EACS European AIDS Clinical Society

Optimizing therapies in HIV suppressed patients

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HIV and ART
Where Are We in 2017 ?

- **Maximal viral suppression** allows
  - blocking all deleterious effects of HIV replication
  - optimal prevention of sexual transmission
- ART should be **universally prescribed** to HIV individuals who need to be aware of such benefits
- Earlier ART is started , better is future
- No cure no remission means long life therapy for up to 6- 7 decades
- Sustain viral suppression : a major challenge

Optimization of ART an evolutive concept over time

- **2000 Ultimate goal was efficacy**
  Improve efficacy even if sacrificing
  for toxicity and complexity (no choice)
- **2010 Simplify daily regimen**
  With efficacy obtained with many regimens
  Simplification was the new goal
  Switching from from TID to BID and QD
- **2015 Individualized optimization**
  To reduce drug exposure
  To adjust based on aging

Reasons for individualizing ART

Adjust ART to each individual

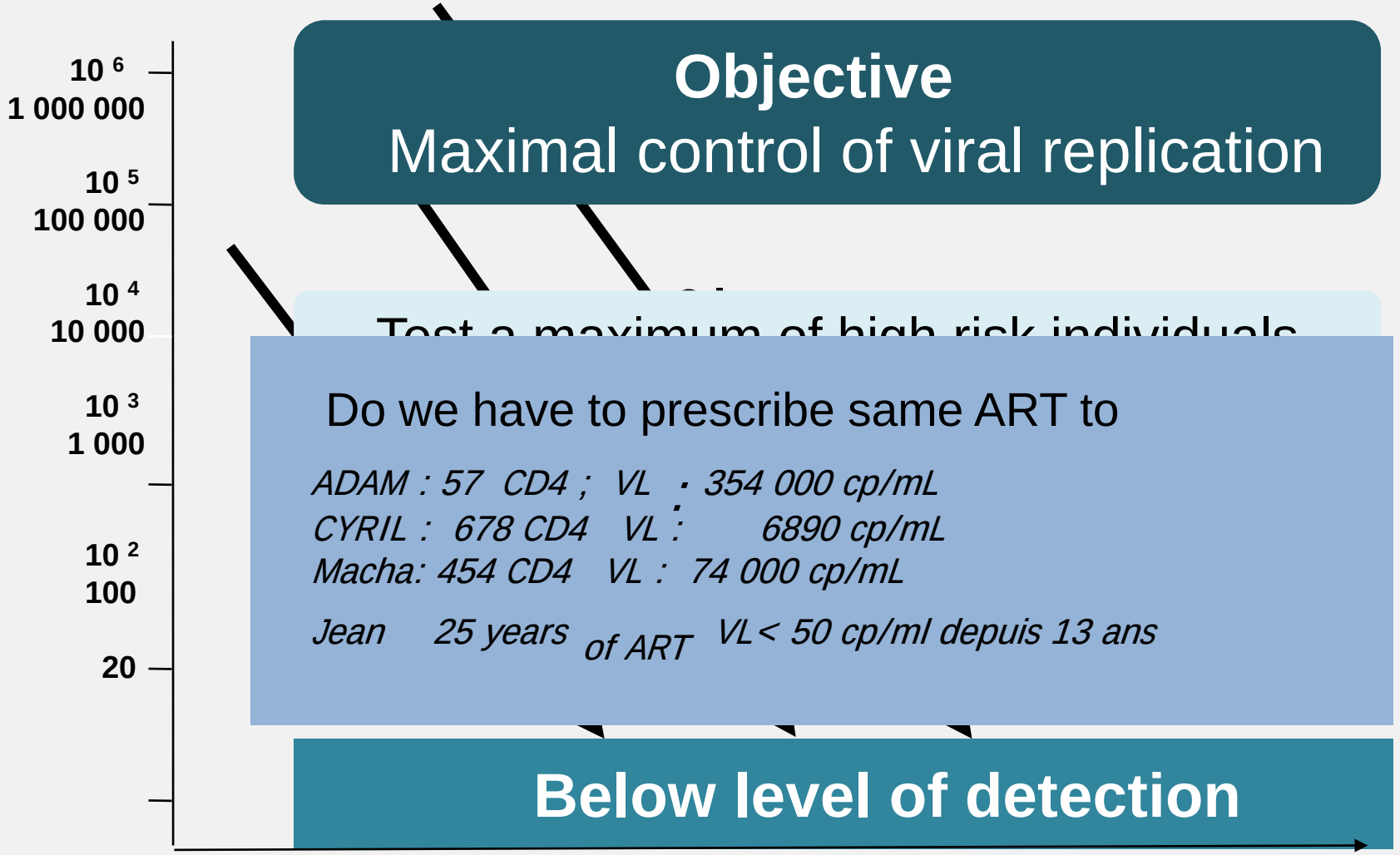
Context

- **Earlier ART Initiation**
  At Pitié Salpétriere 2016
  57% start ART with > 350 CD4
  and 41% with VL< 30 000 cp/mL
- **Recent/New Drugs**
  More potent and robust
- **Decades of Supressive ART**
  Needed with prolonged drug exposure
- **Preserve Drug Options**

Challenges

- Adjust ART to CD4 VL and duration of viral suppression
- Maintain **long life viral suppression**
- **Minimize toxicity** and drug drug interactions
- **Adjust** with aging comorbidities

Antiretroviral Therapy Goals



ART is a life long therapy thoughout decades of life

ART has to be adjusted to different life events

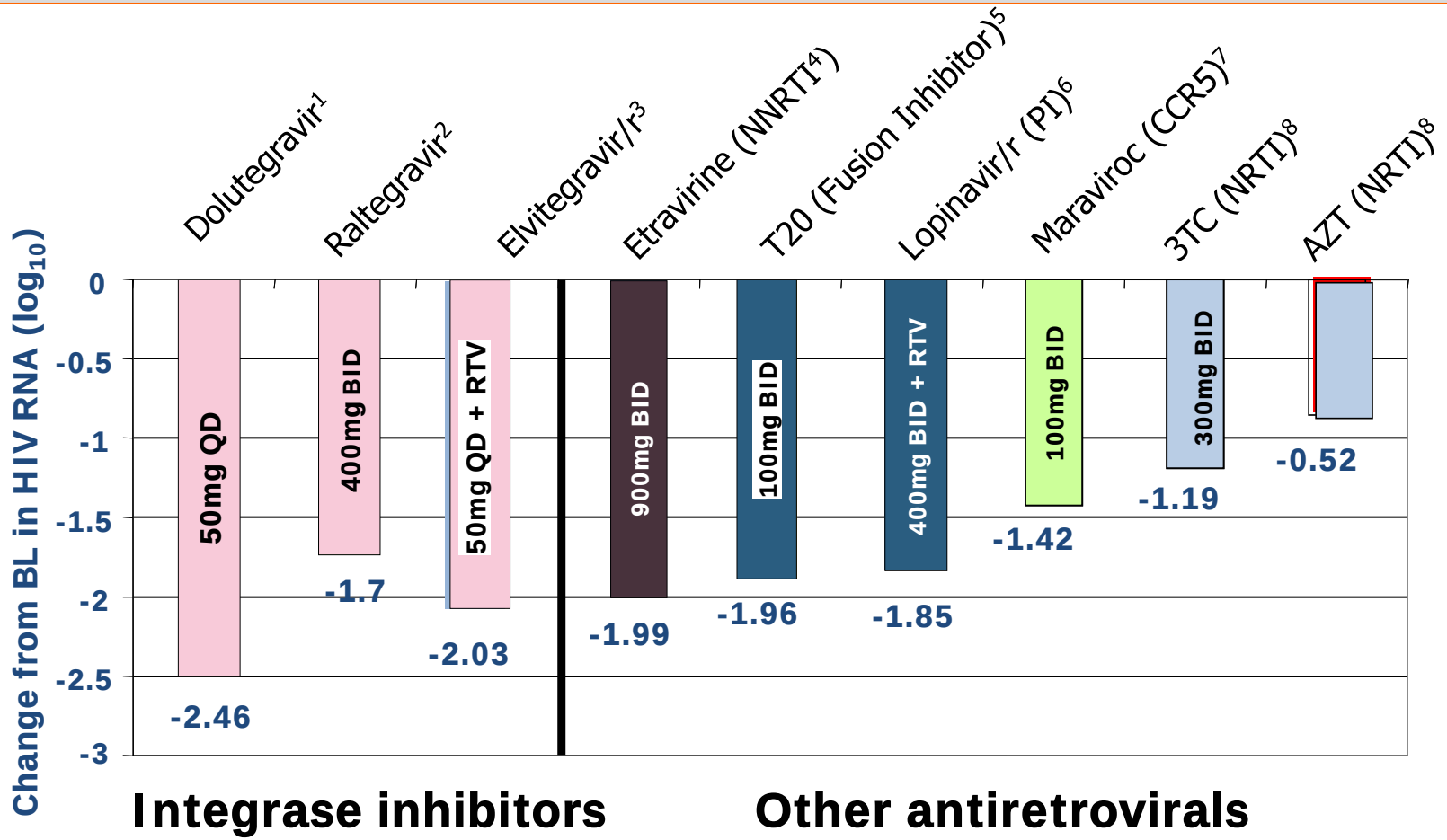
Antiretroviral Drugs : 2017

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

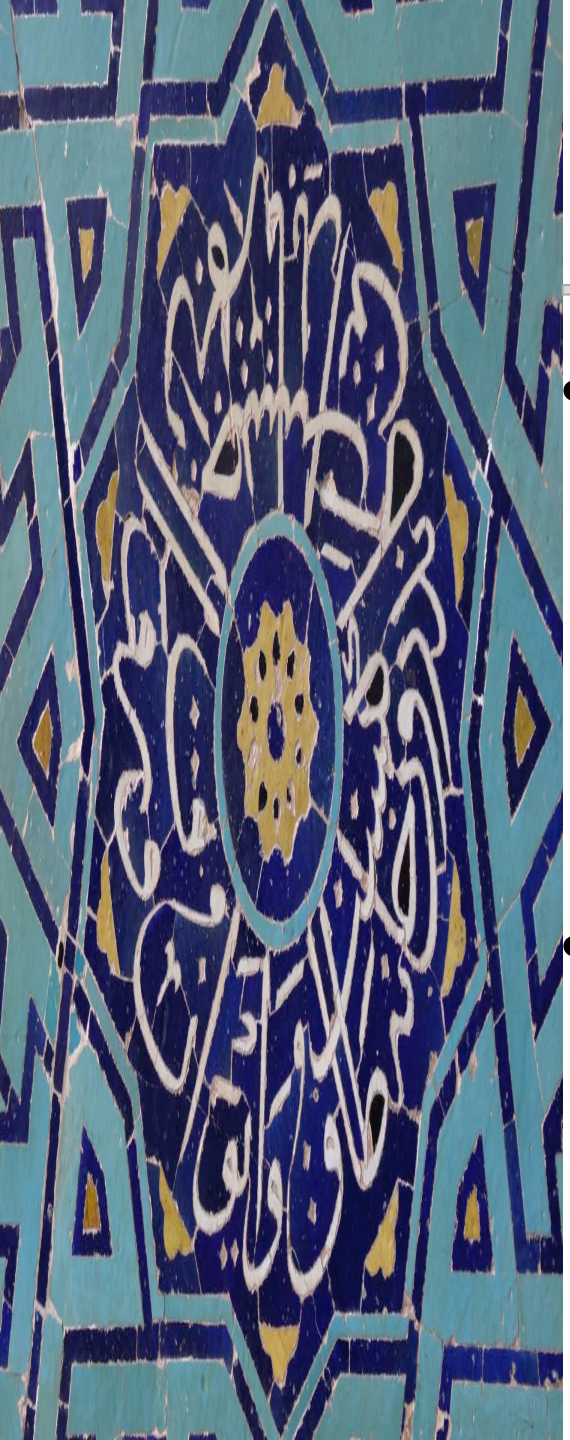
Single tablet regimen

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.*



Individualization of therapy
Precision Medecine

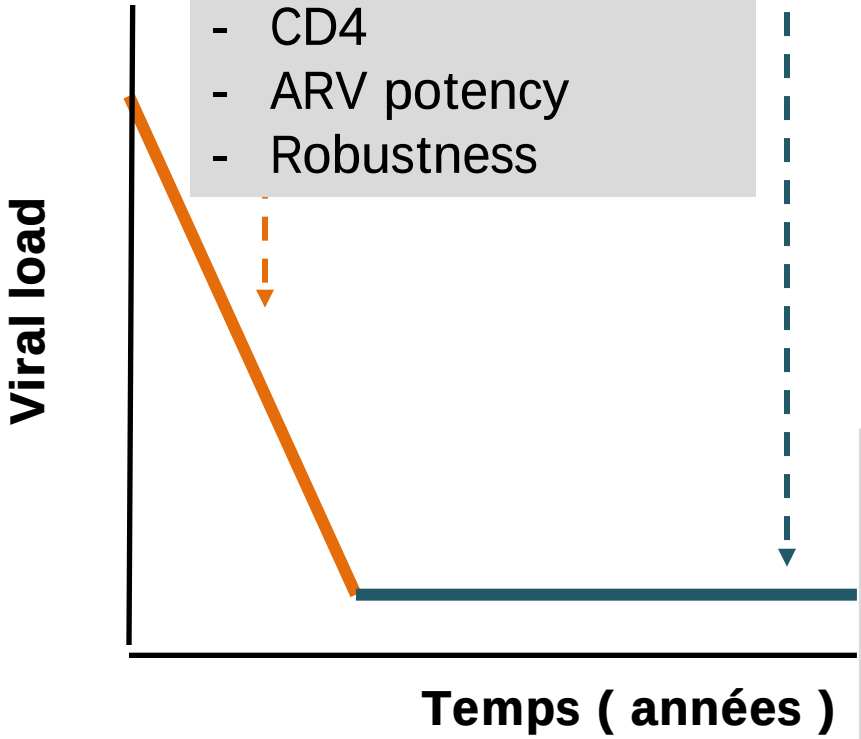
- According to the NIH, precision medicine is “an **emerging** approach for disease treatment and prevention that takes into account individual variability in **genes**, **environmen**t, and **lifestyle** for each person”.
- This is in **stark contrast to a “one size fits all**”, the current approach in treating HIV infection in which disease treatment is developed for the average person.

New paradigm in ART management
Individualization of antiretroviral therapy

Induction

1996 Triple therapy : a revolution

Nb drugs depends on
- HIV RNA
- CD4
- ARV potency
- Robustness



2017

Context has changed

- More potent drugs
- More robust drugs
- Earlier therapy with higher CD4 and lower VL

Objective

- Viral Suppression
- Optimal CD4 and CD4/CD8
- Low DNA

NRTI Nucleosides analogues RTI

- Even though TDF/ABC has replaced D4T or AZT , persists in a much lesser extent a degree of mitochondrial toxicity
- TAF more protective on bone and kidney will replace TDF
- particularly beneficial in aging patients who often cumulates a long past history of NRTI
- TDF/TAF virologically robust; active on HBV
- New NRTI in development ;

NNRTI Non Nucleosides analogues RTI

- Many advantages
  - limited long term adverse effects (no metabolic ; CV or bone renal)
  - Long half life
- Some disadvantages
  - low barrier to resistance
  - new drugs might be better (Doravirine)
- NVP : has been replaced by safer NNRTI
- EFV : CNS psy .. Careful
- RPV : easy ; high tolerability ; combined
- ETR : TDF/TAF virologically robust; active on HBV

Good companions in dual therapies

Protease inhibitors :

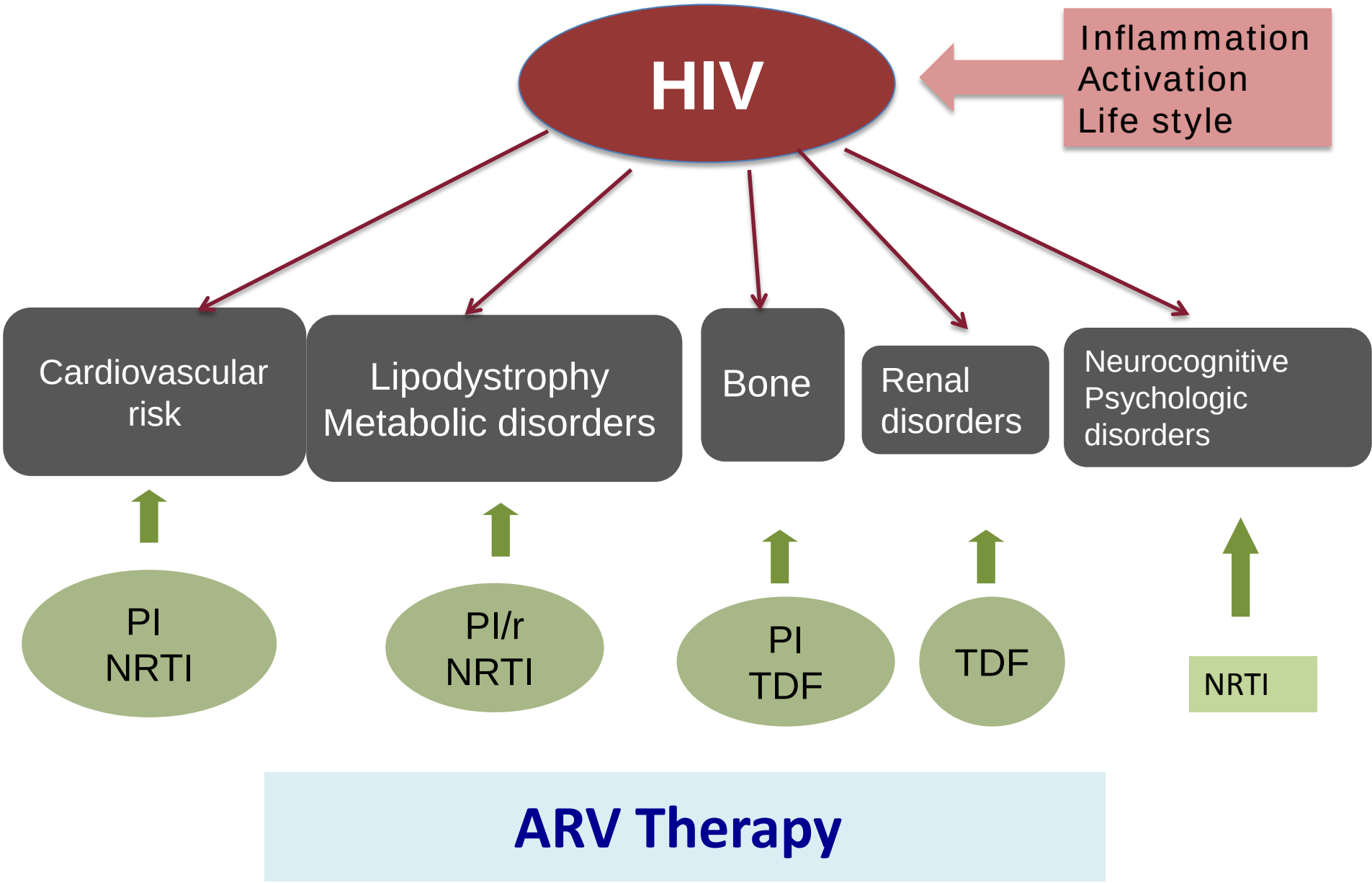
Twenty years of experience

- **Long term efficacy**
  - sustained efficacy over time
- **High genetic Barrier to resistance +++++**
  - never in defect
  - highest among ARV drugs
  - highly forgiving ++
- **Simplicity**
  - QD with no STR except for DRV/c
  - No food effect
- **Tolerability** : known AE and manageable

Integrase Inhibitors : a key role in ART likely to be a cornerstone of ART

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

Interactions of HIV and ARV drugs



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**

Reasons to Switch from a 3-Drug regimen

TOXICITY
Management

Drug burden reduction
Expected VS with less drugs

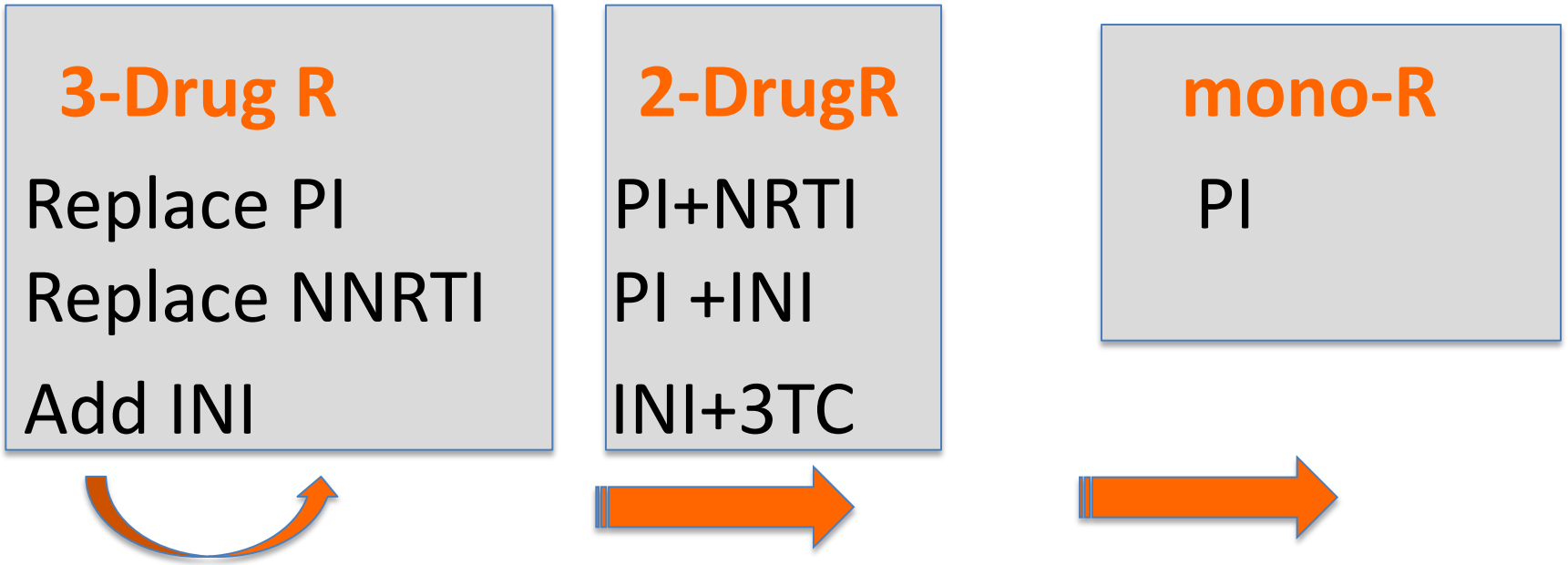
Prevention of Comorbidities
Cardio vasc / Lipids / kidney /bone

Discard resistant drugs
Cost and no expected antiviral effect

Drug Drug interaction
Introduction new Rx
Chemotherapy

Switching : Options

Switch : Modification of a suppressive regimen
Simplification is different from drug reduction



ARV Reduction : Check for sensitivity of remaining drugs

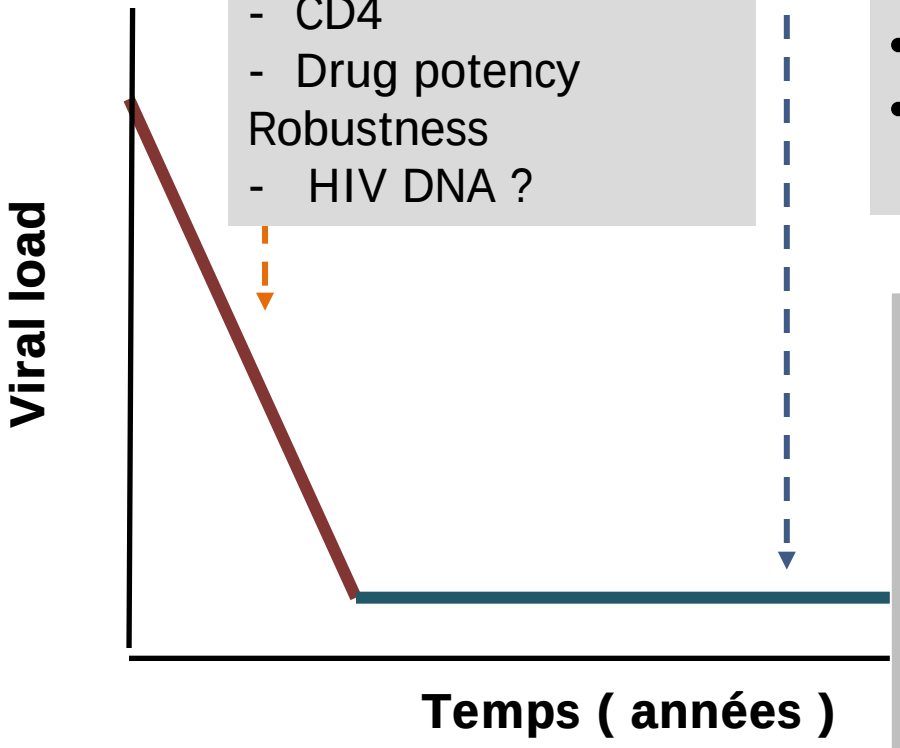
New concepts in Antiretroviral therapy
Individualization of therapy

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 ?

Towards a lighter suppressive ART

Monotherapy

Dual therapies

Dose reduction

Intermittent ART

Protease Inhibitor Monotherapy

Switch Studies

Lopinavir

Darunavir ++

Monoi

Monet

Pivot

Atazanavir

Not robust enough

- **Efficacy**

Non inferior or

Slightly less effective (5%) compared to 3-DR

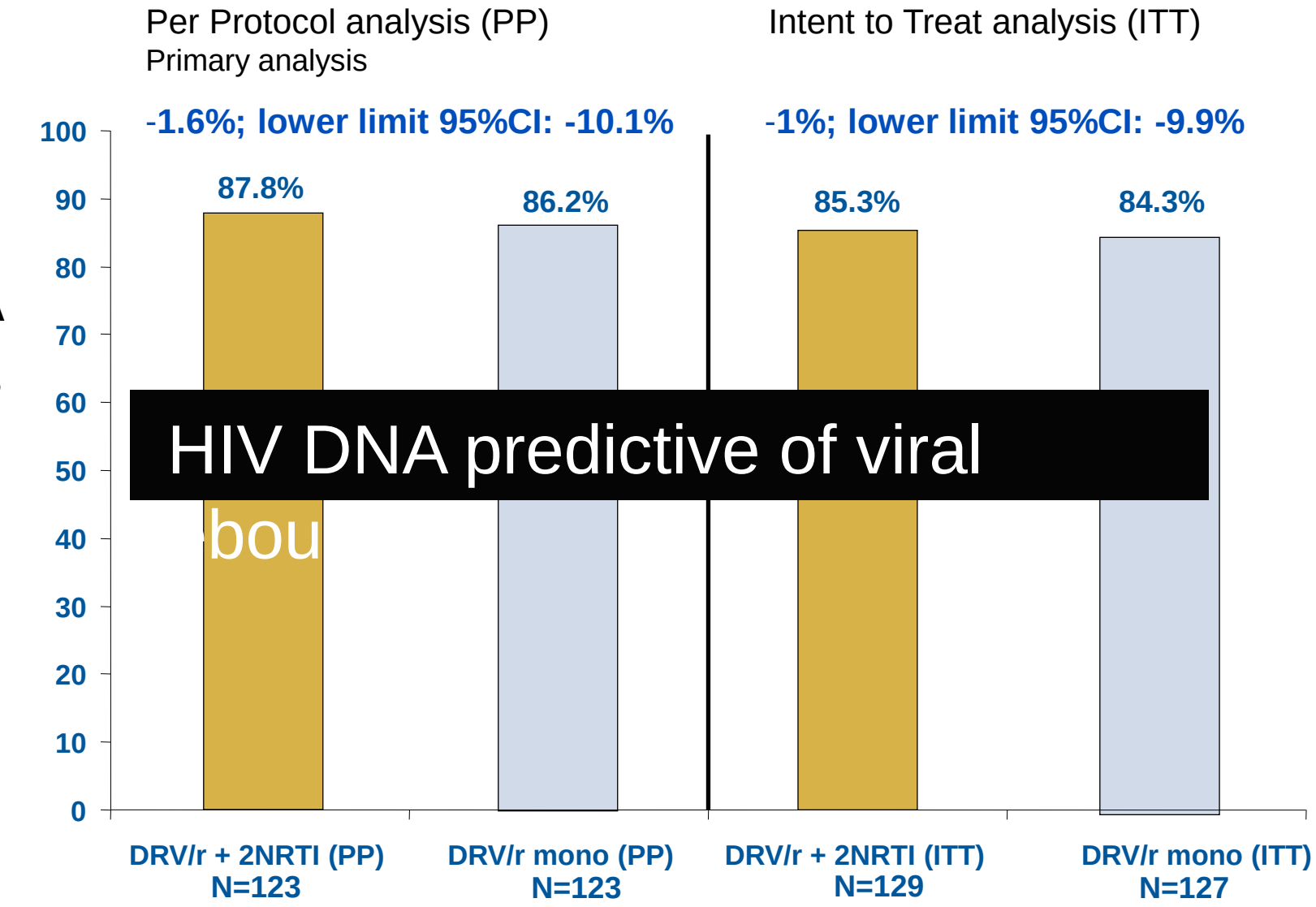
- **Robust:** +++

Very limited resistance in case of viral failure (VF)

- **Simple**
- **Cost** : cheap

World wide avaibility

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

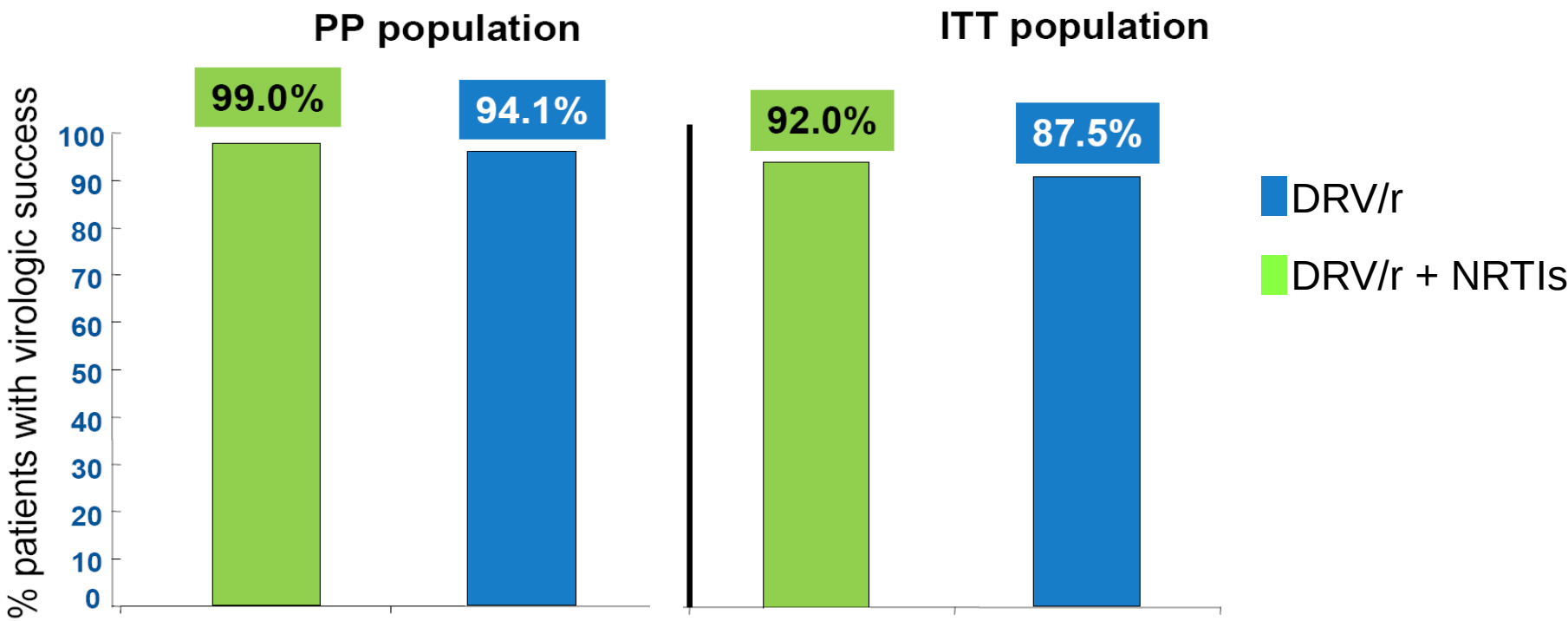


HIV DNA predictive of viral

bou

J. Arribas et al, AIDS 2010

MONOI Darunavir monotherapy in patients with suppressed viremia

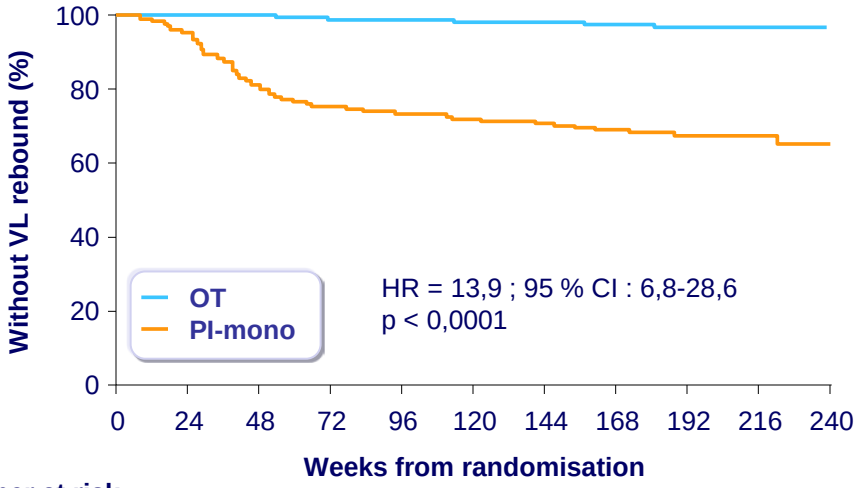


Response	Difference (Lower limit CI)
Rx success (PP, n=204))	- 4.9% (- 9%)
Rx success (ITT, n=225)	- 4.5% (-11%)

PIVOT Study: switch to PI/r monotherapy

Viral rebound and resuppression

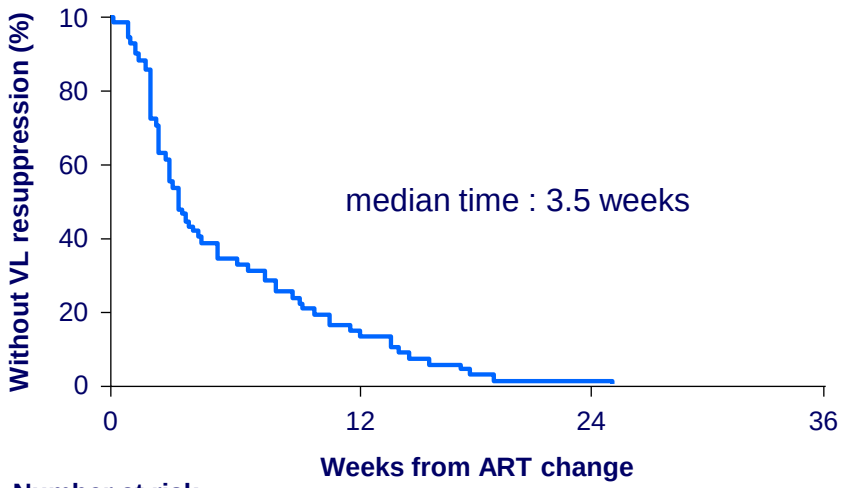
Time to viral rebound



Number at risk

OT	291	289	287	283	280	279	276	247	133	64	10
PI-mono	296	281	240	220	216	210	208	183	100	53	

Time to viral resuppression after change of ART in the PI-mono group



Number at risk

67	11	1	0

- **Confirmed viral rebound (Kaplan-Meier estimate) during follow-up**
  - PI/r monotherapy : 35.0% vs triple therapy : 3.2% (difference : 31.8%) (95% CI : 24.6 to 39.0, p < 0.0001)
  - Rebound on PI/r monotherapy : 24 per 100 person-years during 1st year, 6 per 100 person-years in subsequent years

Paton NI. Lancet HIV 2015;2e:417-26

Switch to Dual Therapy

PI + 3TC

OLE : LPV/3TC
SALT: ATV/FTC
DUAL : DRV/3TC
Gardel naive long term
LPV+3TC

PI+INI

NEAT 01
RAL/DRV
SPARE
HARNESS

INI+3TC

LAMIDOL
GEMINI (I)
DOLULAM

INI+NNRTI

LATTE CABO/RPV
ETRAL RAL/ETR
SWORD DTG/RPV

Switch to Dual Therapy

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Gardel naive long term
LPV+3TC

INI+NNRTI

LATTE CABO/RPV
ETRAL RAL/ETR
SWORD DTG/RPV

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

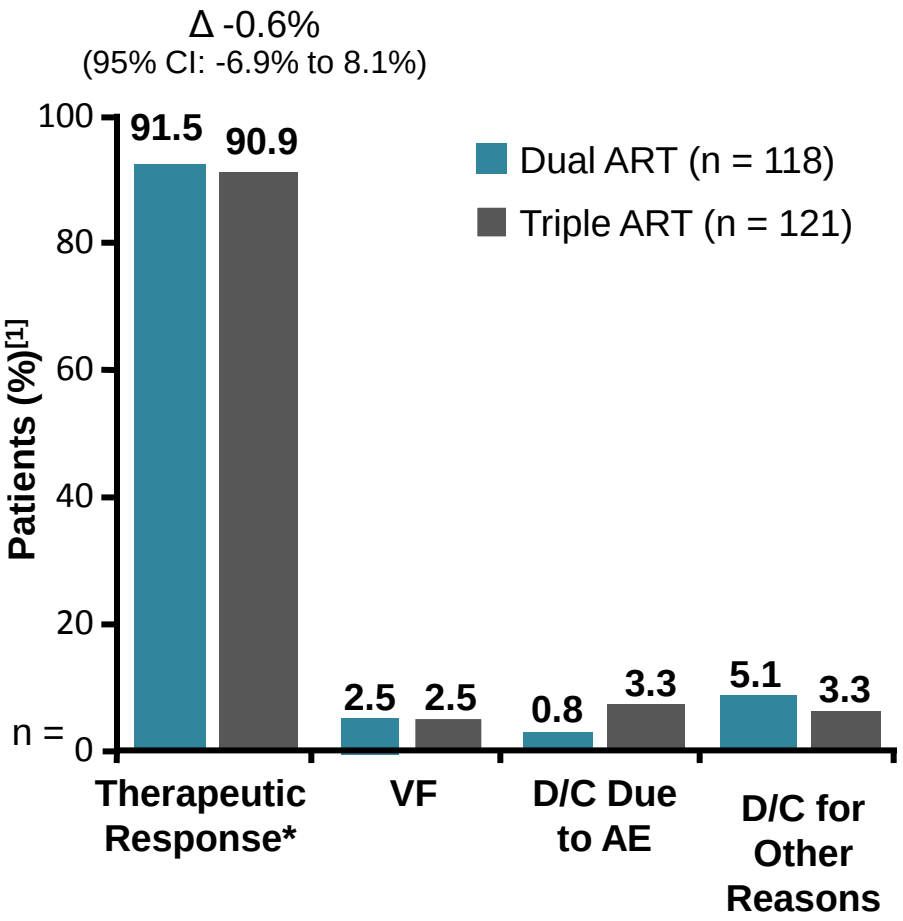
LPV/r 400/100 mg BID
+ 3TC or FTC

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

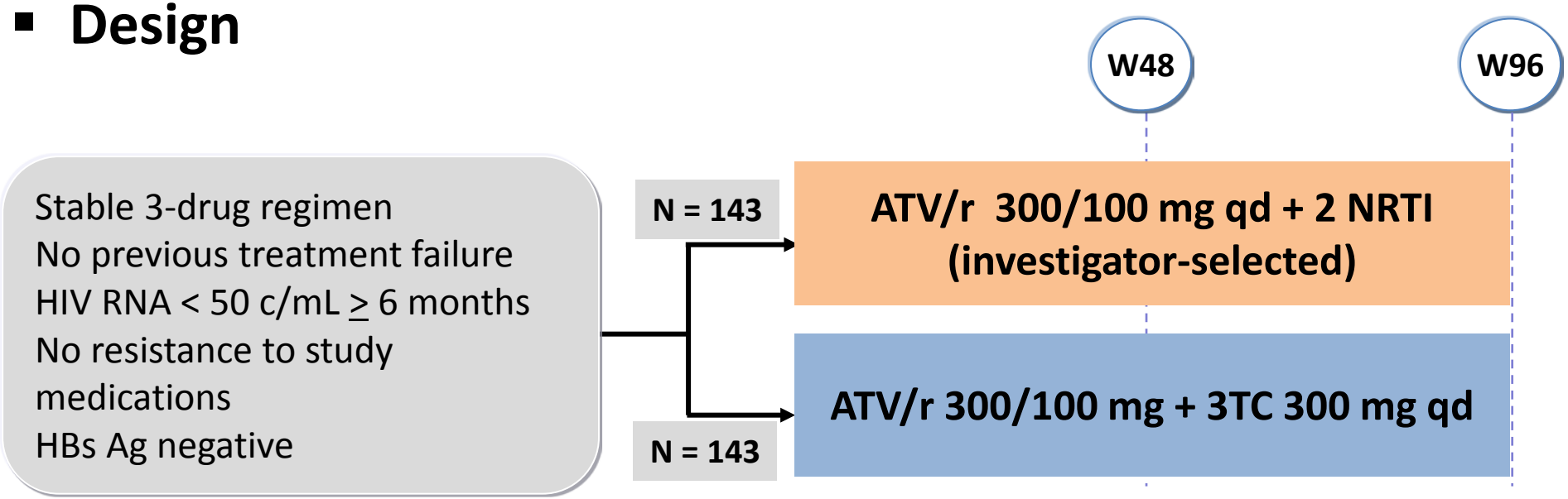
1 pt (dual-ART) tested for resistance; had K103N and M184V

- 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.

SALT Study
Switch to ATV/r + 3TC

- **Design**



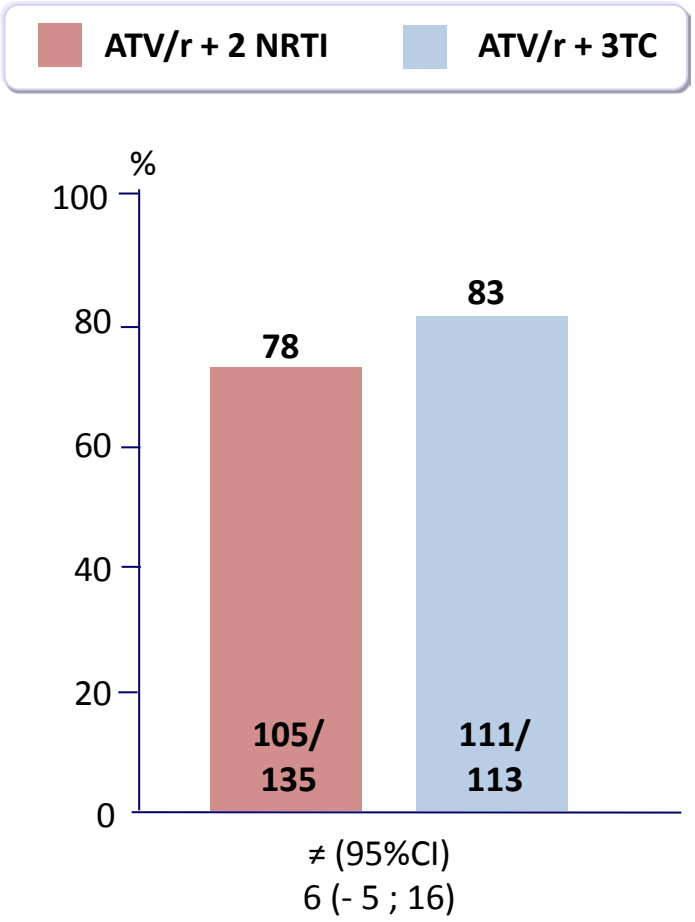
* Randomisation was stratified on active HCV infection and previous treatment (NNRTI, PI/r, CCR5 antagonist, integrase inhibitor)

- **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%

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

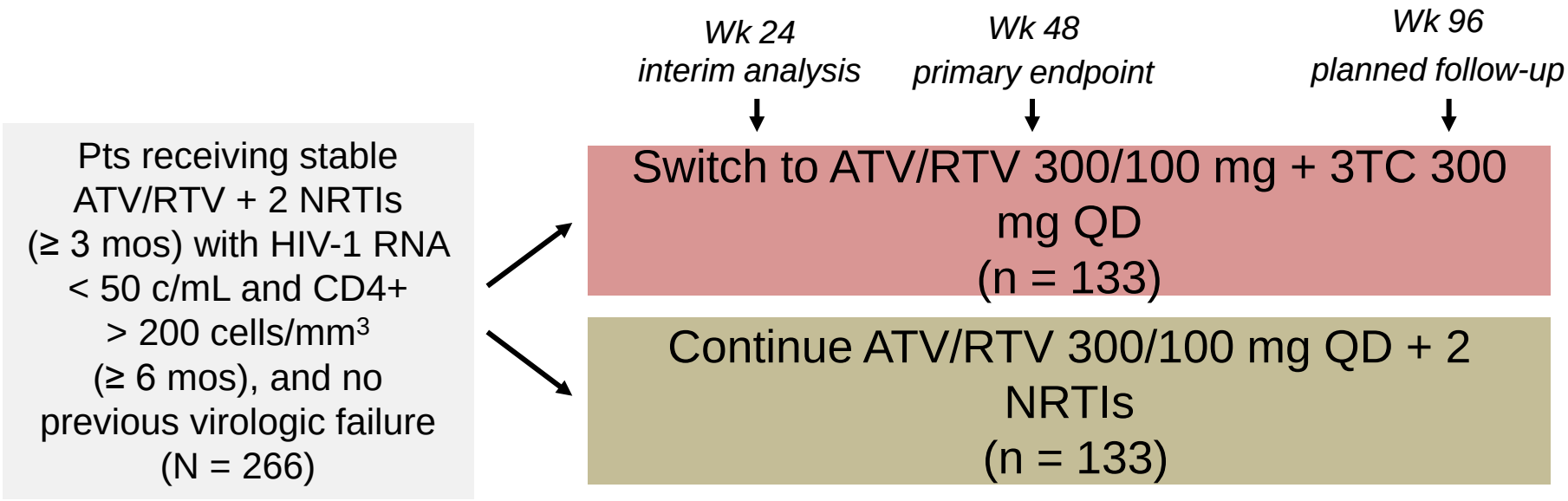
	ATV/r + 2 NRTI N = 141	ATV/r + 3TC N = 140
AEs leading to discontinuation	10 (7.2%)	3 (2.2%)
Severe adverse events (none related to study medication)	8	6

SALT

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

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

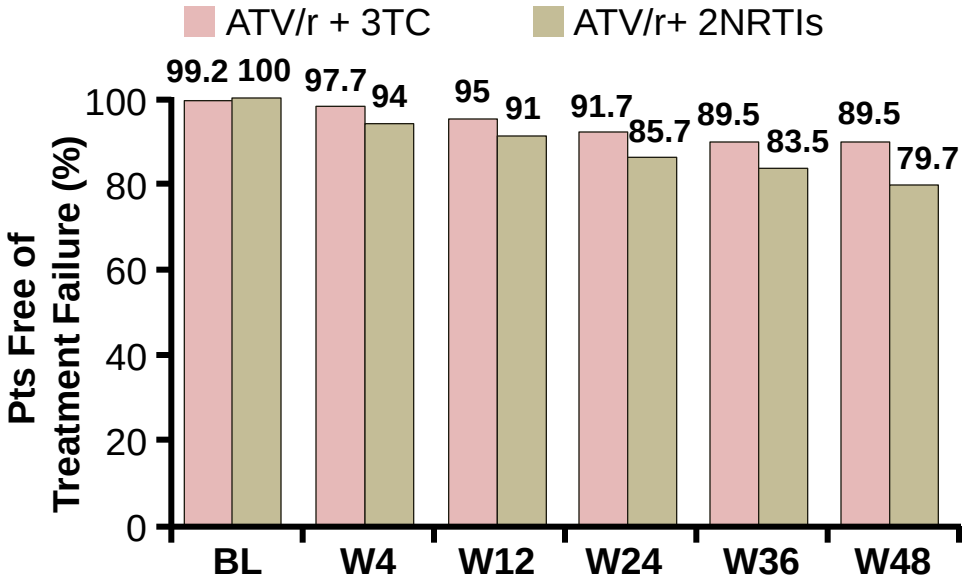
- Randomized, multicenter, open-label phase IV trial
  - Primary endpoint: absence of treatment failure at Wk 48, defined as ART modification for any reason

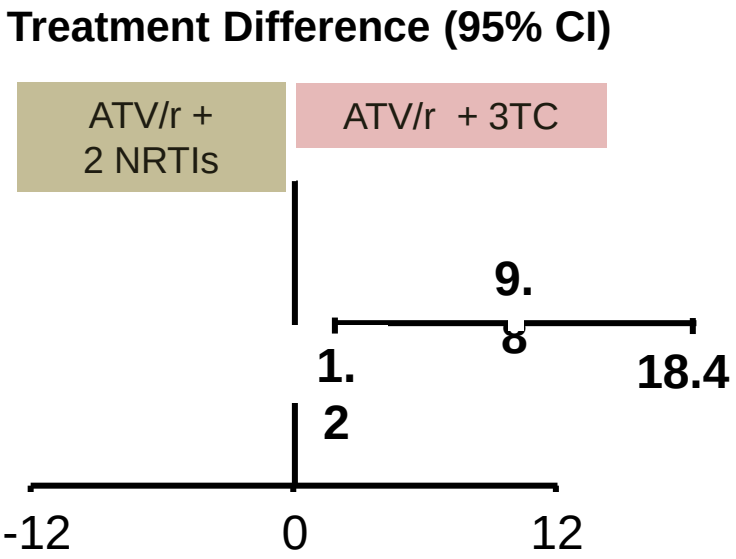


Di Giambenedetto S, et al. EACS 2015. Abstract 867.

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





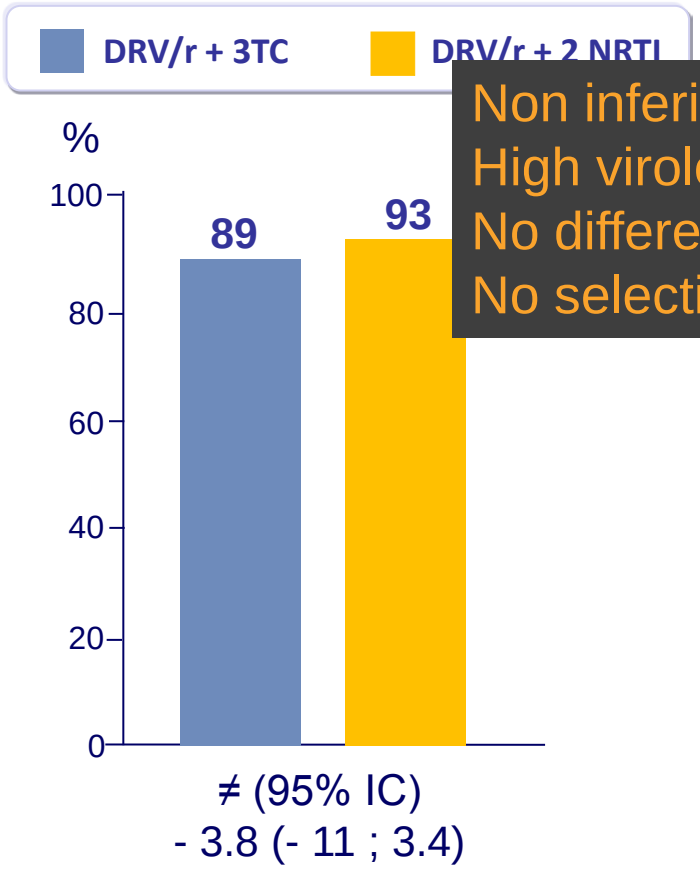
- Significantly greater increases in TC ($P < .01$), LDL ($P < .05$), and HDL ($P < .01$) with ATV/RTV + 3TC vs ATV/RTV + 2 NRTIs at Wk 48
- Mean change in eGFR at Wk 48: +2 mL/min with ATV/RTV + 3TC vs -4 mL/min with ATV/RTV + 2 NRTIs ($P < .001$)

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

DUAL Switch to DRV/r + 3TC

Efficacy and Safety results (W48)

HIV RNA < 50 c/mL at W48 (ITTe, snapshot)



Non inferiority of dual therapy
High virologic suppression rate
No difference in side effects
No selection of resistance muttations

HIV RNA ≥ 50 c/mL

	DRV/r + 3TC	DRV/r + 2 NRTI
		2
		V10I, W71T, D76W in 1 patient

)

	DRV/r + 3TC	DRV/r + 2 NRTI
AEs leading to discontinuation	1 (0.8%)	2 (1.6%)
Grade 2-4 adverse events	15 (11.9%)	18 (14.6%)
Serious adverse events	6 (4.8%)	6 (4.9%)
Adverse events occurring in ≥ 5% of patients in either group	No differences	
Grade 3-4 laboratory abnormalities	4 (3.2%)	4 (3.3%)

Pulido F, HIV Drug Therapy 2016, Glasgow, O331

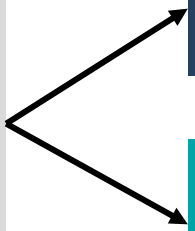
GARDEL: Dual ART LPV/r +3TC

Non inferior to Triple ART in ART naïve patients

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



	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

PI

Dual DRV/r 800/100 +3TC vs TDF+FTC+DRV/r in naïve patients

Phase 4, randomized, multicentric, open label study , *Wk 48 Primary endpoint*

Stratified at screening by HIV-1 RNA (≤ or > 100,000 copies/mL)

145 ARV- naive patients
5 sites in Argentina

- ≥18 years
- 4.5 log HIV copies/ml
- 24% >5 log
- CD4 : 383 /mm3
- No IAS-USA defined NRTI or PI resistance at screening*
- HB(s)Ag negative

Dual therapy
DRV/r 800/100mg QD
+
3TC 300 mg QD
n= 75

Triple therapy :
DRV/r 800/100mg QD
+
3TC /TDF 300/300mg QD
(n=70)

% HIV RNA < 400 cp/mL Wk 24 Interim analysis

ITT snapshot **95%**
On Treatment
100%
Discontinuations 4
Withdraw consent (1)
,SAE (1), LTFU (1) , RASH

ITT snapshot **97%**
On Treatment **99 %**
Discontinuations 1
PDVF 1

P. Cahn IAS 2017

Switch to Dual Therapy

PI + 3TC

- OLE : LPV/3TC
- SALT: ATV/3TC
- ATLAS : ATV/3TC
- DUAL : DRV/3TC
- Gardel long term LPV+3TC

- Effective
- Robust
- Highly accessible in all countries
- Check for HBV
- Cost reduction

Switch to Dual Therapy

PI + 3TC

OLE : LPV/3TC

SALT: ATV/FTC

DUAL : DRV/3TC

Gardel naive long term LPV+3TC

PI+INI

NEAT 01 RAL/DRV

SPARE

HARNESS

Switch to Dual Therapy
PI+INI

- **HARNESS :** ATV/r 300+RAL vs ATV/r +TDF/FTC (72 vs 37pts)
  less effective than 3-DR; more AE (bili)

  Van Lunzen J. JAIDS 2016;71:538-43

- **KITE study** : LPV/RAL vs 3-DR (40 vs 20 pts)
  similar virologic suppression : 1(2-DR) vs 2 (3-DR) failure

  Ofotokun I. AIDS Res Human Retroviruses 2012;28:1196-1206

- **SPARE study** : DRV/RAL vs TDF/FTC/LPV (28 vs 30 pts)
  similar virologic suppression >97

  Nishijima T. PLOS One 2013;8:e73639

Switch to Dual Therapy
PI+INI

- **For whom :**

  Avoiding NRTI : NRTI resistance / mito tox

  NNRTI : Resistance

  No major metabolic complications

  Positive interactions wished DTG or RAL+ ATV

- **Advantage**

  robust

- **Be careful**

  drug drug interactions

Switch to Dual Therapy

PI+INI

NEAT 01
RAL/DRV
SPARE
HARNESS

INI+3TC

LAMIDOL
GEMINI (I)
DOLULAM

Switch to Dual Therapy
Integrase Inhibitor +3TC

Mainly Dolutegravir +3TC

- **Initiation**

  Pilot study PADDLE :

  20 patients ; highly effective

  GEMINI : large RCT

- **Switch**

  Lamidol

LAMIDOL ANRS 167 Switch DTG/3TC
Treatment success of DTG/3TC at W48

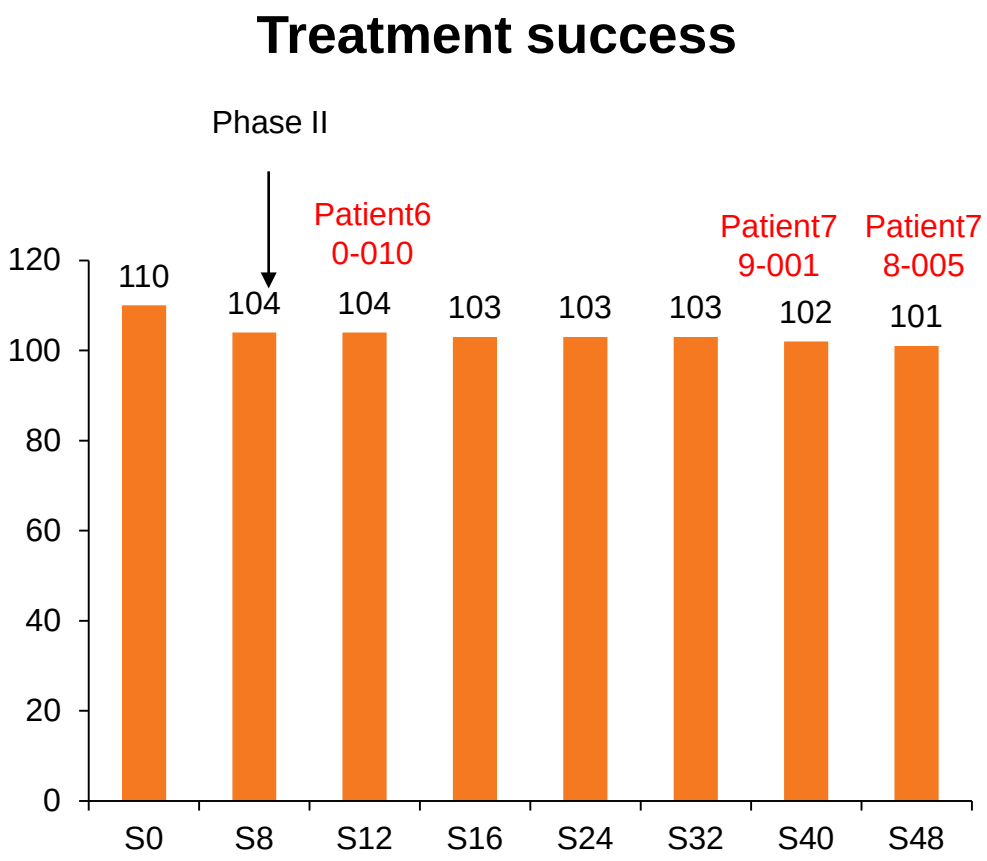
- Pilot open label study
- Switch to DTG/3TC QD
- Therapeutic failure

confirmed VL > 50 copies/ml

Treatment interruption , LFU , death

W48 : 3 strategy failures

- **1 VF at W12** (4 weeks of DTG/3TC)
- 1 lost of FU at W40
- 1 ART modification W48

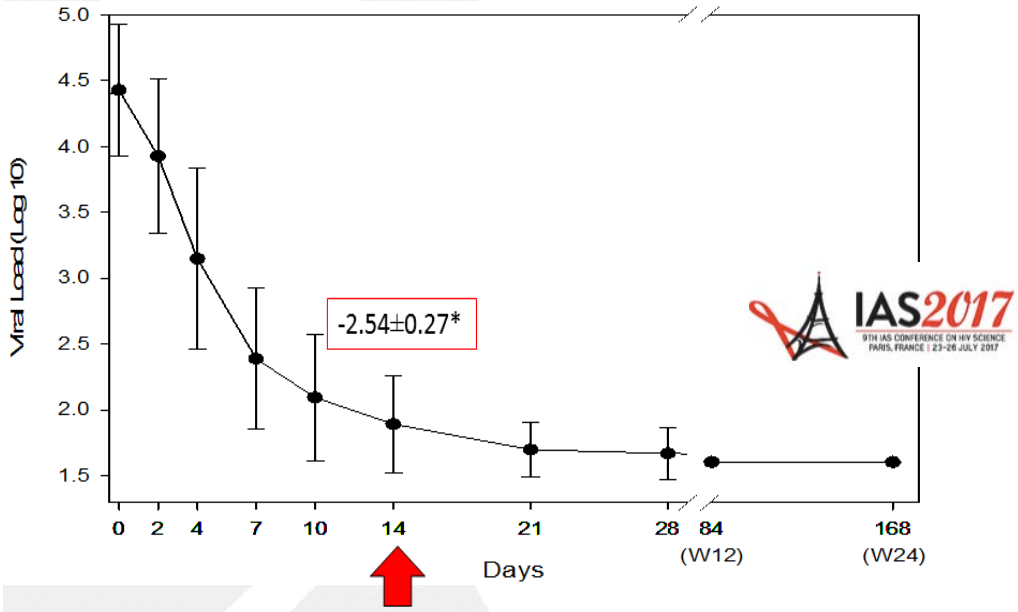


CROI 2017 – from Joly V et al., abstr. 458 actualisé

Dual Therapy with Dolutegravir in HIV-infected ART-naive Patients

- PADDLE Pilot Antiretroviral Design with Dolutegravir (50mg) Lamivudine (300mg)
- 20 patients, ART naive > 5‘000 ≤ 100‘000 c/mL, because of differences of screening to baseline values, 4 patients had VL > 100‘000 c/mL

Results: Viral load decay



*Day 14: Early evolution of viral load (log 10) (mean ± standard deviation).

From week 8 onwards all patients had VL < 50 c/mL

18/20 pts achieved VL < 50 c/mL at Wk 48

1 suicide 1 PDVF at Wk 36

Figueroa MI, et al., et al, AIDS 2016

W96 18 patients were FU No VF; one SAE unrelated ART

Figueroa IAS 2017 Poster MOPEB0287

ACTG 5353 Dolutegravir/3TC in naive pts Primary Outcome: % VL<50 cp/mL W24

Phase II, single-arm, 52-week, pilot study

DTG 50mg + 3TC 300 mg/d in **treatment-naïve patients** with VL ≥1000 and <500,000 cpm

Primary outcome

Virologic success at W24 VL < 50 cpm, using FDA Snapshot definition.

	> 100,000 cpm N=37	≤ 100,000 cpm N=83	Total N=120
Virologic success VL < 50 cpm **[95% CI]**	**33 (89%) [75%,97%]**	**75 (90%) [82%,96%]**	**108 (90%) [83%,95 %]**
Virologic non-success	**3 (8%)**	**2 (2%)**	**5 (4%)**
HIV-1 RNA ≥ 50 cpm	3	0	3
Discontinued study treatment for other reasons while HIV RNA ≥ 50*	0	2	2

[95% Confidence intervals] for proportion of participants with virologic success at Week 24

** Poor adherence; # Lost to follow-up, pregnancy*

Taiwo B IAS Paris 2017

Switch to Dual Therapy

PI+INI

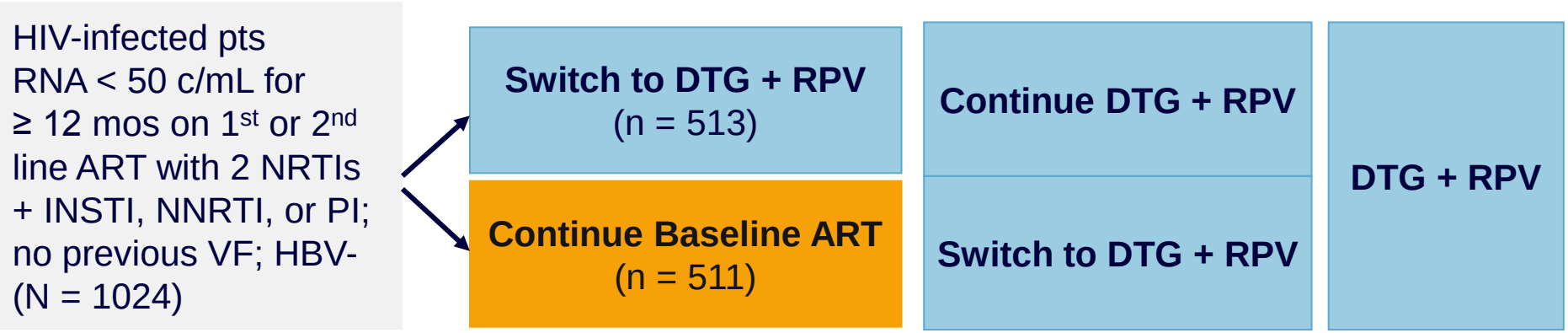
NEAT 01
RAL/DRV
SPARE
HARNESS

INI+NNRTI

LATTE CABO/RPV
ETRAL RAL/ETR
SWORD DTG/RPV

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

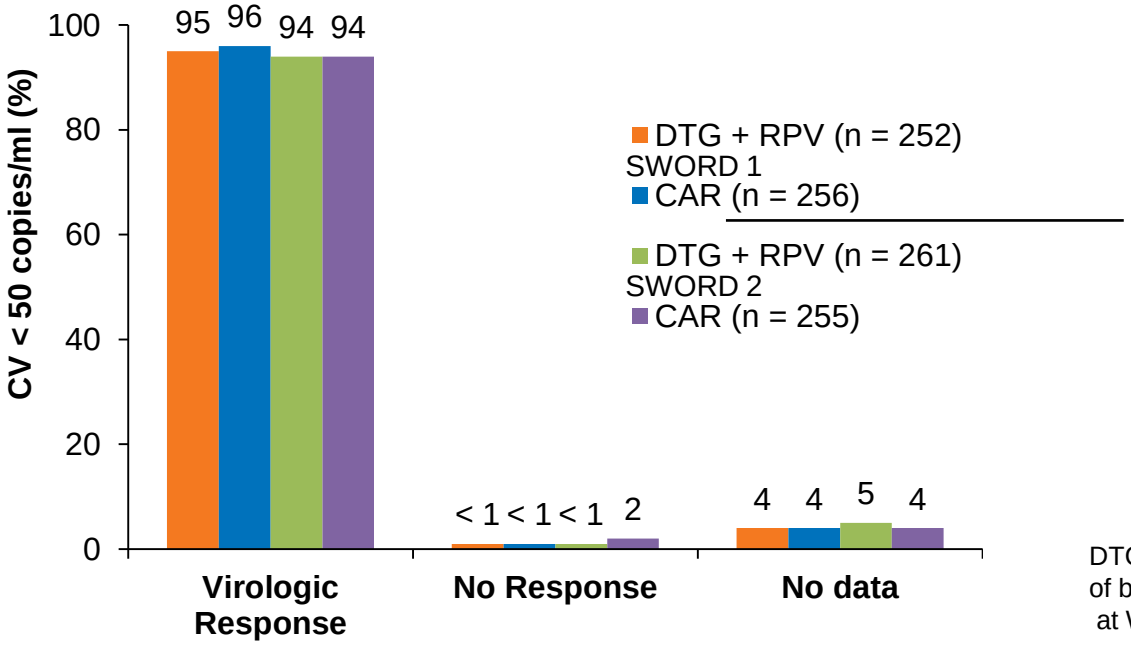
- Randomized, open-label, multicenter phase III trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)

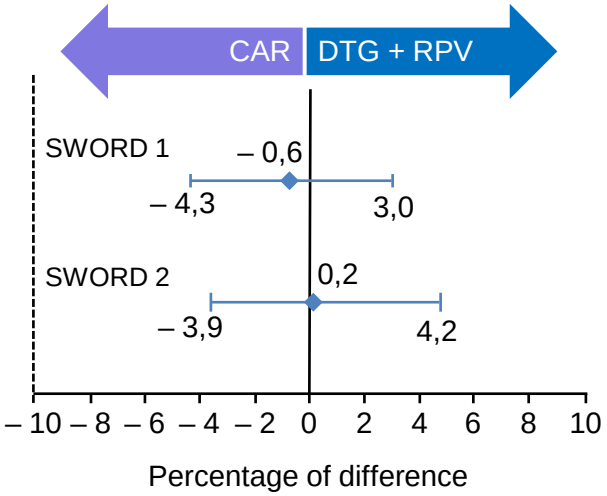


- 70% to 73% of pts receiving TDF at baseline

Llibre JM, et al. CROI 2017. Abstract 44LB.

SWORD 1 & 2 : switch to DTG + RPV
Virological efficacy





DTG + RPV is non inferior compared to maintenance of baseline therapy (ITT-E *snapshot*) at W48 in 2 studies

*CAR : maintain prior treatment * Adjusted for age and 3e agent*

Early phase of switch[a]

	DTG + RPV (n = 513) n (%)	CAR (n = 511) n (%)
Treatment Discontinuation for Virologic Failure	2 (< 1)	2 (< 1)

[a] *Pooled data for SWORD 1 & 2*

CROI 2017 – Adapted from Llibre JM et al., abstr. 44LB

ETRAL :Switch study to RAL/ETR

- Switch study to evaluate a non NRTI Non PI strategy : RAL/ETR

- Single arm study
- End point

Strategy sucess > >95%
with < 8 failures eg virological failures or drug discontinuation

- HIV-1 infected patient, âge ≥ 45 years
- HIV RNA <50 copies/mL since 2 years
- CD4 >200 cells/mm^3
- Stable ART with PI/r > 6 mois
- INI and etravirinenaive
- No mutations eexcept for Pas de mutation INNTI sauf K103N

1 60 patients

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

DXA scan
- Os
- Tissu

S48 Primary end point
Succès strategie

S 96 end of study

Katlama C et Al IAS Paris 2017 abstract MOPEB0314

ETRAL : switch from PI regimen to RAL/ETR

- 160 patients

  CD4 current/nadir 700 /209

  ART duration 16.8 years

  Duration of VS 6.9 years

- ART *QD 73% BID 27%*

  2 NRTIs + PI/r 65%

  NNRTI + PI/r 7%

  mono PI/r 21%

- Comorbidities

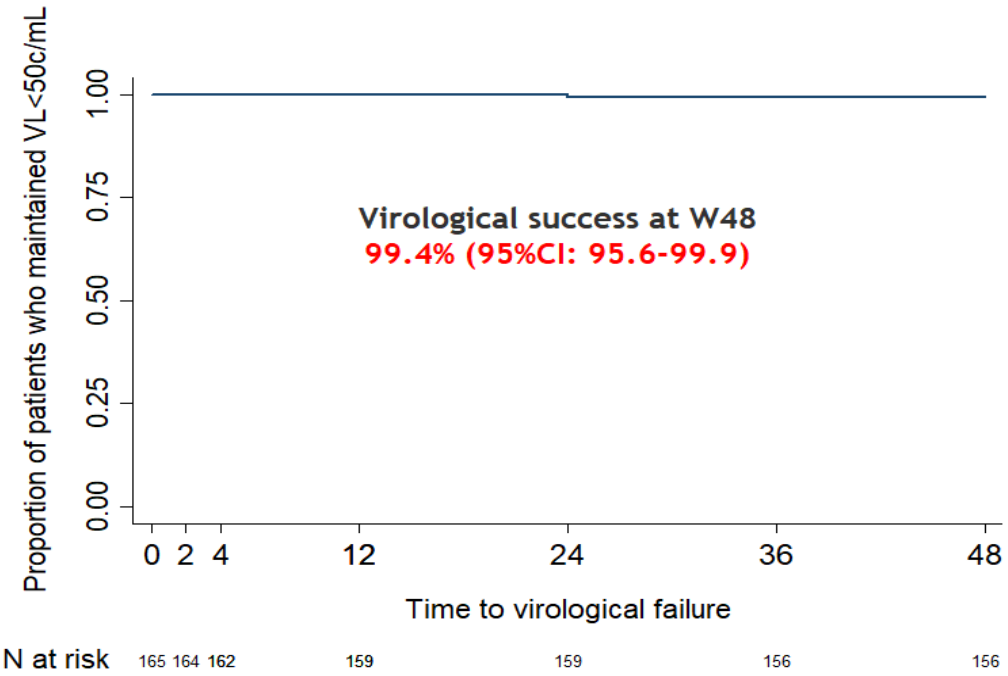
  Dyslipidemia 27%

  High Blood Pressure 25%

  Diabetes 8%

  Cardiovascular event 3%

- Co-medications med nb 5



One Protocol defined virological failure W24 11 607/18472
ETR R RAL S

Katlama C et Al IAS Paris 2017 absT MOPEB0314

ETRAL : switch from PI regimen to RAL/ETR
Evolution of Lipids Glucose and Renal n = 165

	D0	W48	Δ W48 – D0	P-value	Mean % change (±sd)
Glomerular Filtration Rate (GFR) (ml/min/1.73 m^2);**n(%)**	90.3 (17.2)	88.2 (17.6)	-2.1 (9.8)	**0.0011**	**-2.0% ±11.5**
Cholesterol (mmol/L)	5.44 (1.14)	5.19 (1.05)	-0.25 (1.05)	**0.0188**	**-2.8% ±18.1**
HDL-Cholesterol (mmol/L)	1.38 (0.47)	1.48 (0.49)	0.09 (0.35)	**0.0002**	**+9.4% ±26.3**
LDL-Cholesterol (mmol/L)	3.30 (0.94)	3.09 (0.98)	-0.21 (0.89)	**0.0084**	**-3.6% ±27.7**
Non-HDL-Cholesterol (mmol/L)	4.06 (1.10)	3.71 (1.05)	-0.35 (1.00)	**<0.0001**	**-6.0% ±22.7**
Triglycerides (mmol/L)	1.66 (0.97)	1.34 (0.82)	-0.32 (0.93)	**<0.0001**	**-10.5% ±45.3**
Ratio Triglycerides/HDL	1.45 (1.35)	1.11 (0.96)	-0.30 (1.16)	**<0.0001**	**-12.3% ±53.1**
Glycaemia (mmol/L)	5.40 (1.22)	5.49 (1.31)	0.09 (0.91)	0.4171	2.5% ±14.7

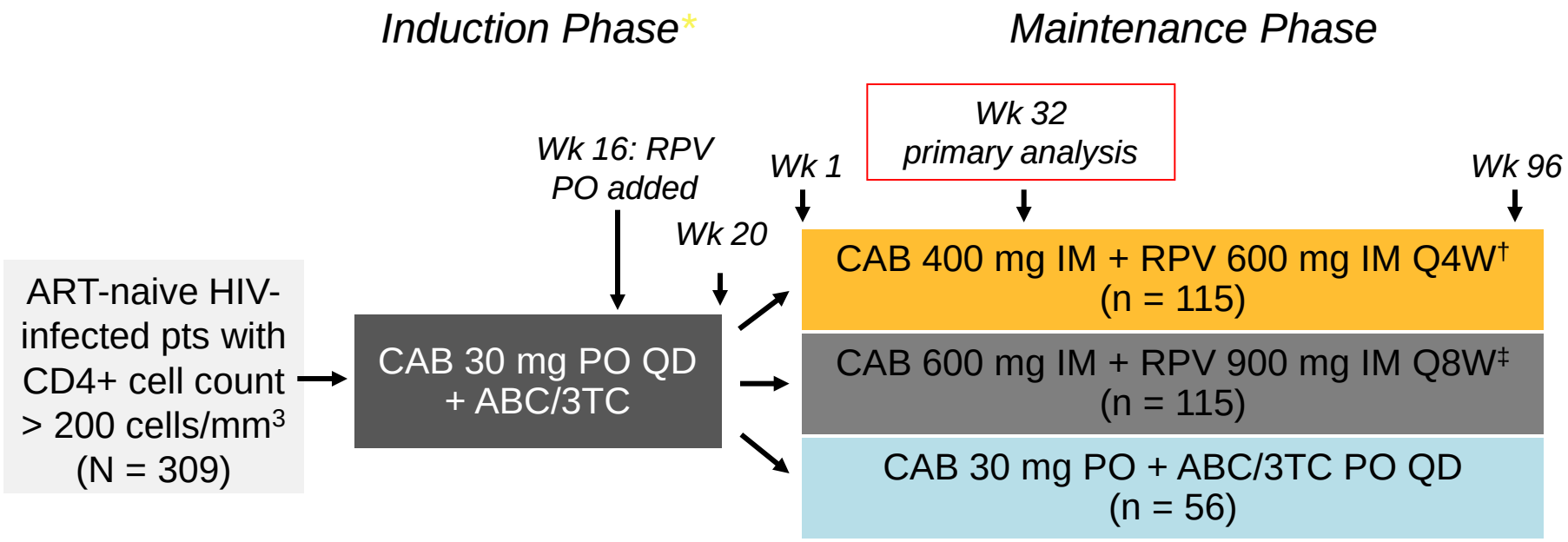
*At D0 : **45** / **165** patients with lipid lowening agents*
*At W48 : **47** / **159** patients with lipid lowening agents*

The missing data has been replaced by the last available value (LOCF method**)*

Katlama C et Al IAS Paris 2017
abstract MOPEB0314

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**

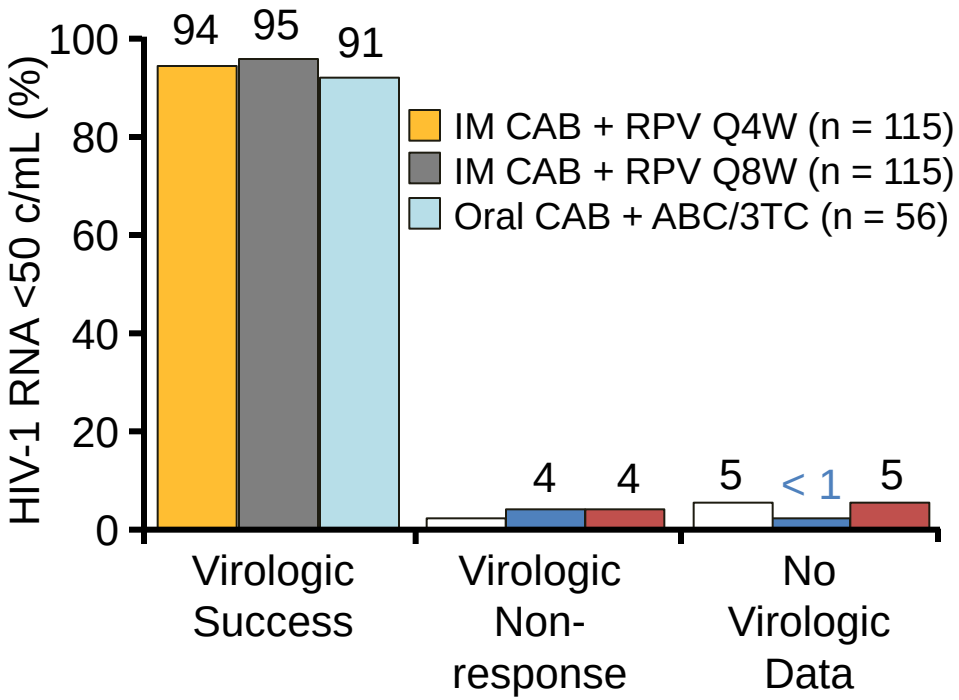
Outcome, % (n)	IM CAB + RPV Q4W (n = 115)	IM CAB + RPV Q8W (n = 115)	Oral CAB + ABC/3TC (n = 56)
Virologic success (HIV-1 RNA < 50 copies/mL)	91 (105)	92 (106)	89 (50)
Virologic nonresponse	< 1 (1)	7 (8)	2 (1)
No virologic data	8 (9)	< 1 (1)	9 (5)

- 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

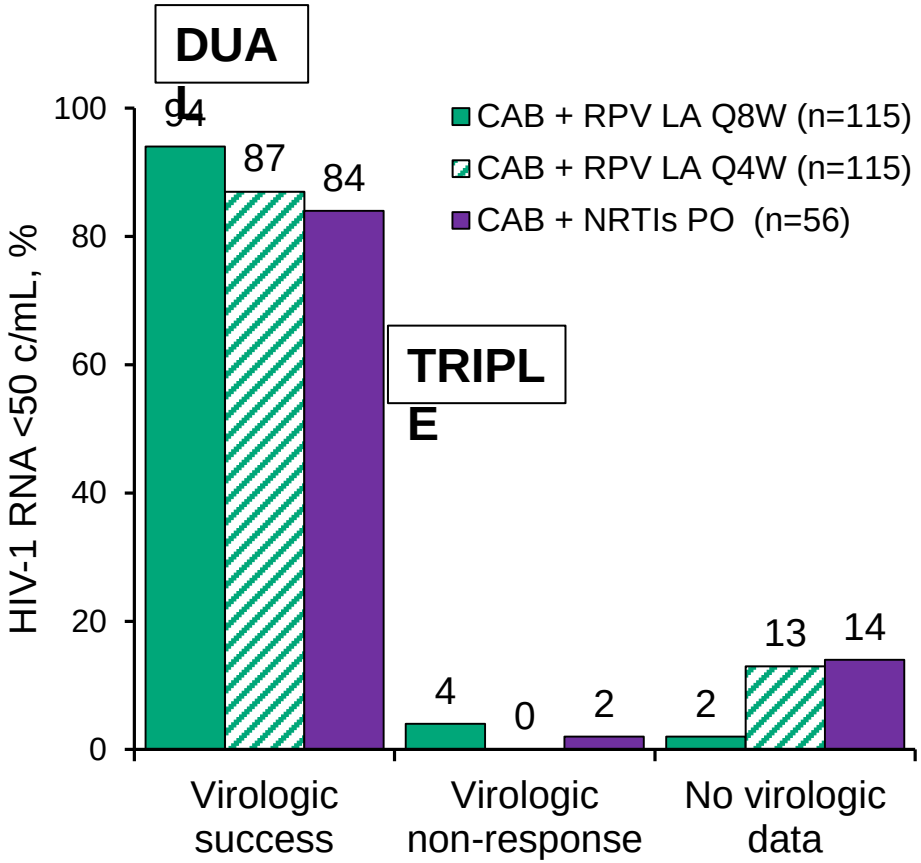
- Most frequent ISRs were pain (67%), swelling (7%), and nodules (6%)
  - ISR events/injection: 0.53
  - 99% of ISRs grade 1/2; none grade 4
  - 1% of pts withdrew for ISRs

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

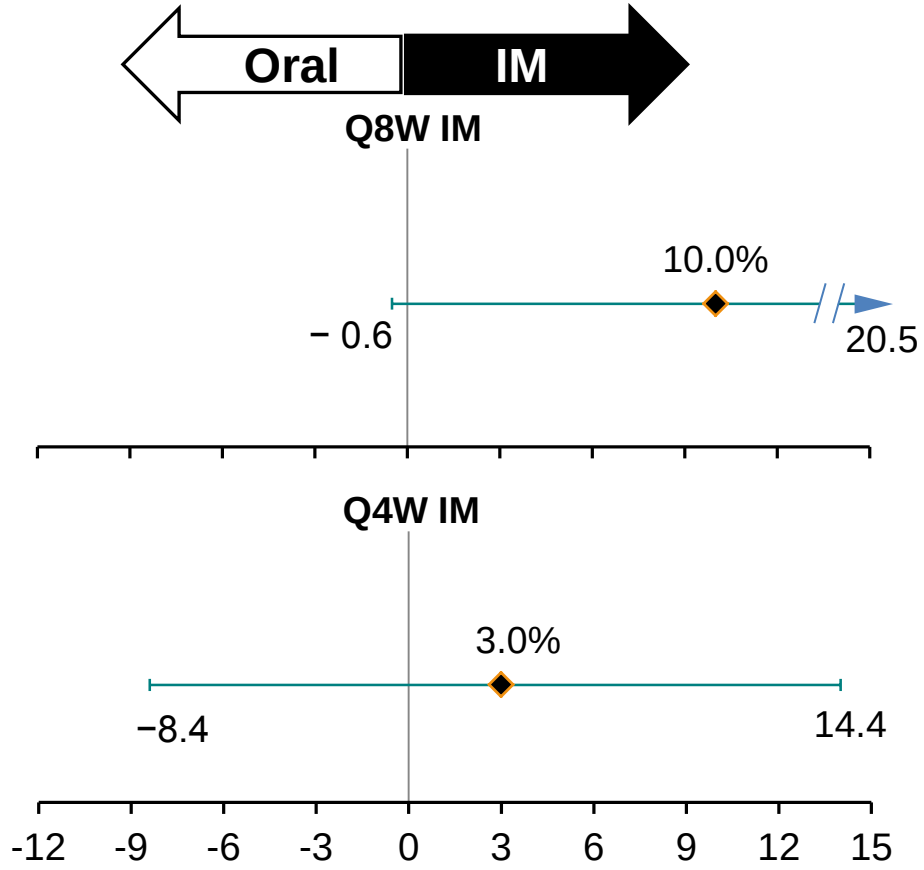
Margolis DA, et al. CROI 2016. Abstract 31LB.

LATTE-2 Week 96 HIV-1 RNA <50 c/mL - ITT-ME (Snapshot)

Virologic outcomes



Treatment differences (95% CI)



Source: Eron et al. IAS 2017 Paris, France. Abstract MOAX0205LB.

Towards a lighter suppressive ART

Intermittent ART

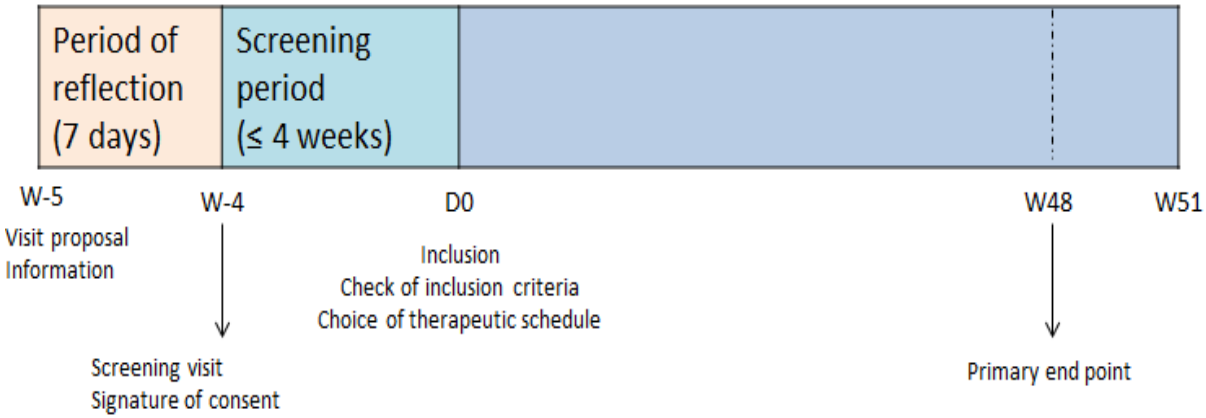
4D study

Breather

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

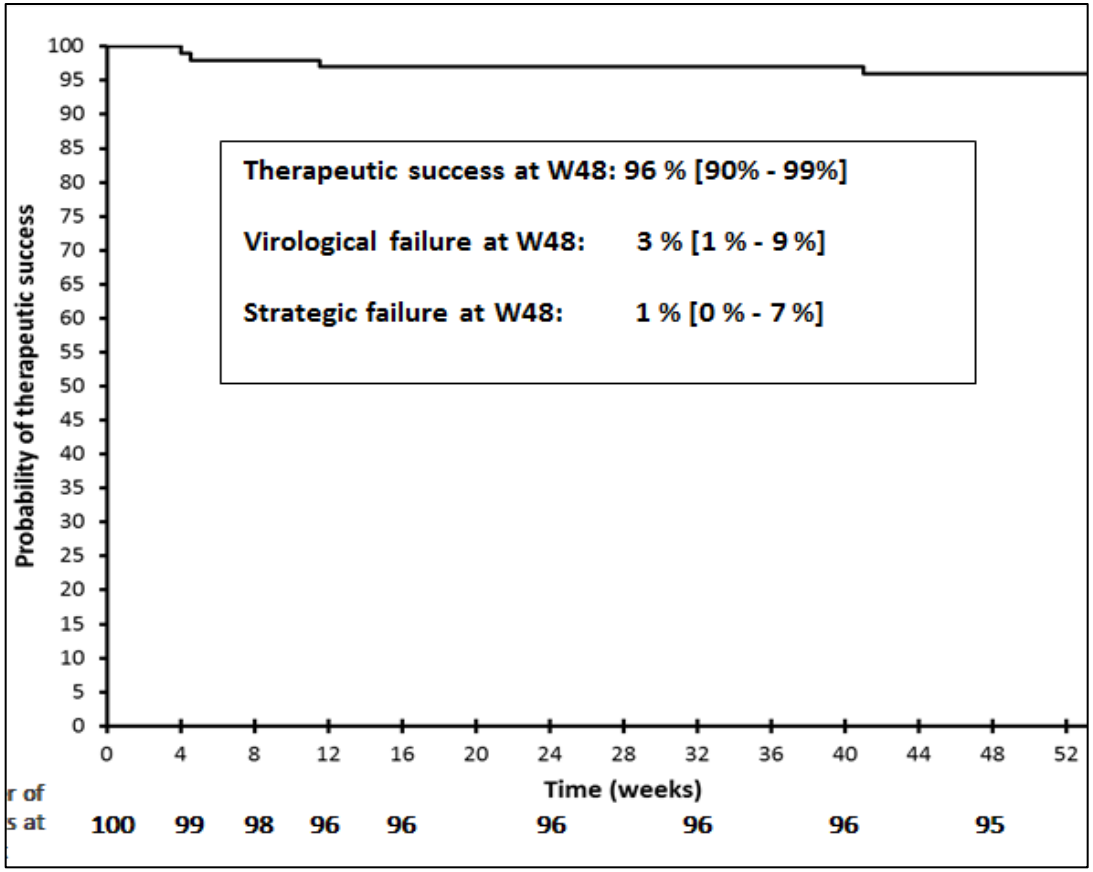
Samples collected within the visit off have been done at the end of the 3-days off

	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**

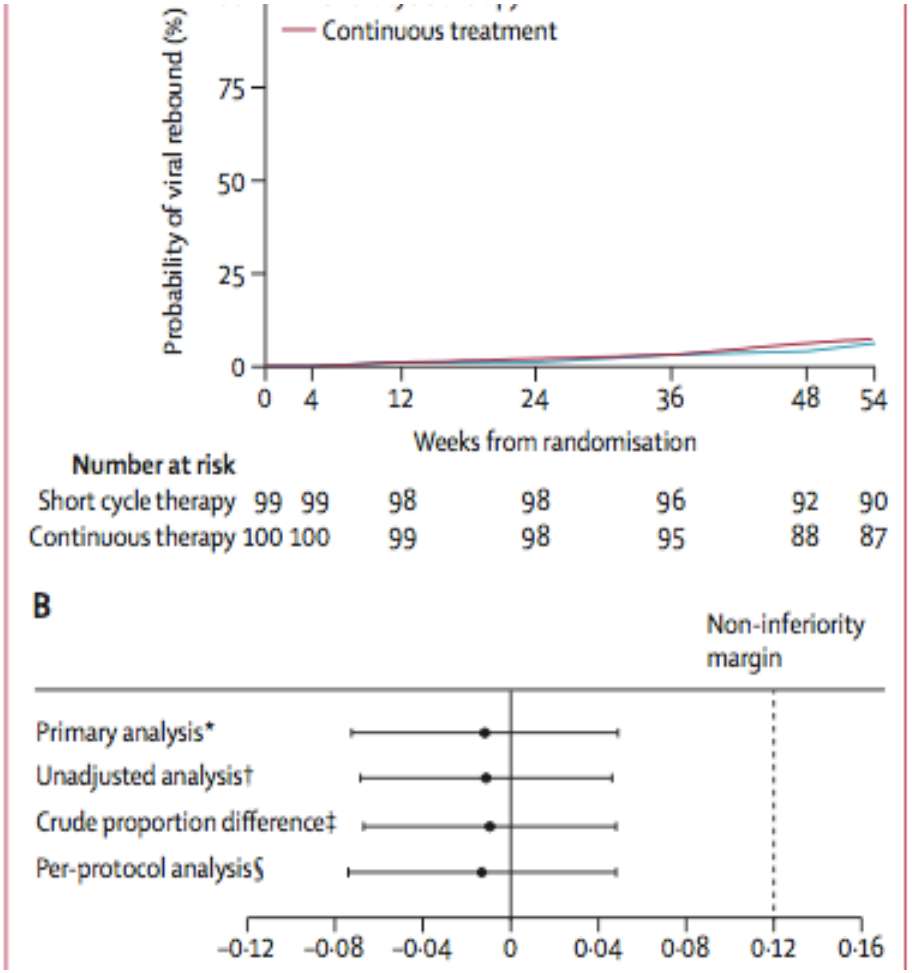
  No resistance ++
- 1 strategic failure discontinuation at W4 due to anxiety
- One patient discontinued the study at W12 for Pregnancy and was censored at the date of study discontinuation

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.



Switching what do I do ?

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..

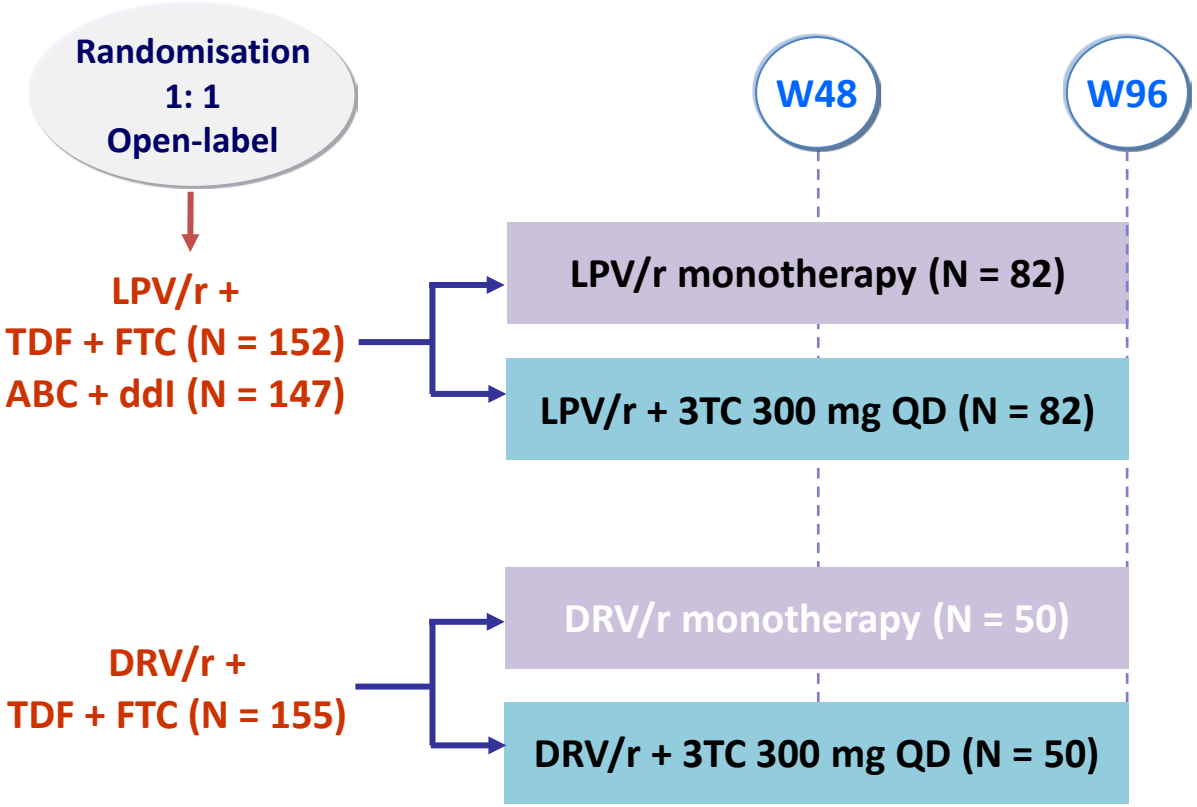
  some failures may be slow to appear

Switching with limited virology

MOBIDIP Study: switch to PI/r + 3TC vs PI/r mono

Design

≥ 18 years
HIV RNA ≤ 200 c/mL > 6 months on 2LADY study (2nd line study in Cameroon, Senegal, Burkina Faso) on LPV/r + TDF + FTC or LPV/r + ABC + ddI or DRV/r + TDF + FTC
Stable cART in past 3 months
No prior virological failure
CD4 > 100/mm³
Adherence ≥ 90%
HBs Ag negative



Objective

- Primary Endpoint: failure rate at W96 by ITT, defined as 1) a confirmed HIV RNA ≥ 500 c/mL, 2) reintroduction of the NRTI backbone or 3) interruption of the PI
- March 2016: Monotherapy arm discontinued following DSMB meeting

Ciaffi L, Lancet HIV 2017, May 28, 2017 (Epub ahead of print)

MOBIDIP : switch to PI/r + 3TC vs PI/r mono W48

	PI/r monotherapy N = 133	PI/r + 3TC N = 132
HIV RNA < 50 c/mL, %	80	83
CD4/mm^3, median	498	472
Nadir CD4 < 100/mm^3, %	56	52
PI/r = DRV, %	42	33
Months on first-line cART, median	50	50
Months on second-line cART, median	37	38
M184V at first failure, % Resistance to one 2nd line-drug, % Resistance to two 2nd line-drug, %	95 61 15	97 60 11
Failure, ITT, % (95% CI) Virological failure, N NRTI reintroduction, N Death, lost to follow-up, N	24.8 (17.7 – 33.0) 28 * 2 3	3.0 (0.8-7.6) (p < 0.001) 3 * 0 1

* All failure resuppressed to HIV RNA < 200 c/mL a median of 10 weeks after NRTI reintroduction

MOBIDIP

Ciaffi L, Lancet HIV 2017, May 28, 2017 (Epub ahead of print)

Is it safe on reservoir and compartments to use reduced drug regimen ?

- **Viral reservoir HIV DNA ?**

MONARK : Similar decrease in mono vs TRI : - 0.79 (mono) vs 0.68 (TRI) log HIV DNA /10^6 PBMC

RFERENCE

MONOI: Similar decline in HIV DNA from BL to W96 (- 0.51)

Lambert-niclos Plos one 2012

BINUKE : decrease -0.4 log

with 464 copies/10^6 PBMCs (IQR 195 – 1168 copies/106 PBMCs) at baseline to 206 copies/10^6 PBMCs (IQR 65–340 copies) at W24

Seang S et al. J Antimicrob Chemother. 2014

- **Viral replication in genital compartment ?**

MONARK : 10 pts ; no viral production in sperm

Light ART in real life

ART in 3 large Hospitals in Paris
COREVIH IDF Centre n=11 116 (99%)

Evolution des stratégies thérapeutiques depuis 2013

Types de stratégies	2013	2014	2015	2016 (1)	
	%	%	%	n	%
Trithérapie	82%	83%	82%	**8881**	**80%**
2 NRTI+1NNRTI	42%	42%	32%	3331	30%
2 NRTI+IP/r	36%	29%	17%	1477	13%
2 NRTI+II	10%	17%	27%	3442	31%
2 NRTI+1IP/non boosté	5%	4%	2,4%	82	1%
Autres trithérapies	7%	8%	3,6%	549	5%
Bithérapie	9%	9%	11,9%	**1500**	**14%**
Monothérapie	4%	4%	3,2%	**409**	**4%**
Multi-thérapie (>=4 molécules)	5%	4%	3,2%	**315**	**3%**
total patients sous trt	**10153**	**10406**	**10835**	**11105**	

(1) En 2016 : 11 pts avec traitement ARV en double aveugle : protocole de recherche clinique

ART strategies

HIV-1 infected patients on ART Pts n=11 116 (99%)

ART strategy per hospital site

Types de stratégies	Global		PSL		SAT		TNN	
	n	%	n	%	n	%	n	%
Trithérapie	8 881	80,0%	3 161	73,8%	3296	84,3%	2424	82,9%
2 NRTI+1NNRTI	3 331	30,0%	1 250	29,2%	1226	31,4%	855	29,2%
2 NRTI+II	3 442	31,0%	1036	24,2%	1400	35,8%	1006	34,4%
2 NRTI+IP/r	1 477	13,3%	661	15,4%	431	11,0%	385	13,2%
2 NRTI+IP/non boostée	82	0,7%	82	1,9%		0,0%		0,0%
Autres Trithérapies	549	4,9%	132	3,1%	239	6,1%	178	6,1%
Bithérapie	1 500	14,8%	855	20,0%	363	9,29%	282	9,6%
Monothérapie	409	4,05%	195	4,55%	149	3,81%	65	2,22%
Multi-thérapie (>=4 molécules)	315	3,12%	72	1,68%	90	2,30%	153	5,23%
Total sous traitement	11 105		4 283		3 898		2 924	

1 or 2-DR regimen : PSL (**25**%), SAT (**13**%), TNN (**12**%)

Mono or dual strategies in real life Pitié Salpétrière Experience 2016

	Initiation n=150	Suppressive ART n=4283
3-DR	n=125 83%	n= 3161 73.8%
2-DR	n=14 9.3%	n= 855 20 %
1-DR	n=7 4.6%	n = 195 4.5 %

Mono or dual STRATEGIES : PSL (25%)

Clinical Infectious Diseases

MAJOR ARTICLE

HIV/AIDS

The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of HIV Infection in the United States

Michael P. Girouard,[1,2] Paul E. Sax,[3,4] Robert A. Parker,[1,4,5] Babafemi Taiwo,[6] Kenneth A. Freedberg,[1,2,4,7,8,9] Roy M. Gulick,[10] Milton C. Weinstein,[9,11] A. David Paltiel,[12] and Rochelle P. Walensky[1,2,3,4,7]

Comparaison of - 3DR-DTG

- Ind Maintenance with 3-DR then DTG-3TC
- DTG-3TC

Results : Similar 5-year survival rate (90% efficacy)

- **NAIVE patients**

  2-DR prefered strategy if VS > 90%

  If 50% uptake

  Ind Maint DTG+3TC : saving **550 millions USD** in 5 years

  2-DR DTG+3TC : **800 millions USD**

- **SWITCH 25% of all suppressed patients** : **saving > 3 billion USD**

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 once viral load is durably suppressed

Conclusions

- Individualization of ART is a key challenge for a chronic disease with currently no option to stop Rx
- Dual ART with potent forgiving drugs is a realistic ART option for in naive patients with low to moderate viral load and good immune status
- Darunavir or DTG combined to 3TC as a worldwide option is highly promising ; solid news will emerge in 2018
- New drugs highly potent and with high genetic barrier to R should be investigated as dual ART such as new NRTIs or INI

I am a senior : What are my needs

- Maintain viral suppression
- Discard drug with limited activity
- Reduce drug burden
- Limit NRTI exposure : cumulative time: 26 years
- Limit PI exposure
- Minimize drug drug interactions

- Can we switch to a dual regimen ?

  INI+PI ?

  INI + 3TC ?

  INI + NNRTI ?

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

- **Aging comorbidities**

- heart bone muscle
- mild loss / disturbances in memeory

- **Decreased renal function**

  Drug accumulation

- **Poly-comedications**

  More drug drug interactions

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

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

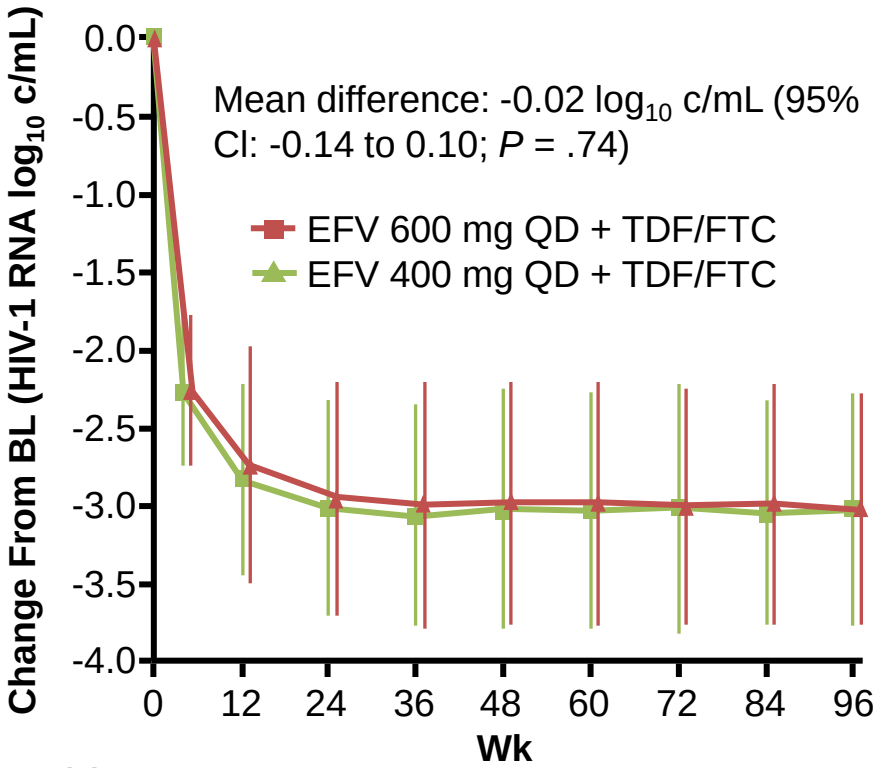
	HIV-1 RNA < 200 cp/ml W48		
	NC=F	**ITT**	**PP**
EFV* 400 mg + Placebo + TDF/FTC n = 324	90.0 %	94.1 %	98.3 %
EFV* 600 mg + TDF/FTC n = 312	85.8 %	92.2 %	97. 4 %

- 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

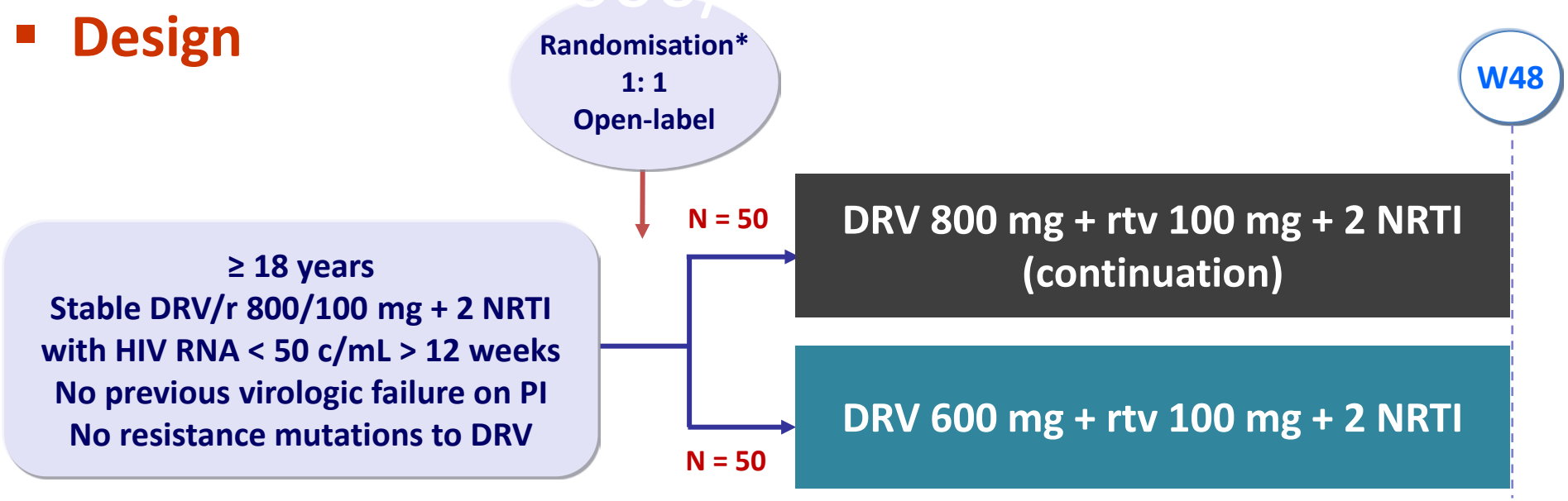
- Mean change in CD4+ cell count from BL greater with 400-mg vs 600-mg EFV (P = .03)
- Rate of EFV-related AEs lower with 400-mg vs 600-mg dose: 37.7% vs 47.9% (P = .01)
- Trend toward lower rate of discontinuation for EFV-related AEs with 400-mg vs 600-mg dose: 8.3% vs 15.5% (P = .07)
- Frequency of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

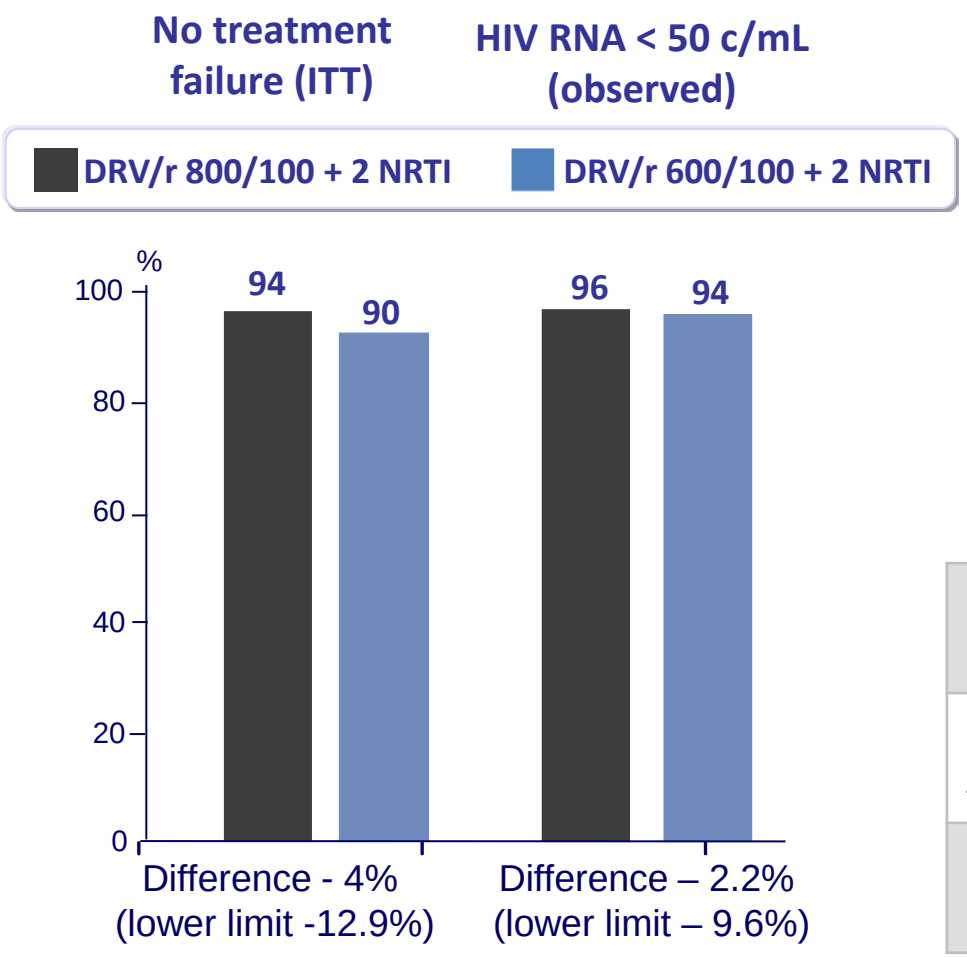
Objective

- 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

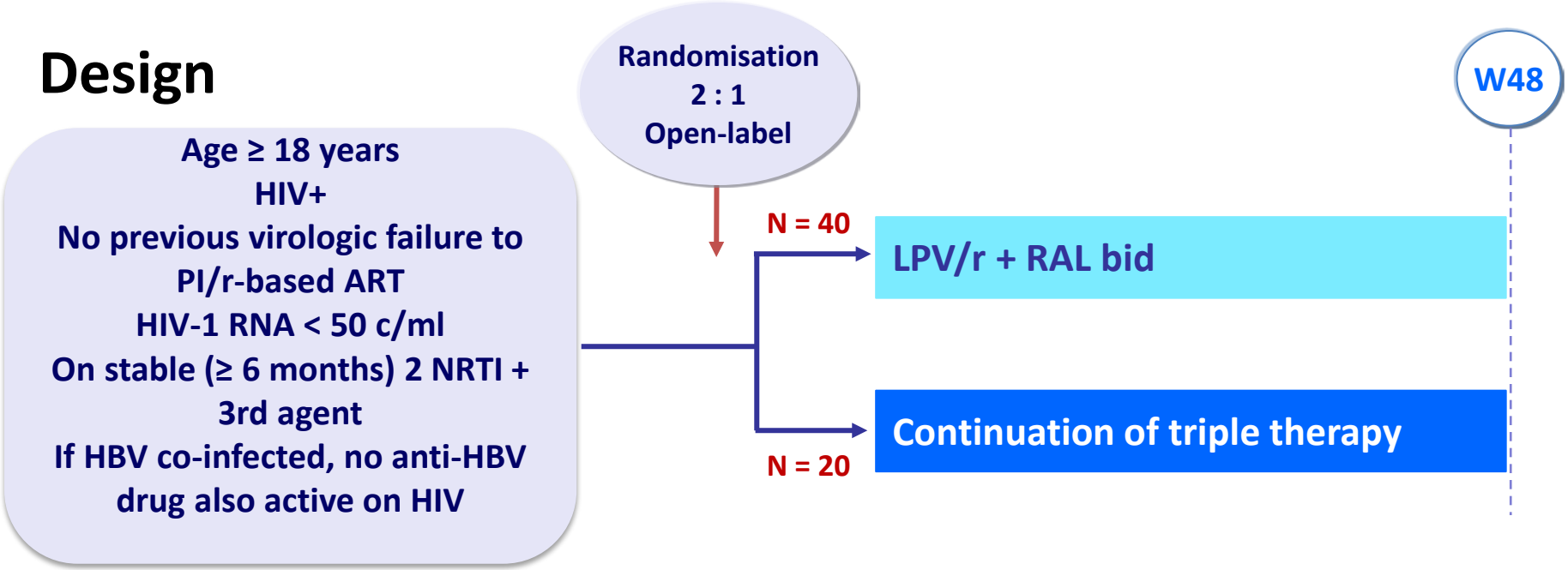
Full PK analysis

	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

KITE Study: switch to LPV/r + RAL

- **Design**



- **Objective**
  - Primary endpoint: proportion with HIV RNA < 50 c/mL during study visits, by treatment arm and time on study
  - Time cumulative event- free treatment failure (first of 2 consecutive HIV RNA > 400 c/mL or ARV change), estimated by Kaplan-Meier

KITE

Ofotokun I. AIDS Res Human Retroviruses 2012;28:1196-1206

KITE Study: switch to LPV/r + RAL

Baseline characteristics (mean), and disposition

	LPV/r + RAL N = 40	Continued triple ART N = 20
Age, years	46	48
Female, %	35	40
HIV RNA < 50 c/mL, %	88	95
CD4/mm^3	484	512
ART at entry, %		
LPV/r-based	40	40
Other PI/r-based	20	15
NNRTI	38	35
TDF-containing	53	65
On lipid-lowering agent, %	25	20
Discontinuation at W48, n		
Withdrew consent	2	0
Not study drug related	2	0
Study drug related	1	0
Lost to follow-up	0	1

KITE

Ofotokun I. AIDS Res Human Retroviruses 2012;28:1196-1206

KITE Study: switch to LPV/r + RAL

Outcome - Efficacy

	LPV/r + RAL N = 40	Continued triple ART N = 20
Virological reponse, % HIV RNA < 50 c/mL over the 48-week study HIV RNA < 50 c/mL at W48 HIV RNA < 50 c/mL in patients completing 48 weeks	 92.7 91.7 91	 88 88.2 89
Absence of treatment failure over 48 weeks, %	92.4	90
Confirmed virologic failure	N = 1	N = 2
Immunological response Mean CD4/mm^3 cell counts adjusted for baseline	 535	 574
Adherence score, mean Missing no doses in past 4 days	0.06 93.5%	0.32 (p = 0.002) 77.4% (p = 0.009)

KITE

Ofotokun I. AIDS Res Human Retroviruses 2012;28:1196-1206

KITE Study: switch to LPV/r + RAL

- **Safety over 48 weeks**
  - No serious AE
  - Moderate or severe diarrhea: 10 patients (25%) in the LPV/r + RAL group and 1 patient (5%) in the triple ART group (p = 0.08)
  - Moderate or severe myalgia: more frequent in the triple ART group (25%) compared to the LPV/r + RAL group (0%) (p = 0.002)
  - Total cholesterol and triglycerides for the LPV/r + RAL arm were statistically significantly increased during the follow-up periods (p = 0.008 for total cholesterol and p = 0.008 for triglycerides)
  - No difference between treatments arms over time was significant for total body fat (p = 0.60), trunk fat (p = 0.72), arm fat (p = 0.93), and leg fat (p = 0.72)
  - Similarly, no difference between treatments arms over time was significant for total BMD (p = 0.50), pelvis BMD (p = 0.56), or spine BMD (p = 0.72)

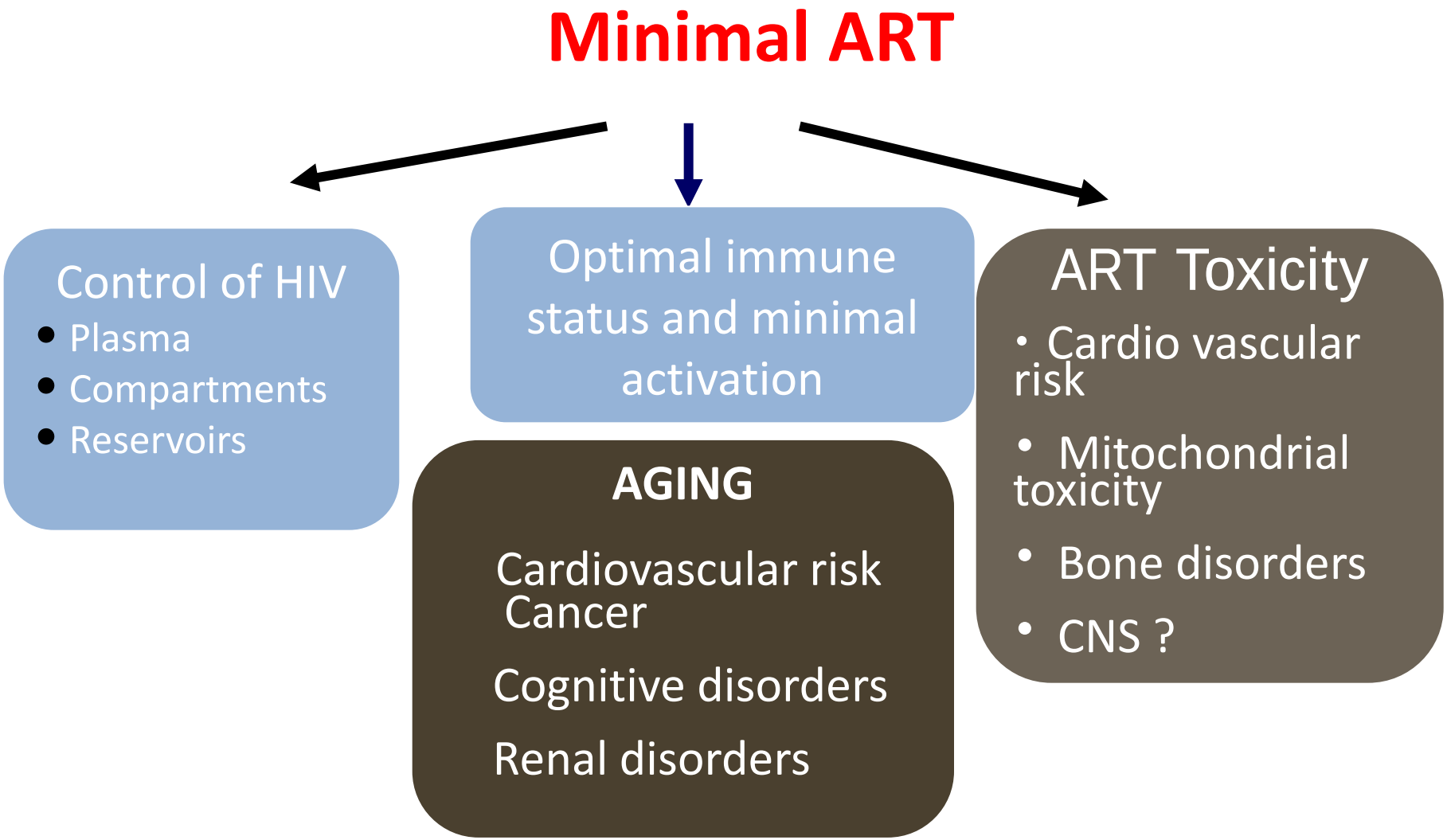
Ofotokun I. AIDS Res Human Retroviruses 2012;28:1196-1206

KITE Study: switch to LPV/r + RAL

- **Conclusion**
  - In virologically suppressed patients on HAART, switching therapy to the NRTI sparing LPV/r + RAL combination produced similar sustained virologic suppression and immunologic profile as standard HAART
  - Adverse events were comparable between arms, but the LPV/r + RAL arm experienced higher triglyceridemia
  - Limitations
    - Small sample size
    - AEs self-reported, open-label unblinded design

Ofotokun I. AIDS Res Human Retroviruses 2012;28:1196-1206

Need for individualized therapy in Long-term virological suppression



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]	

I am a senior : What are my needs ?

- Maintain viral suppression
- Discard drug with limited activity
- Reduce drug burden
- Limit NRTI exposure : cumulative time: 26 years
- Limit PI exposure
- Minimize drug drug interactions

- Can we switch to a dual regimen ?

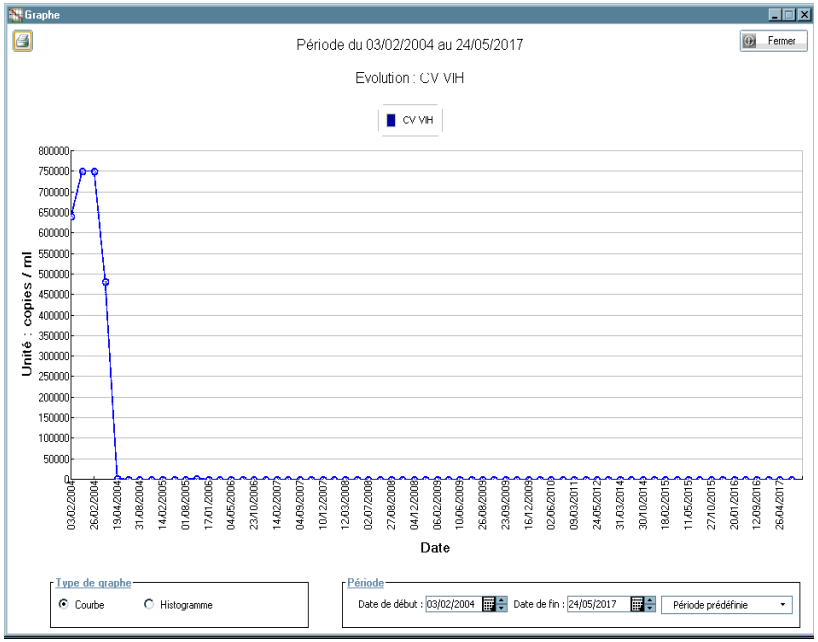
  INI+PI ?

  INI + 3TC ?

  INI + NNRTI ?

I choose to be enrolled in ETRAL

Long term viral suppression
Individualization of therapy



COREVIH IDF Centre

From 8957 patients

55 % with VS > 5 years

26% with VS > 10 years

2017

- More potent and robust drugs
- Long years with viral suppression

Which reduced strategies to maintain ?

➢ maximal viral suppression in plasma , reservoirs and compartments

- high immune profile
- low activation

Which predictive markers of success ?

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

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.

Mono ART **initiation**

- Mono PI

  Monark

  Mono DTG

Maraviroc/PI

MVC/ Modern

Dual ART initiation

2 NRTI TDF 3TC FTC

PI/NNRTI LPV/EFV ACTG

Protease Inhibitors /3TC

LOPI/3TC GARDEL

DRV /3TC ANDES

INI + IP NEAT-01

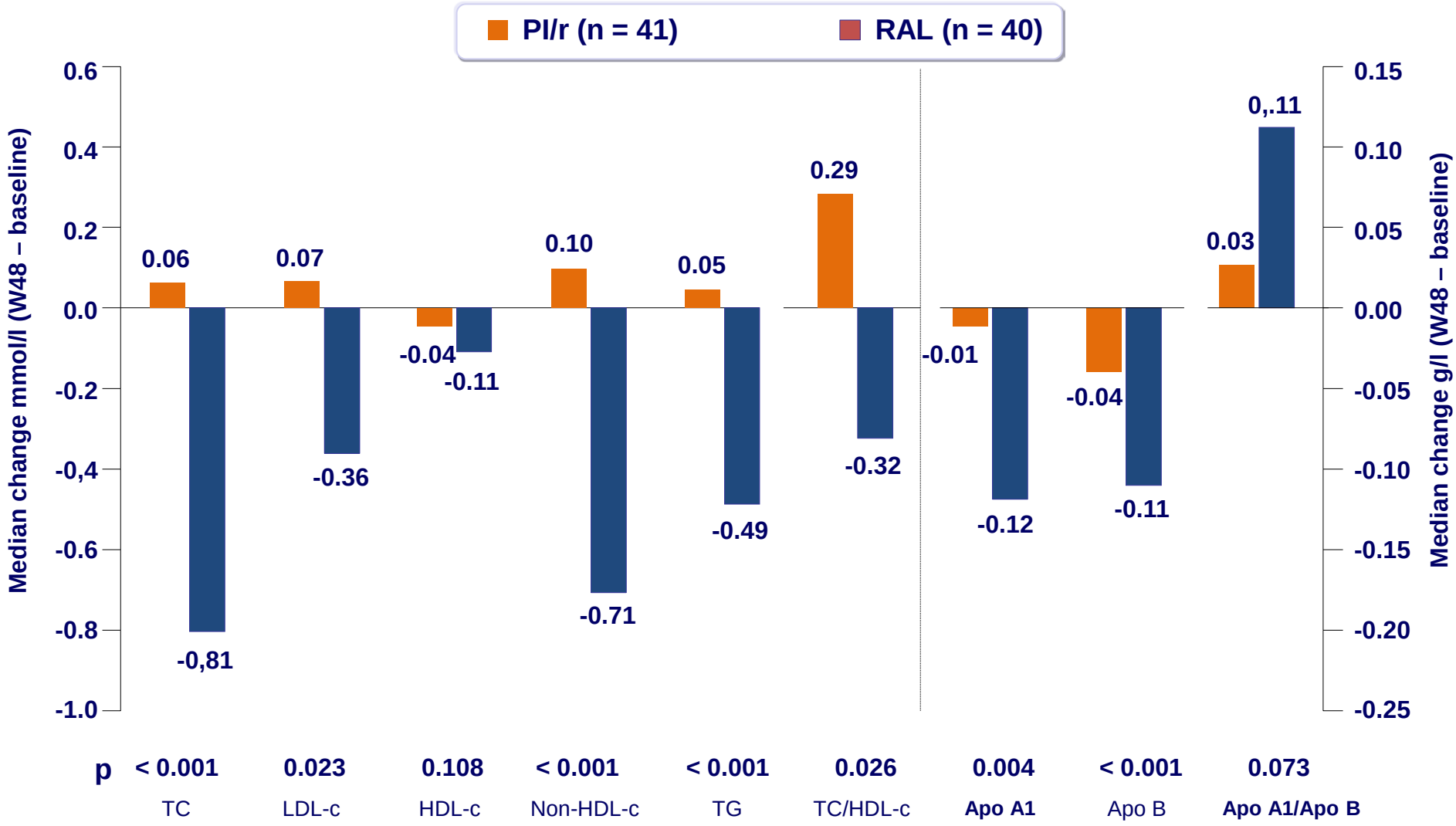
DTG/3TC

PADDLE

ACTG 5353

SPIRAL-MET: Switch from PI to RAL induce a decrease in lipids

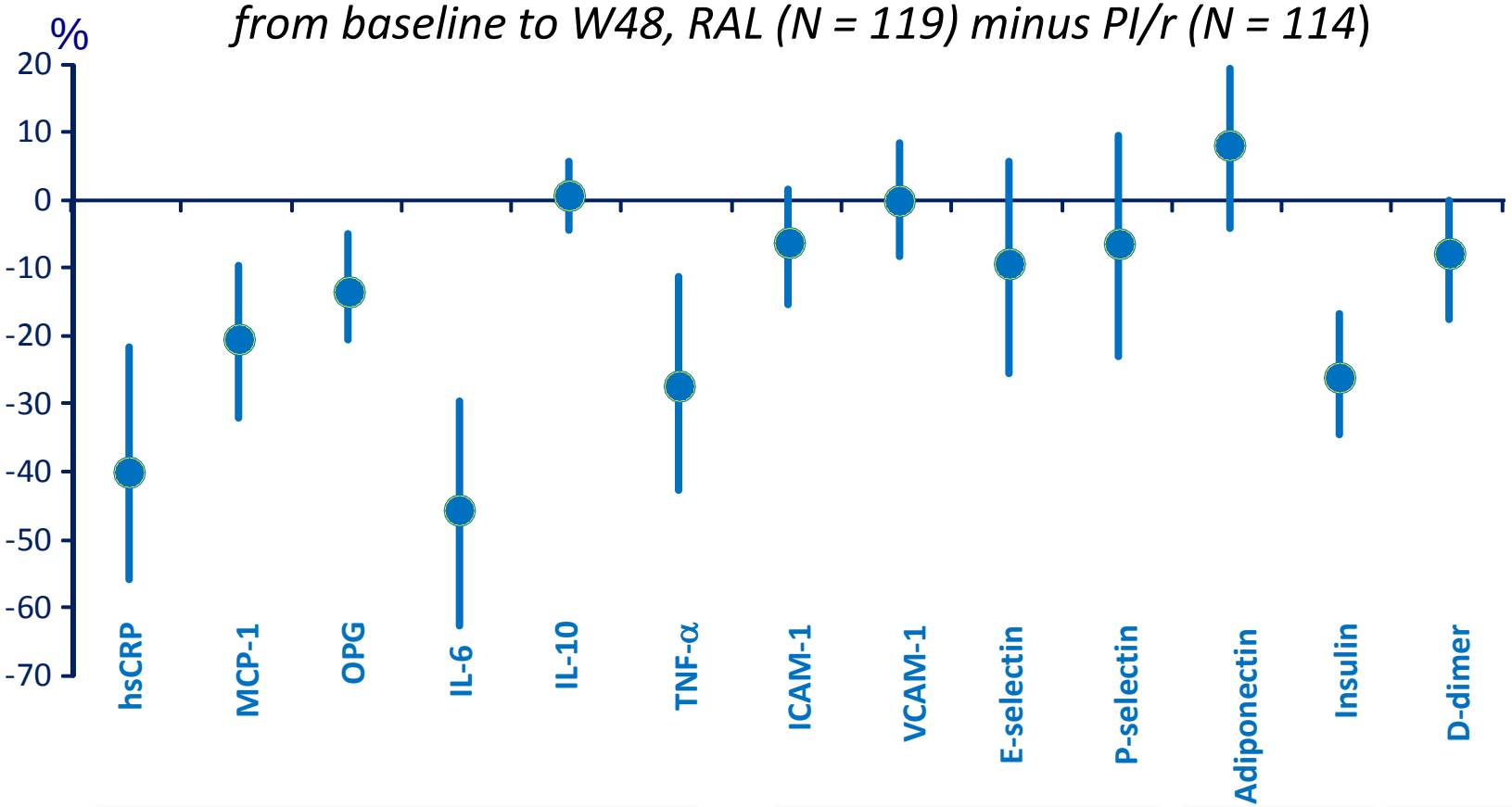
AIDS 2010, 24:000–000



Saumoy M, Atherosclerosis 2012;225:200-7

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

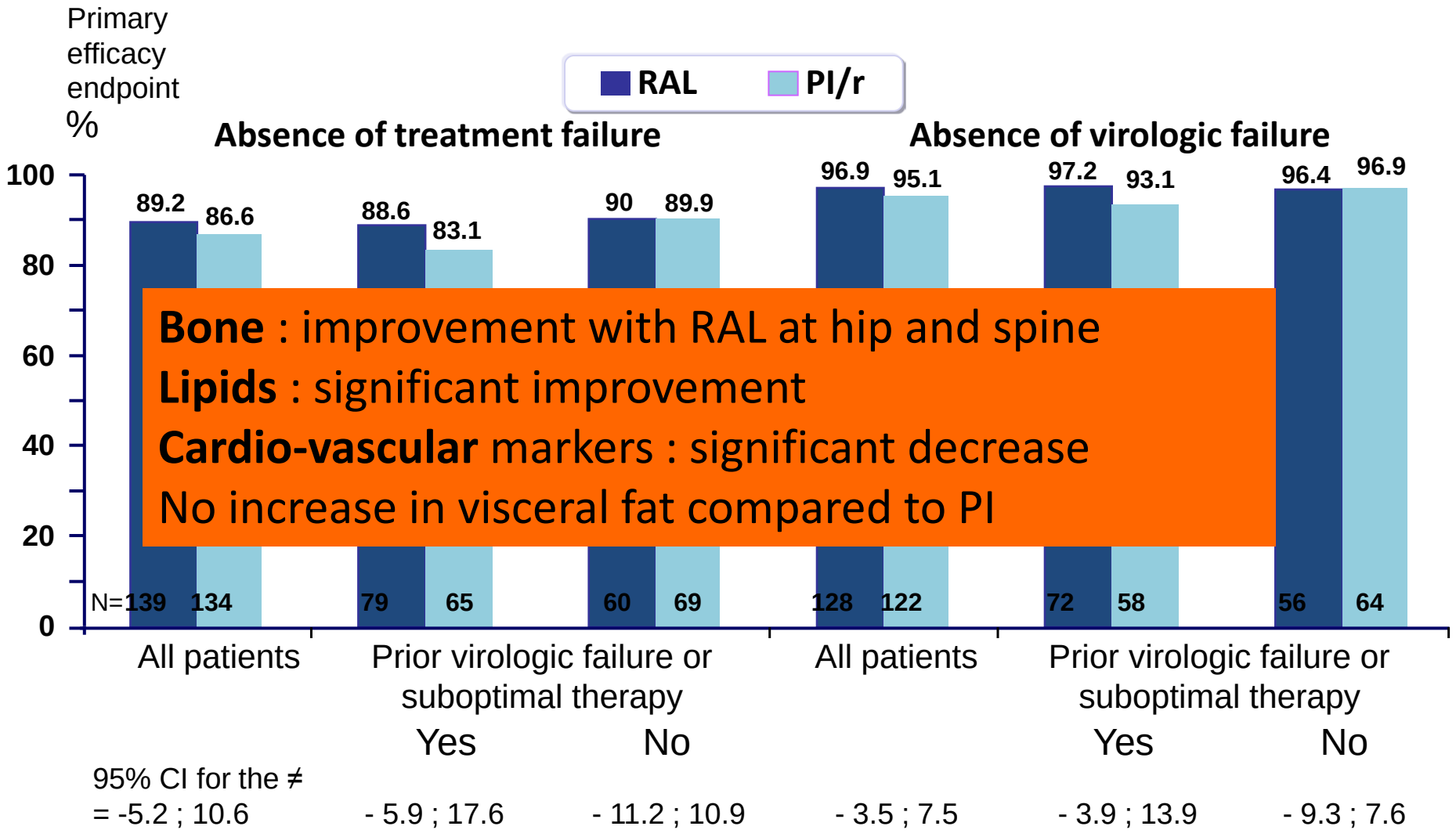
Cardiovascular biomarkers: median (95% CI) difference of percent change from baseline to W48, RAL (N = 119) minus PI/r (N = 114)



Martinez E, AIDS 2012;26:2315-26

SPIRAL

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