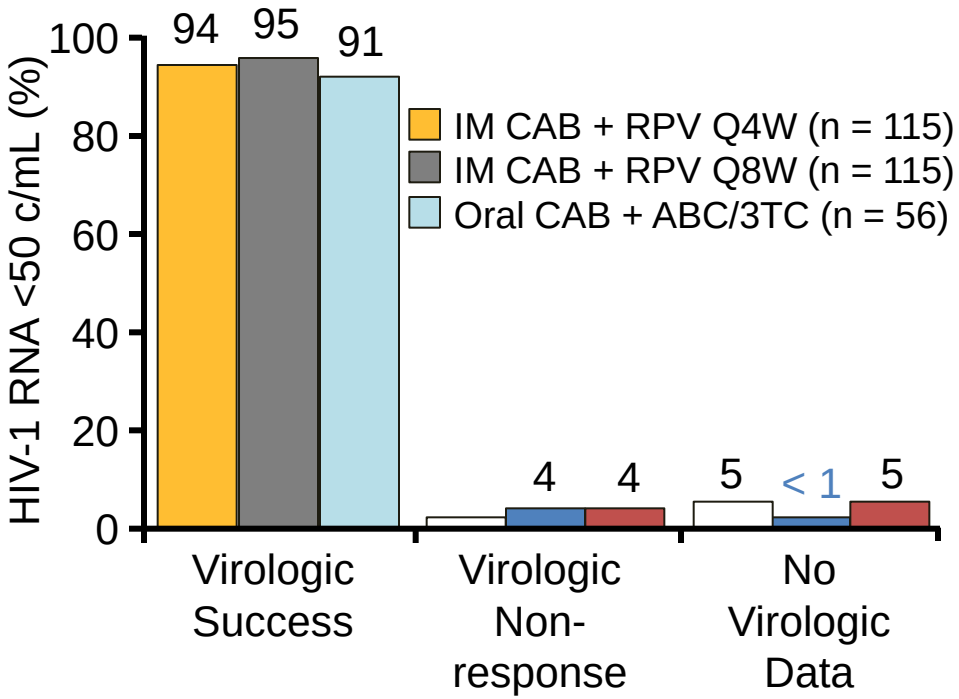
Outcome, % (n)	IM CAB + RPV Q4W (n = 115)	IM CAB + RPV Q8W (n = 115)	Oral CAB + ABC/3TC (n = 56)
Virologic success (HIV-1 RNA < 50 copies/mL)	91 (105)	92 (106)	89 (50)
Virologic nonresponse	< 1 (1)	7 (8)	2 (1)
No virologic data	8 (9)	< 1 (1)	9 (5)

- 99% of ISRs for IM grade 1 (82%) or 2 (17%); none grade 4 pain (67%), nodules (7%), swelling (6%)
- Reported ISRs decreased over time (86% Day 1, 29% Wk 48)
  - 2/230 pts (< 1%) withdrew for ISRs (both in Q8W arm)
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%
  - Oral arm, 2%

Margolis DA, et al. AIDS 2016. Abstract THAB0206LB

LATTE-2: Cabotegravir IM + Rilpivirine IM
Wk 32 Efficacy and Safety

Treatment Differences (95% CI):
Q4W IM vs Oral: 2.8 (-5.8 to 11.5)
Q8W IM vs Oral: 3.7 (-4.8 to 12.2)



- No INSTI, NNRTI, or NRTI resistance mutations detected

- Most frequent ISRs were pain (67%), swelling (7%), and nodules (6%)
  - ISR events/injection: 0.53
  - 99% of ISRs grade 1/2; none grade 4
  - 1% of pts withdrew for ISRs

AEs, %	Pooled IM Arms (n = 230)	Oral Arm n = 56)
Drug-related grade 3/4 AEs (excluding ISRs)	3	0
Serious AEs	6	5
AEs leading to withdrawal	3	2

Margolis DA, et al. CROI 2016. Abstract 31LB.

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

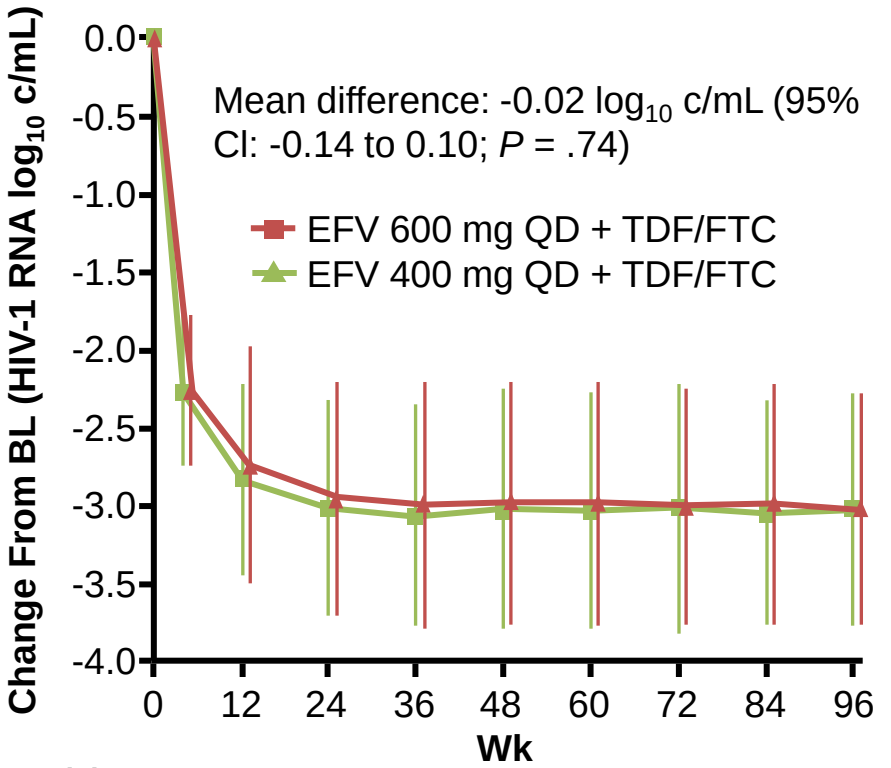
	HIV-1 RNA < 200 cp/ml W48		
	NC=F	**ITT**	**PP**
EFV* 400 mg + Placebo + TDF/FTC n = 324	90.0 %	94.1 %	98.3 %
EFV* 600 mg + TDF/FTC n = 312	85.8 %	92.2 %	97. 4 %

- 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.

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

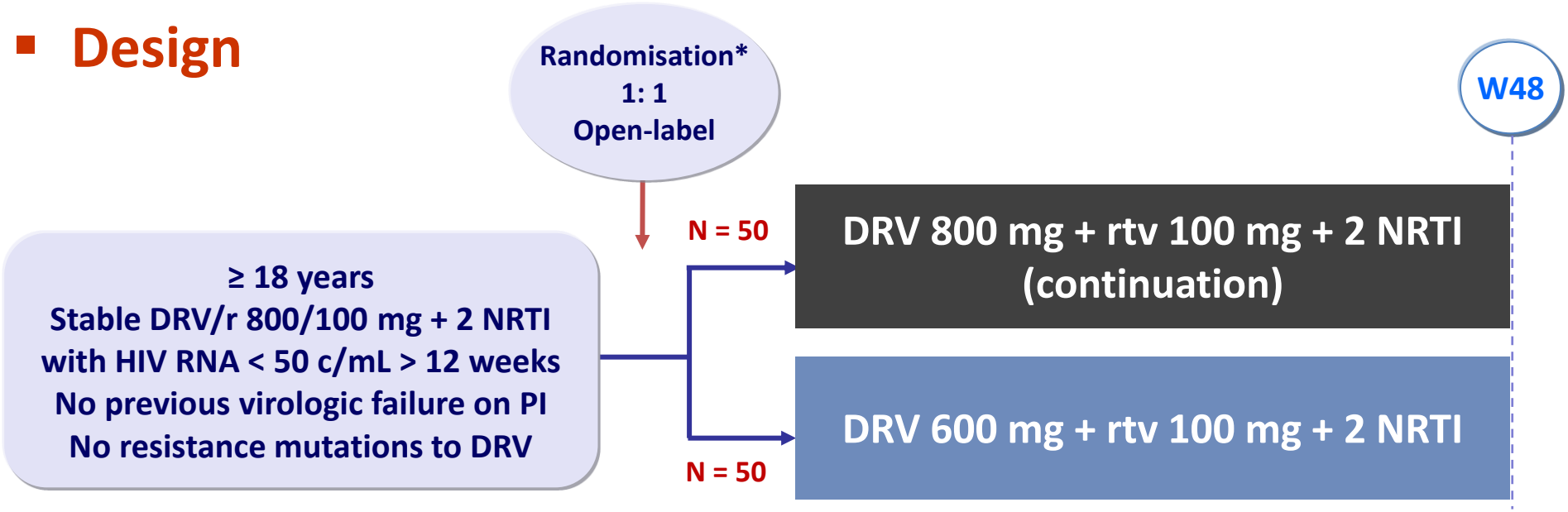
- Mean change in CD4+ cell count from BL greater with 400-mg vs 600-mg EFV (P = .03)
- Rate of EFV-related AEs lower with 400-mg vs 600-mg dose: 37.7% vs 47.9% (P = .01)
- Trend toward lower rate of discontinuation for EFV-related AEs with 400-mg vs 600-mg dose: 8.3% vs 15.5% (P = .07)
- Frequency of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

Carey D, et al. Glasgow HIV 2014. Abstract O421.

Dose reduction

DRV600 Study: switch DRV/r from 800 mg 600/100 mg

- **Design**



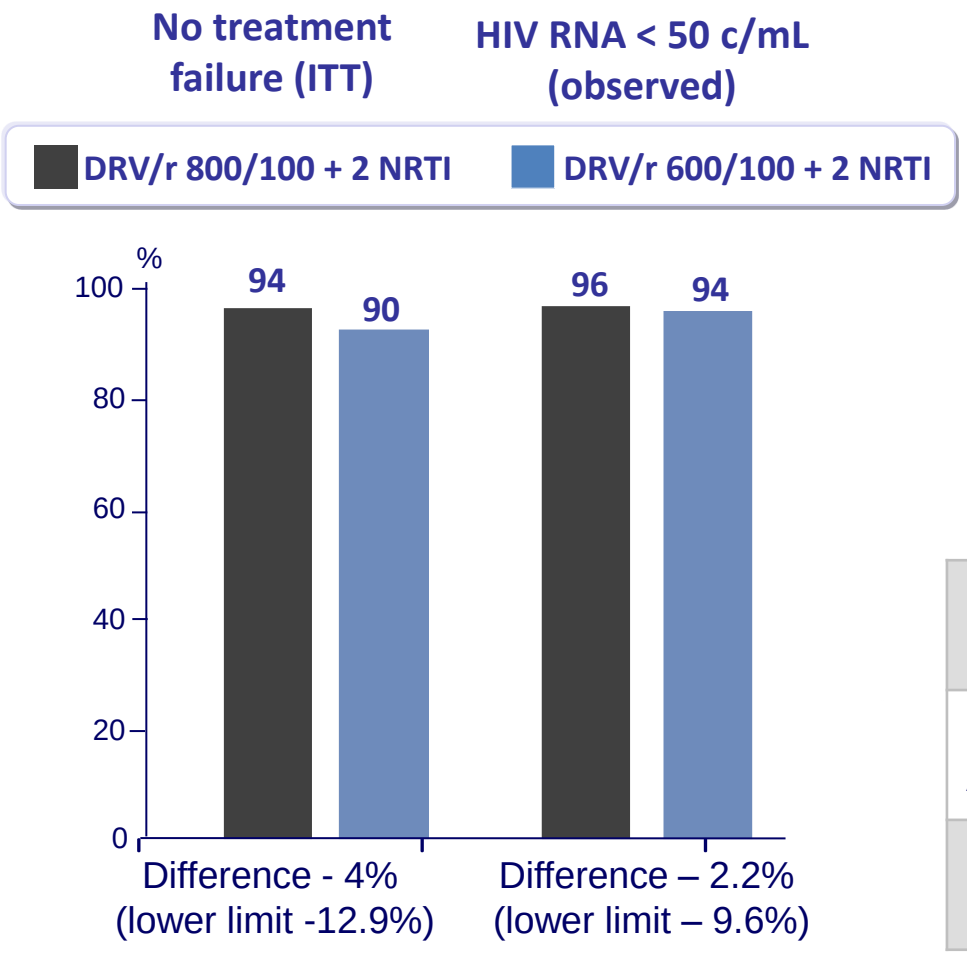
* Randomisation was stratified on HIV RNA (≤ or > 100,000 c/mL) prior to ART start

- **Objective**
  - Primary Endpoint : proportion with treatment success at W48 (ITT analysis)
    - Assuming 90% efficacy at W48, sample size of 100 provide 80% power to detect a minimum difference of 15% in efficacy
  - Other endpoints : observed analysis of virologic efficacy, PK substudy, cost-efficacy analysis

Molto J. J AntimicrobChemother 2015;70:1139-45

Dose reduction

DRV600 Study: switch to DRV/r 600/100 mg



Genotype done in 3/5 VF :
no emergence of resistance

DRV/r 800/100 n = 50
DRV/r 600/100 n = 50
Mean age, years 45
BL CD4/mm^3 : 591
Nadir CD4/mm^3 : 201
Median Duration of HIV RNA < 50 c/mL (weeks), median 107

Safety

	DRV/r800/100	DRV/r 600/100
Gastrointestinal AE of grade ≥ 2	**N = 6**	**N = 4**
Lipid elevations	**N = 5**	**0**

No discontinuation for AE

DRV600

Molto J. J AntimicrobChemother 2015;70:1139-45

Dose reduction
DRV600 Study: switch to DRV/r 600/100 mg

- **Phamacokinetics**
  - Mean DRV C_{trough} : 2.21 ± 1.44 mg/dL for DRV/r 800/100 vs
    : 2.19 ± 1.50 mg/dL for DRV/r 600/100 (p = 0.94)
  - No significant difference in AUC nor other PK parameters between the 2 groups

Full PK analysis

	DRV/r800/100 N = 15	DRV/r 600/100 N = 15	
	Mean (90%CI)	Mean (90%CI)	Geometric mean ratio DRV600/DRV800(90% CI)
AUC_{0-24} (mg.h/L)	83.99 (72.92 – 96.73	76.66 (66.56 – 88.29)	0.91 (0.75 – 1.10)
C_{max} (mg/L)	6.63 (5.92 – 7.42)	6.52 (5.82 – 7.29)	0.98 (0.84 – 1.15)
C_{trough} (mg/L)	1.84 (1.45 – 2.32)	1.60 (1.26 – 2.02)	0.87 (0.63 – 1.21)

Molto J. J AntimicrobChemother 2015;70:1139-45

Towards a lighter suppressive ART

Intermittent ART

4D study

Breather

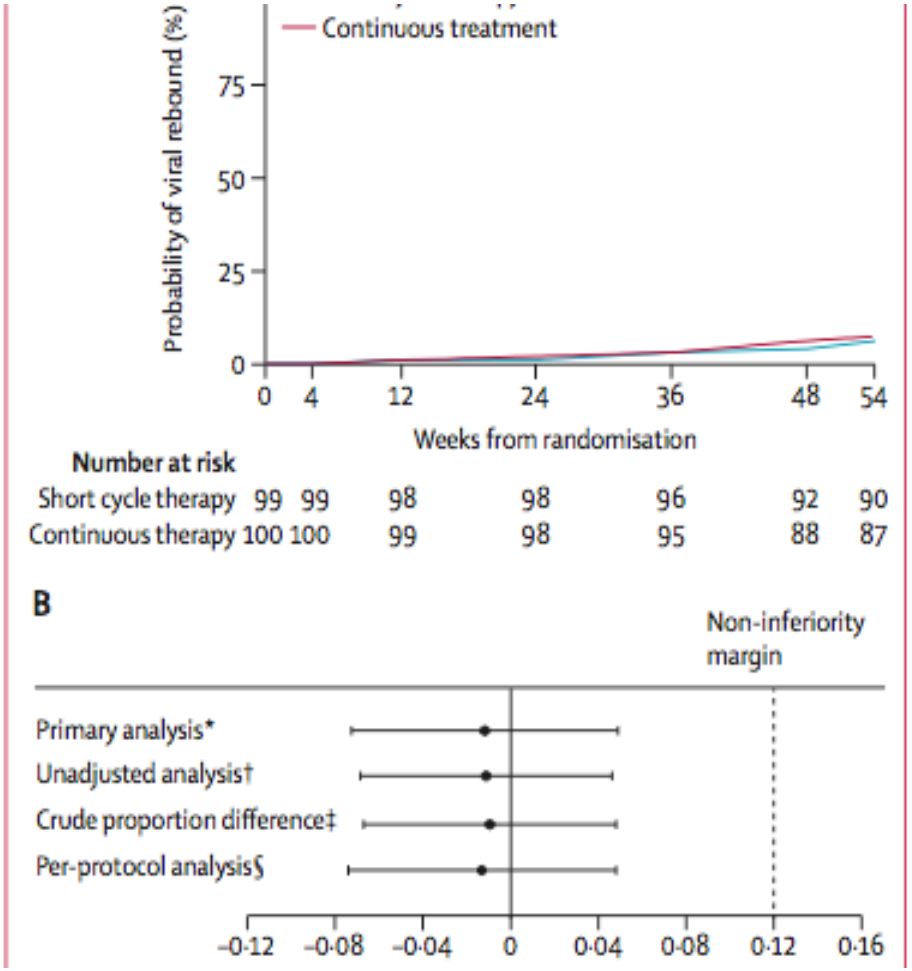
Intermittent Therapy

Breather : a week off is safe

Open label RCT
199 patients 8-24 year old
CD4> 350 VL< 50 cp/mL
Median age : 14 yo
AZT/3TC/EFV :53%
TDF/FTC/EFV :23%
ABC/3TC/EFV : 22%

Intermittent : 5days /2 off ART
Continuous : 7 days ART

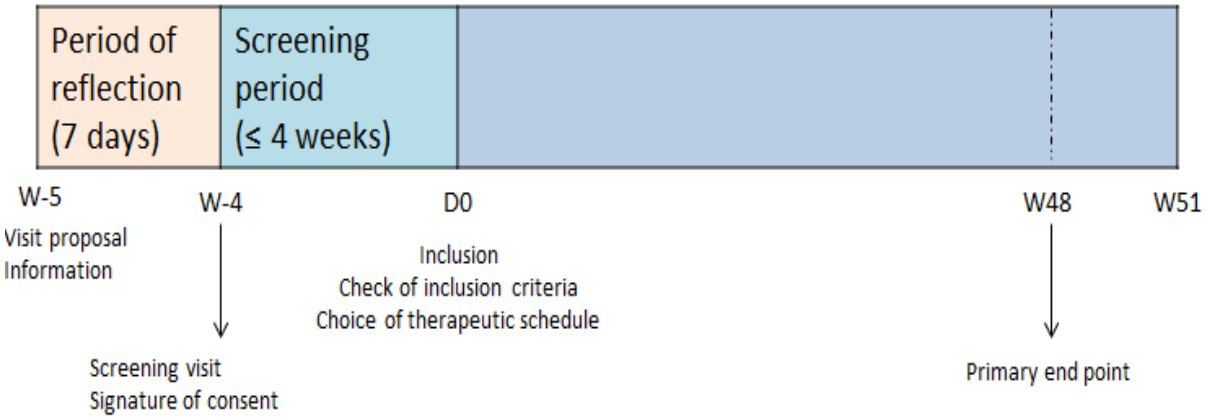
Viral rebound > 50 cp/ml
6 pts Interm ART vs 5 cont ART
difference –1·2%, 90% CI –7·3 to 4·9, test for difference, bootstrap p=0·75; figure 2A).
Thus, the 4·9% upper band of the two-sided 90% confidence limit was well within the 12% non-inferiority margin.



Intermittent Therapy
4D study ANRS 162

- age>18 years
- current ART with 2 NRTI = NNRTI or PI/b
- no treatment modification in the last 4 months
- plasma VL< 50 c/ml for at least one year
- no resistance mutation to the drugs in current regimen

- 100 patients enrolled
- 6 years VL< 50 cp/mL
- NNRTI –ART : 70% EFV 40% RPV 26%)
- IP DRV:29% ATV 13%



2 weekly modalities of antiretroviral taken

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
on	on	on	on	off	off	off
off	on	on	on	on	off	off

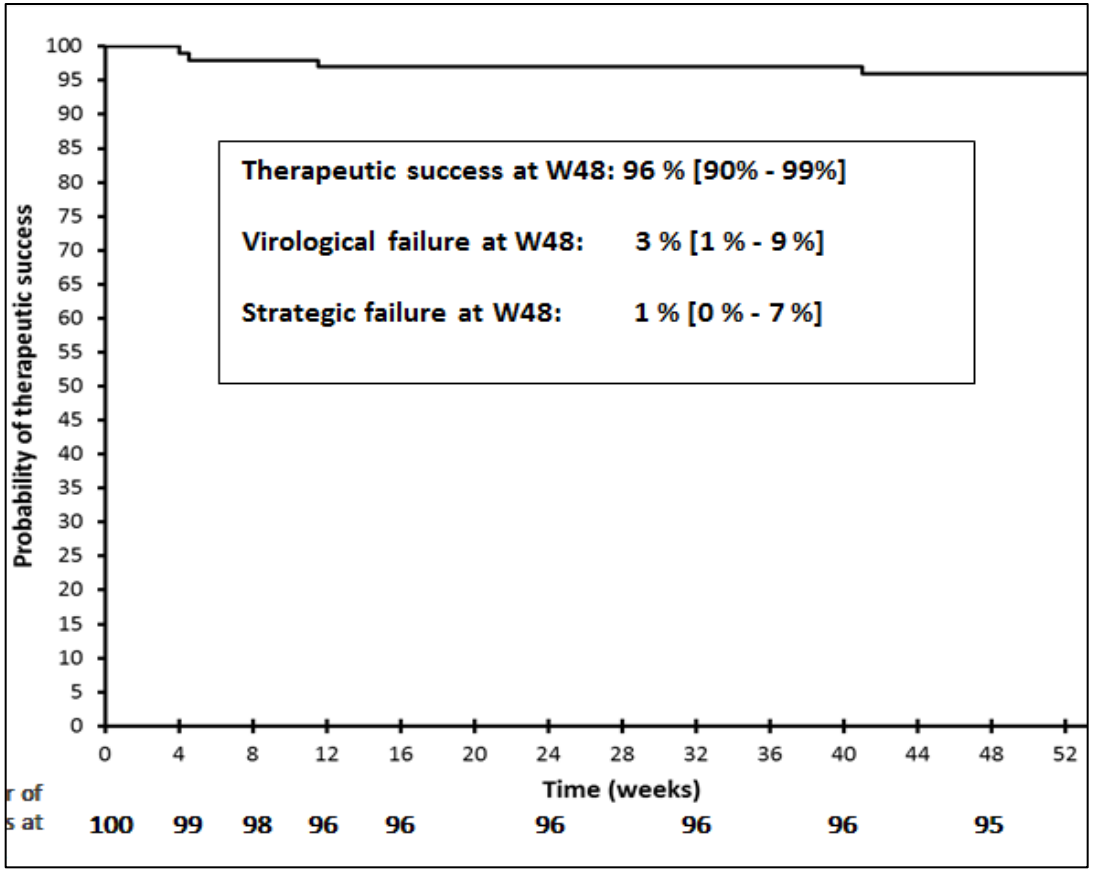
Samples collected within the visit off have been done at the end of the 3-days off

	D0	W4	W8	W12	W16	W24	W32	W40	W48	W51
Samples time point	on	off	off	off	on	off	off	on	off	off

Intermittent Therapy

4D study ANRS 162

Kaplan-Meier Curve of probability of therapeutic success.



- **3 virological failures**

  No resistance ++
- 1 strategic failure discontinuation at W4 due to anxiety
- One patient discontinued the study at W12 for Pregnancy and was censored at the date of study discontinuation

Traitements ARV 2015

Pts sous ARV n=10. 841 (97%)

Stratégies par site

Types de stratégies	PSL		SAT		TN	
	n	%	n	%	N	%
Trithérapie	**3137**	76%	**3200**	86%	**2518**	84%
2NRTI+1NNRTI	1309	32%	1260	34%	898	30%
2NRTI+IP/r	728	18%	605	16%	474	16%
2NRTI+Inhib. de l'intégrase	890	22%	1082	29%	953	32%
2NRTI+IP non boosté	77	2%	110	3%	264	2%
Autres Trithérapies	133	3%	142	4%	391	4%
Monothérapie	147	**4%**	124	**3%**	74	**3%**
Bithérapies	**766**	**19%**	**291**	**8%**	**236**	**8%**
Multi-thérapie (>=4 molécules)	73	2%	106	3%	165	6%
Total sous traitement	4123		3721		2993	

Mono and dual suppressive Antiretroviral Therapy
Pitie Salpetriere Hospital 2015

n= 3748 Patients						
Médian value (%) IQR	**Monotherapy** n=140 (4%)		**Dual Therapy** n=710 (19%)		**Triple drug Therapy** n=2898 (77%)	
H/F (%)	69% / 21%		68% / 32%		69% / 31%	
Age	52 [46-59]		53 [48-61]		49 [42-56]	
ART regimen	DRV/r LPV/r ATV/r DTG	97 (69%) 9 (6%) 10 (7%) 24 (17%)	INI +NNRTI +NRTI +IP/r 2 NRTI 1 NRTI+IP/r NNRTI+IP/r Autres	283 (40%) 60 (8%) 66 (9%) 94 (13%) 77 (11%) 49 (7%) 81 (11%)	2 NRTI+NNRTI 2 NRTI + INI 2 NRTI+IP/r 2 NRTI+IP Autres	1240 (43%) 831 (29%) 630 (22%) 72 (2,5%) 125 (4,4%)
ART duration (years)	16,8 [9-20]		18 [8-21]		10,7 [5-18]	
Nadir CD4 /mm3 (IQR)	227 [159-319]		196 [93-319]		225 [109-341]	
CD4/mm3 (IQR)	663 [525-824]		627 [474-828]		611 [449-805]	
First line ART	3 (2,1%)		53 (7,5%)		384 (13,3%)	
Switch ART	137 (97,9%)		657 (92,5%)		2514 (86,7%)	
Current regimen duration(mths)	23 [10-54]		15 [7-39]		28,2 [12-61]	

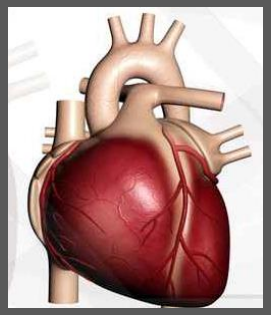
Long life management of HIV infected patient

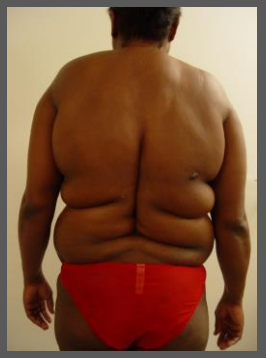
HIV

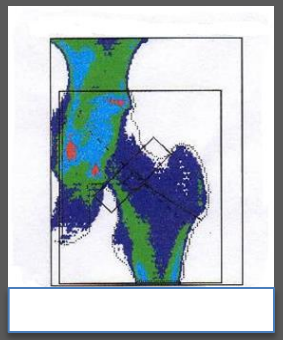
ART

Age

Co-morbiditiess







ART early

ART minimal

Healthy living
- diet
- exercice
- prevention

Learning points

- Viral suppression is the only dogma in ART management
- Many possible options with less but more potent and robust drugs in long term suppressed patients
- Consider all ART history
- Less drugs should be a priority