EACS European AIDS Clinical Society

Optimizing ART in HIV suppressed patients

Pr Christine Katlama

Sorbonne University Paris VI
Pitié-Salpêtrière Hospital, Paris
Pierre Louis institute

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

HIV and ART
Where are we in 2018 ?

Bad news

but nothing new

HIV is an integrated virus

- No cure
- No remission
- No therapeutic vaccine
- Rebound of VL after 10 days off ART

Long Life ART mandatory

up to 6- 7 decades

Good news

- Durable VS with ART
- No transmission

- No escape in VL if ARV drugs effective and taken
- Long term therapy reduced blood HIV DNA
- Immmune restoration in long term

The « undetectable Status »
To be kept for life

How to get there ?

- Taking ARV drugs
- Taking the right drugs
- On ART as earlier as possible
- Lower is VL
- Higher is CD4
- Faster comes VS
- Better is immune reconstitution

Stay suppressed

- Life-long therapy : a major challenge
- *Mean age for starting ART*
- *mid thirties*
- Compliance
- Education
- Patient empowerment
- Empathy

ART is a life-long therapy
Treatment individualization

Stigma
Violence
Repression

Life issues
Partner loss; unsecurity
Unemployment; poverty
Migration ;

Aging
Comorbidities

Childhood
adolescent

Several decades of uninterrupted ART

ART has to be adjusted to different life events

Reasons for individualizing ART Using drug reduced strategies

Context

- Earlier ART initiation
- Recent / New drugs more potent and robust
- Decades of suppressive ART needed with prolonged drug exposure
- Preserve drug options

Challenges

- Reduce chemical burden
- Maintain long life viral suppression
- Keep ART simple
- **Minimize toxicity Adjust to comorbidities**
- Avoid **drug-drug interactions**
- Optimize

The Dogma

- Viral load undetectable

Rather than the number of drugs

- Undetectable = untransmittable

Why more drugs if we can get /maintain viral suppression with less

Antiretroviral drugs 2018

NRTI	NNRTI	Protease Inhibitors	Integrase Inhibitors	Others
TDF TAF ABC 3TC/FTC	Nevirapine Efavirenz[6] Rilpivirine Etravirine Doravirine	Lopinavir Atazanavir Darunavir	Raltegravir Elvitegravir Dolutegravir **Bictegravir**	Maraviroc Enfuvirtide Ibalizumab

Coming soon 3-DR TAF/FTC/BIC Bictarvy
3-DR DOR/TDF/3TC Delstrigo
2-DR DTG/RPV Juluca

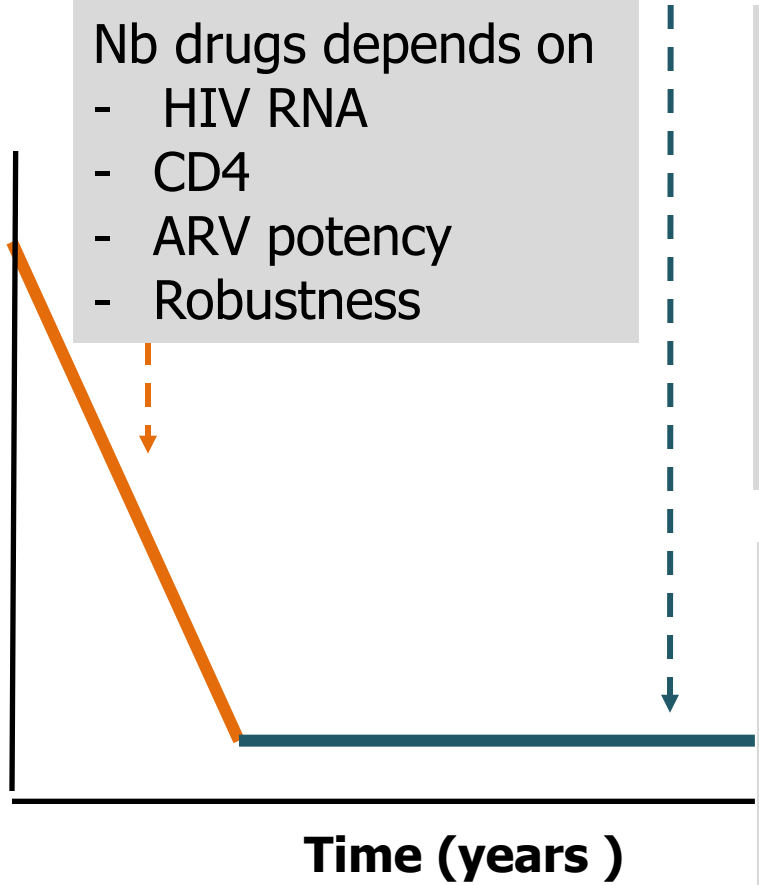
Comprimes Combinés ComBOS

				
TDF/FTC/EFV Atripla[R]	TDF/FTC/RPV Eviplera[R]	TDF/FTC/EVG/c Stribild[R]	TAF/FTC/EVG/c Genvoya[R]	ABC/3TC/DTG : Triumeq [R]

New paradigm in ART management
Individualization of antiretroviral therapy

Induction

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



1996 Triple therapy : a revolution

2018

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 HIV DNA

Why Switching a suppressive therapy

- Simplify regimen (pill number and frequency)
- Tolerability
- Comorbidity
- Drug-drug interactions
- **Reduce drug burden**
- Discard resistant ARV
- **Cost**

- Maintain viral suppression to avoid resistance
- Need to consider
  - Previous ART
  - Previous resistance
  - Likelihood of adherence
  - Drug–drug or drug–food interactions
  - Comorbid conditions

Reducing drug burden

Innovative dual Therapies

Initiation

IP /3TC
LOPI/3TC GARDEL
DRV /3TC ANDES

INI + IP
RAL/DRV NEAT-01
LPV/RAL Progress

DTG/3TC
PADDLE
ACTG 5353
GEMINI

Maintenance

IP /3TC
- LOPI/3TC
- DRV /3TC
- ATV/r /3TC

INI +NNRTI
RAL/ETR ETRAL
DTG/RPV
SWORD
CAB/RPV LATTE

DTG +3TC
Lamidol Tango

PI 3TC

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	W96 ITT Snapshot
LPV/r 400/100mg BID + 3TC 150 mg BID n=217	88.3 %	90.3%
LPV/r 400/100mg BID + 3TC /FTC + NRTI n=209	83. 7 %	84.4 %

- 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. Lancet Infect Dis. 2014;14:572-580.

G/3TC

Dual Therapy in naive patients initiation

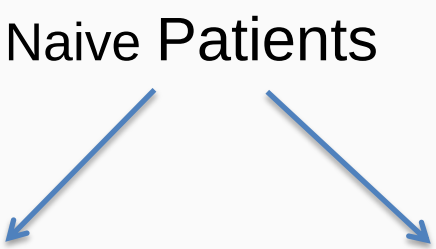
DTG/3TC vs DTG/TDF/FTC

GEMINI 1 &2

- 1433 naive patients
- HIV RNA
  1000-500 000 cp/ml
- CD4 > 200/mm3
- PrEP ou PEP allowed if >1 month
- no HBV infection
- Med VL : 4.45 log HIV RNA

% > 100 000 : 20%

CD4 : 427 :mm3



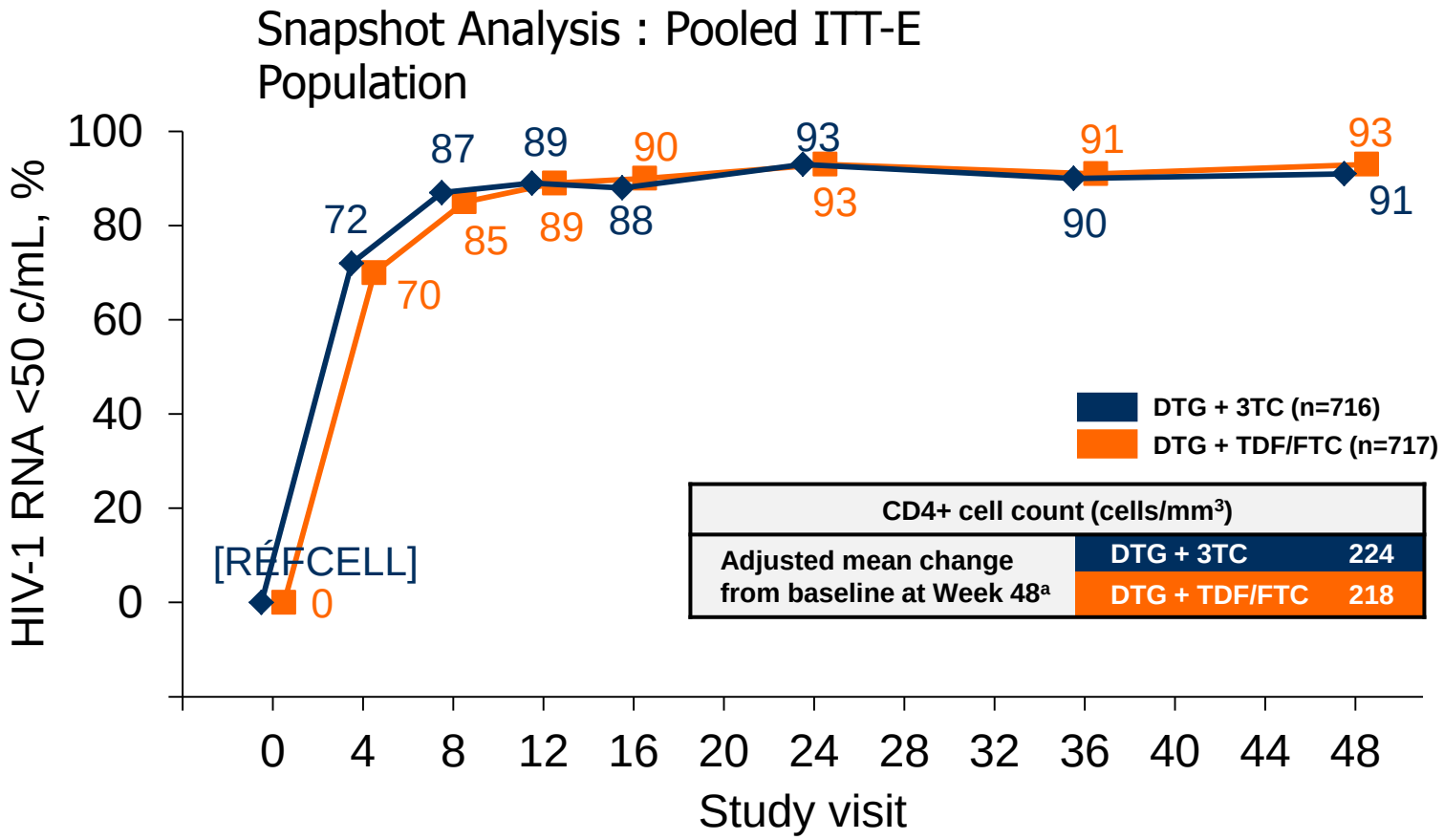
End point : % VS at W48

Follow up : continuation phase for DTG/3TC group

1433 patients

GEMINI Dual Therapy in naive patients

DTG/3TC vs DTG/TDF/FTC



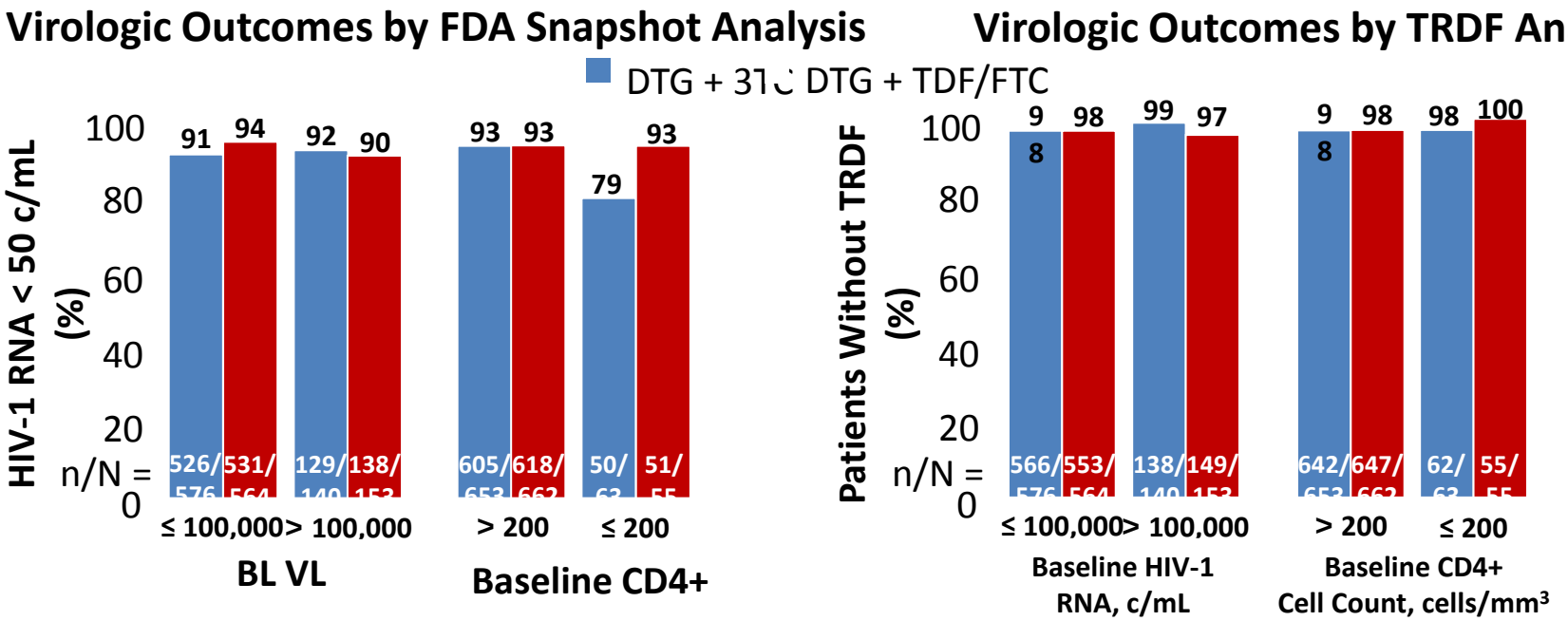
- [a]Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

GEMINI Dual Therapy in naive patients

DTG/3TC vs DTG/TDF/FTC

Virologic Response at W48 by Baseline HIV-1 RNA and CD4+



- TRDF includes confirmed virologic withdrawal, withdrawal for lack of efficacy or treatment-related AEs, and participants meeting protocol-defined stopping criteria

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

3-Drug regimen Switch Studies

Within Class

- EFV → RPV[1]
- RAL or DTG[3] → EVG[2]
- DTG → BIC[4]
- DRV/r → DRV/c/FTC/TAF[5]
- ATV/r,LPV/r
- TDF or ABC → TAF[6,7]

Between Class

- Boosted PI → RPV[8]
- Boosted PI → EVG,[9] DTG,[10] or BIC[11]
- NNRTI → EVG[12] or DTG[3]

CHECK sensitivity of companion drugs

1. Mills AM, et al. HIV Clin Trials. 2013;14:216-223.
2. Mills A, et al. HIV Clin Trials. 2014;15:51-56.
3. Trottier B, et al. Antivir Ther. 2017;22:295-305.
4. Sax PE, et al. IDWeek 2017. Abstract 1380.
5. Orkin C, et al. Lancet HIV. 2018;5:e23-e34.
6. Gallant JE, et al. Lancet HIV. 2016;3:e158-e165.
7. Winston A, et al. Lancet HIV. 2018;5:e162-e171.
8. Palella FJ Jr, et al. AIDS. 2014;28:335-344.
9. Arribas JR, et al. Lancet Infect Dis. 2014;14:581-589.
10. Gatell JM, et al. AIDS. 2017;31:2503-2514.
11. Daar E, et al. IDWeek 2017. Abstract LB-4.
12. Pozniak A, et al. Lancet Infect Dis. 2014;14:590-599.

Towards a light suppressive ART

- Adjust ARV to ZERO replication.
- Reduce drug burden and limit potential unknown toxicities
- Adjust to comorbidities
- Spare ARV individual capital

1-DR Monotherapy

3-DR dose reduction

2-DR Dual therapy

3-DR Intermittent

Reduce drug exposure
On which drugs to rely ?

- **Potency**
- **Viologic Robustness** high genetic barrier to resistance
- **Primary resistance :** low
- **Simplicity QD**
- **PK robustness** ½ life long; no/minimal DDI
- **No side effects**

⇒ **NRTI**

TDF/FTC
TAF/FTC

⇒ **NNRTI**

RPV/ DOR

⇒ **PI**

DRV /c

INI

DTG/BIC **/RAL**

MONO

Protease Inhibitor Monotherapy

Switch Studies

Darunavir ++

Monet : *non inferior*

Monoi : *non inferior AT*

Pivot :

Atazanavir

Lopinavir

Not robust enough

- **Efficacy**

Non inferior or

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

- **Robust:** +++

No resistance in case of viral failure (VF)

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

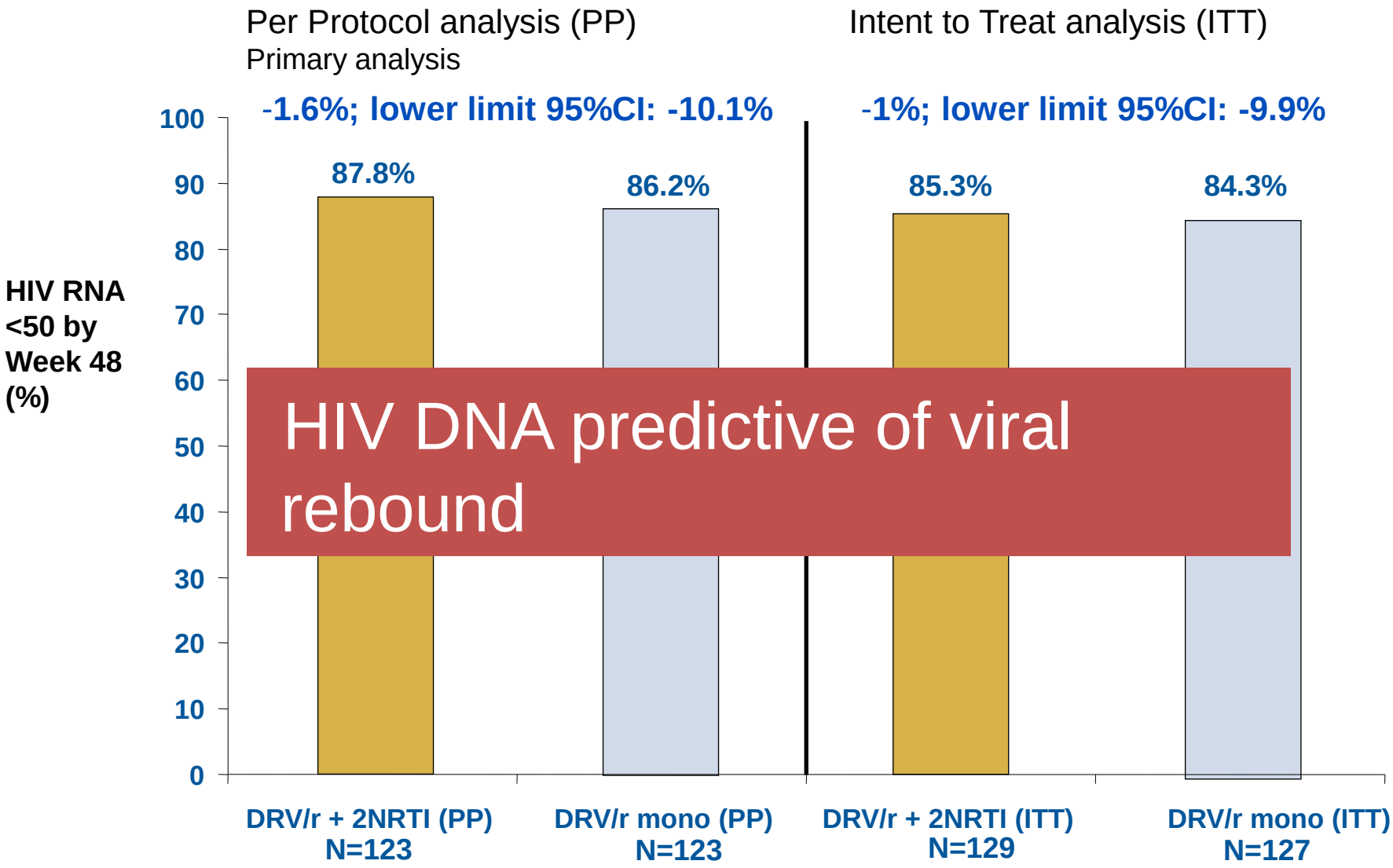
World wide avaibility

Dolutegravir monotherapy

Not to be used in standard conditions

MONO

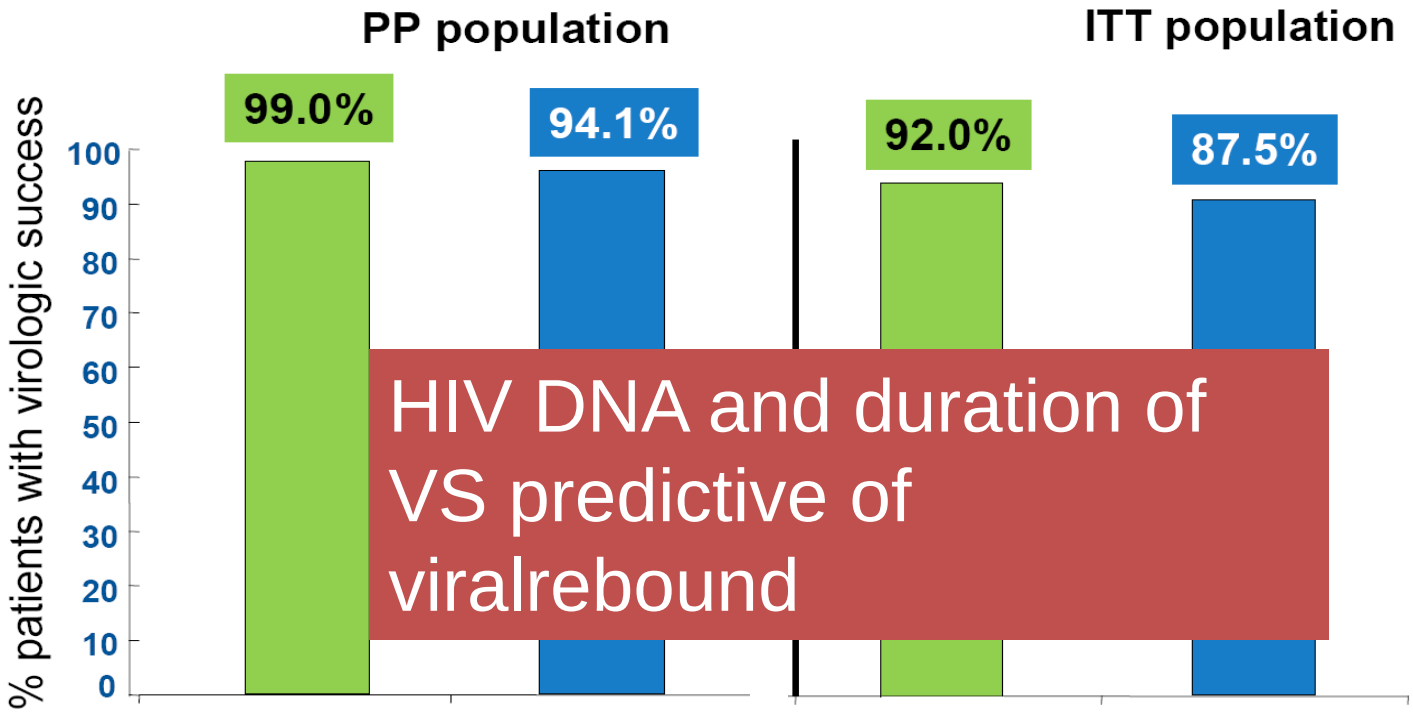
MONET: Primary Efficacy Analysis: HIV RNA <50 copies/mL at Week 48



J. Arribas et al, AIDS 2010

MONO

MONOI Darunavir monotherapy in patients with suppressed viremia



HIV DNA and duration of VS predictive of viralrebound

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

Dose Reduction

Drug reduced suppressive ART

3-DR dose reduction

- Many ARV too highly dosed
- Reduce toxicity

EFV 400 mg

Darunavir

600 or 400 mg

3-DR dose reduction

Efavirenz 400 mg

Darunavir/r 400/100 mg

Darulight

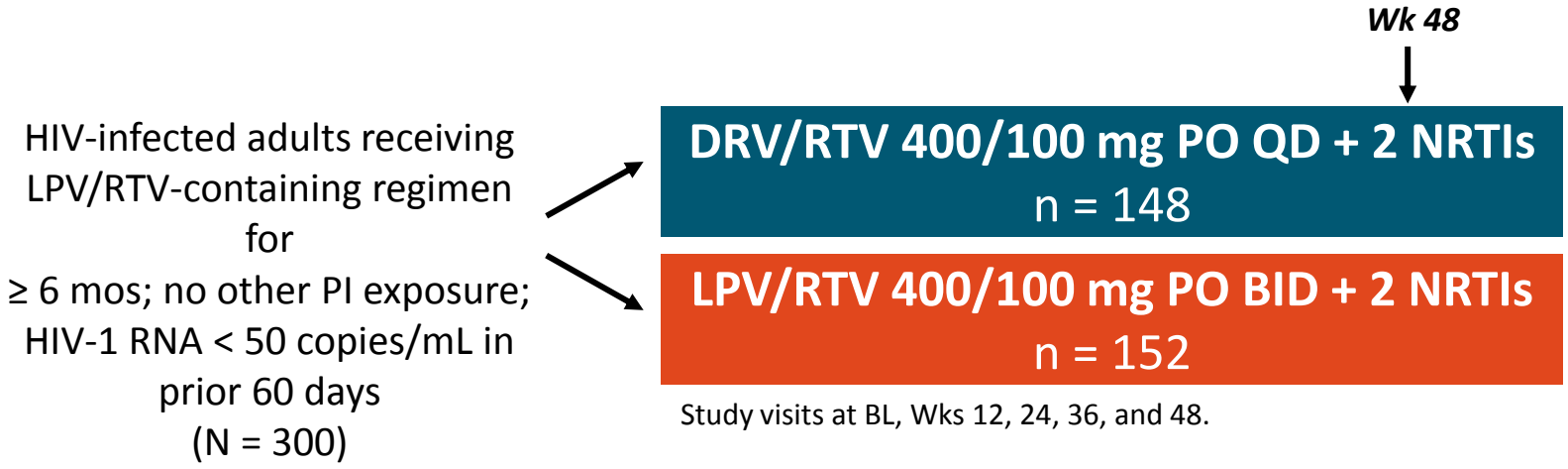
WHHRI 052

Darunavir/r 600/100

Dose Reduction

WRHI 052: Switch to DRV RTV 400/100 mg vs Remaining on LPV/RTV in Virologically Suppressed Adults

- Randomized, open-label phase IIIb study in Johannesburg, South Africa

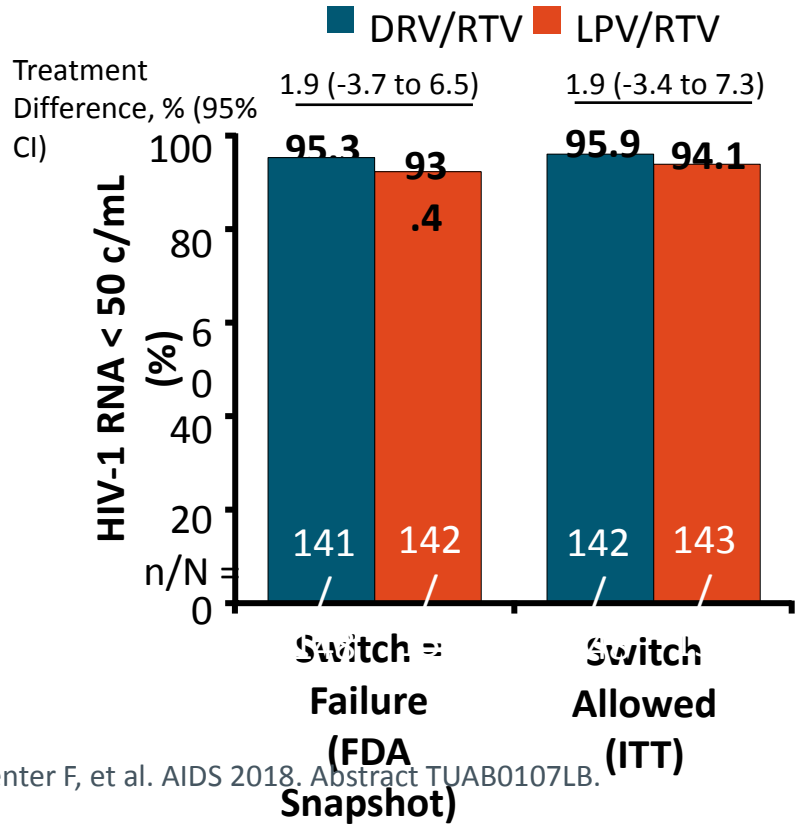


- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA Snapshot, switch = failure analysis

Venter F, et al. AIDS 2018. Abstract TUAB0107LB.

WRHI 052: Switch to DRV RTV 400/100 mg vs Remaining on LPV/RTV

Virologic Response at Week 48



Venter F, et al. AIDS 2018. Abstract TUAB0107LB.

- Genotypic analysis performed on samples with HIV-1 RNA > 200 c/mL at any time to Wk 48

Resistance Mutation, n	DRV/RTV (n = 4)	LPV/RTV (n = 6)
No PI or NRTI	3	2
PI	0	0
NRTI	1	4*
▪ M184V	1	3
▪ K219E	0	1
▪ K65R	0	1
▪ Y115E	0	1
▪ K70R	0	1

*May be archived from virologic failure in first-line setting.

Dual therapy in virally suppressed patients

PI + 3TC

OLE[1] : LPV/3TC

SALT[2]: ATV/FTC

DUAL[3]: DRV/3TC

[1] *Arribas JR. Lancet Infect Dis 2015; 2015; 15:785-92*
[2] *Perez-Molina JA. Lancet Infect Dis 2015;15:775-84*
[3] *Pulido F, HIV Drug Therapy 2016*

PI + INI

NEAT 01 RAL/DRV[1]

SPARE[2]

HARNESS[3]

[1] *Raffi F. Lancet 2014;384:1942-51*
[2] *Nisjhima Plos One 2013*
[3] *Van Lunzen J. JAIDS 2016;71:538-43*

DTG + 3TC

LAMIDOL[1]

TANGO [2]

DOLULAM[3]

[1] *Joly V, CROI 2017, Abs. 458*
[2] *En cours*
[3] *Reynes J, HIV 2016, Abs. P080*

INI + NNRTI

LATTE CABO/RPV [1]

ETRAL RAL/ETR[2]

SWORD DTG/RPV[3]

[1] *Margolis DA. AIDS 2016, Durban, Abs. THAB0206LB*
[2] *Katlama C et Al IAS Paris 2017 abstract MOPEB0314*
[3] *Llibre JM. CROI 2017, Abs. 44LB*

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

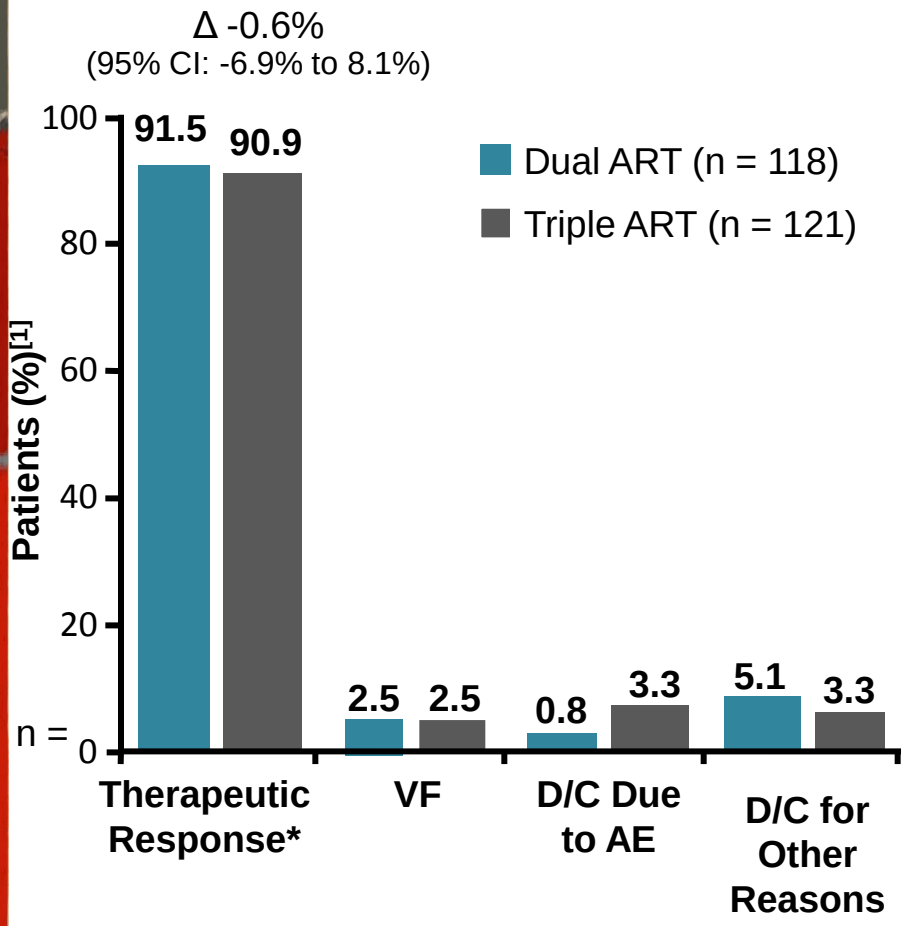
LPV/r 400/100 mg BID + 3TC or FTC

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



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

- VF in 3 pts in each arm

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

NO PI resistance

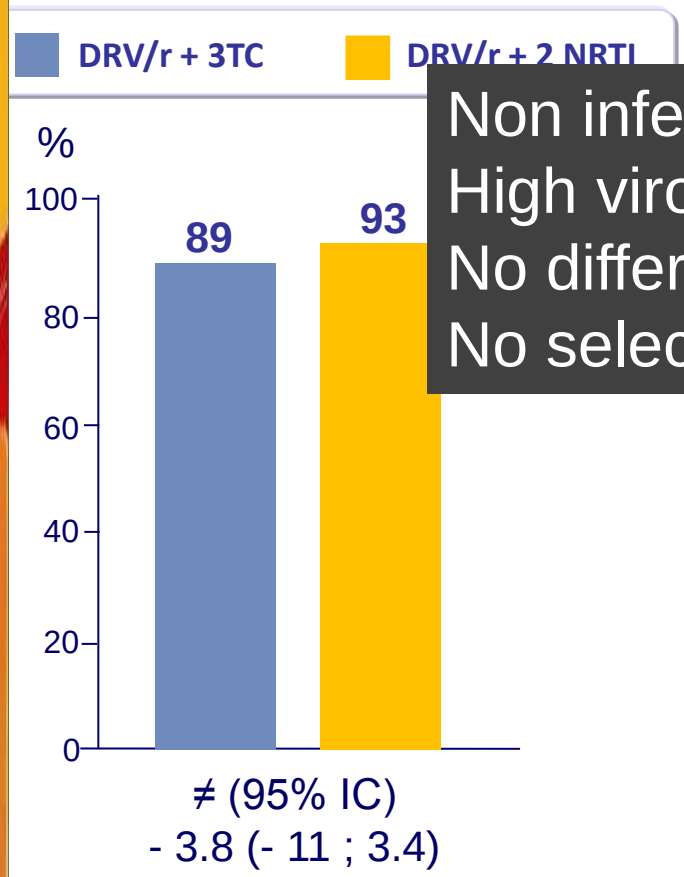
- greater increases in TC (*P* = .02), numerically greater increases in TG (*P* = .09) in dual-ART arm
- May be due to discarding TDF
- Benefit in creatinine in 2-DR

Switch
2- DR

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 + 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

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
- No resistance
- Highly accessible in all countries
- In case R to NNRTI/INI
- Check for HBV
- Cost reduction

Dual therapy switch

DTG + RPV SWORD-1 et SWORD-2

- 2 RCT

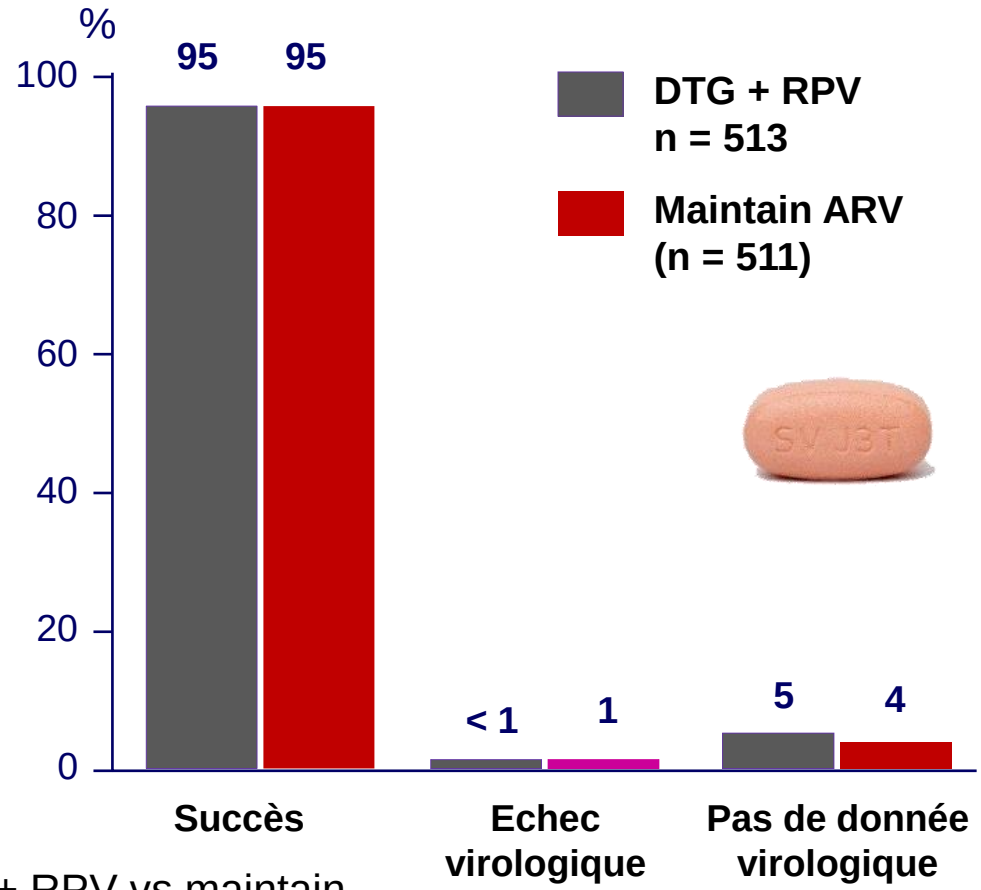
DTG/RPV : 511 pts

Maintain ARV : 513 pts

- CD4: 611 /mm3
- TAR

TDF : 75% NNRTI:54%

IP: 26% INI:20%



Adjusted difference (IC 95 %) DTG + RPV vs maintain ART poursuite ARV en cours

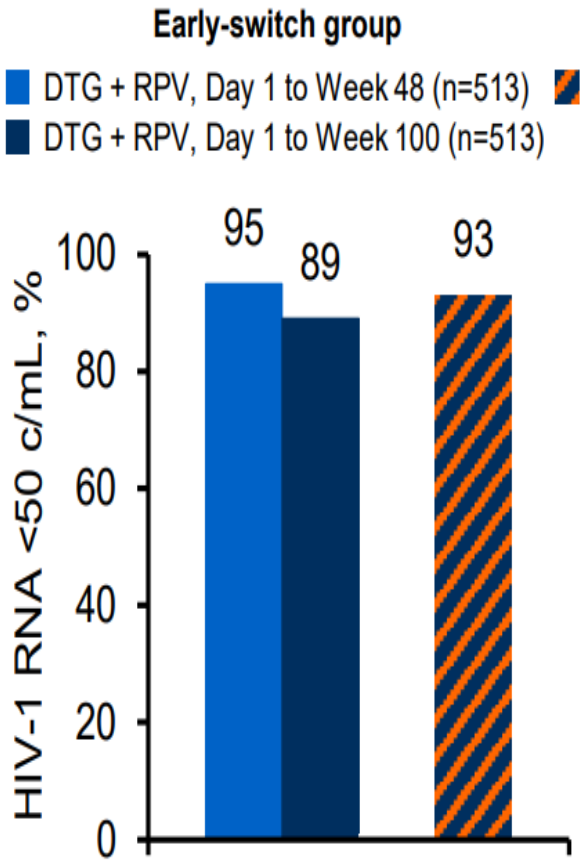
- SWORD-1 (508 patients) : - 0,6 (- 4,3 à + 3,0)
- SWORD-2 (516 patients) : + 0,2 (- 3,9 à + 4,2)

1 seul cas resistance K101K
Sensible RPV

Switch 2- DR

Dual therapy switch
DTG + RPV SWORD-1 et SWORD-2

HIV-1 RNA <50 c/mL (FDA Snapshot) at Week 48 and Week 100



n, %	Early-switch group: DTG + RPV Week 48[2]	Early-switch group: DTG + RPV Week 100	Late-switch group: DTG + RPV Week 100
Virologic success	486 (95)	456 (89)	444 (93)
Virologic nonresponse	3 (<1)	13 (3)	10 (2)
Data in window, not <50 c/mL	0	5 (<1)	3 (<1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	3 (<1)
Discontinued while not <50 c/mL	1 (<1)	1 (<1)	0
Change in ART	0	0	4 (<1)
No virologic data	24 (5)	44 (9)	23 (5)
Discontinued because of AE or death	17 (3)	27 (5)	11 (2)
Discontinued for other reasons[a]	7 (1)	17 (3)	9 (2)
Missing data during window but on study	0	0	3 (<1)

- 1. Llibre et al. Lancet. 2018;391:839-849.
- aOther reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Slides THPEB047.

Switch 2- DR

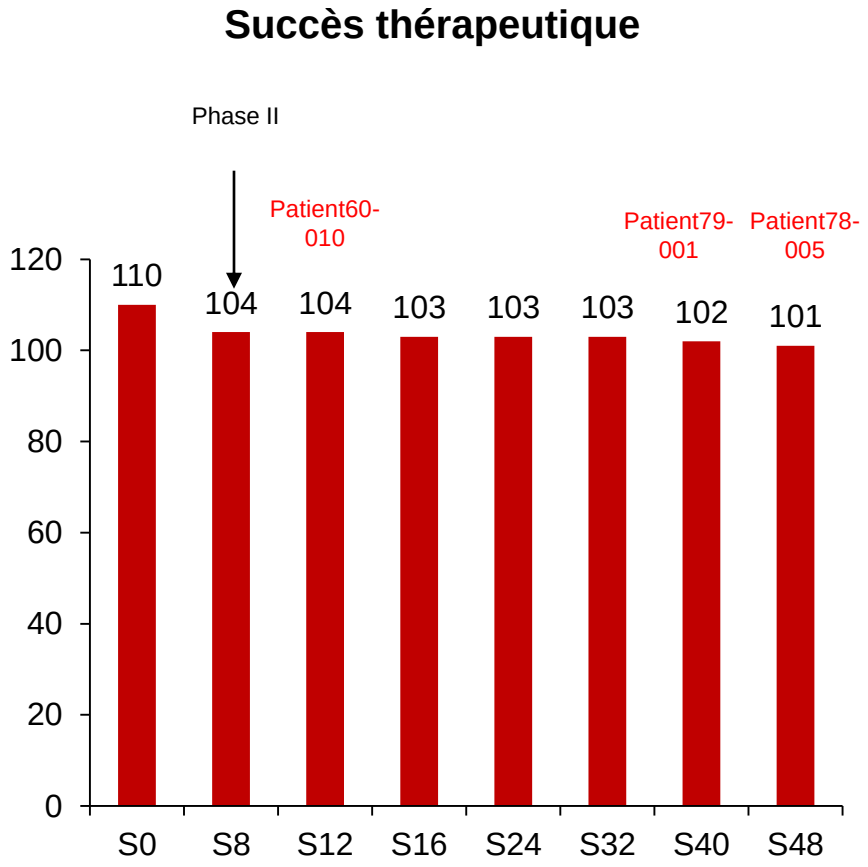
Dual therapy switch

DTG/3TC LAMIDOL ANRS 167

- Etude ouverte , un seul bras
- Switch to DTG/3TC QD
- Échec thérapeutique avec CV > 50 copies/ml ; interrruption TAR , PDV , décès

W48 : **3 échecs**

- **1 échec à S12**
- 1 PDV à S40
- 1 modification TAR S 48

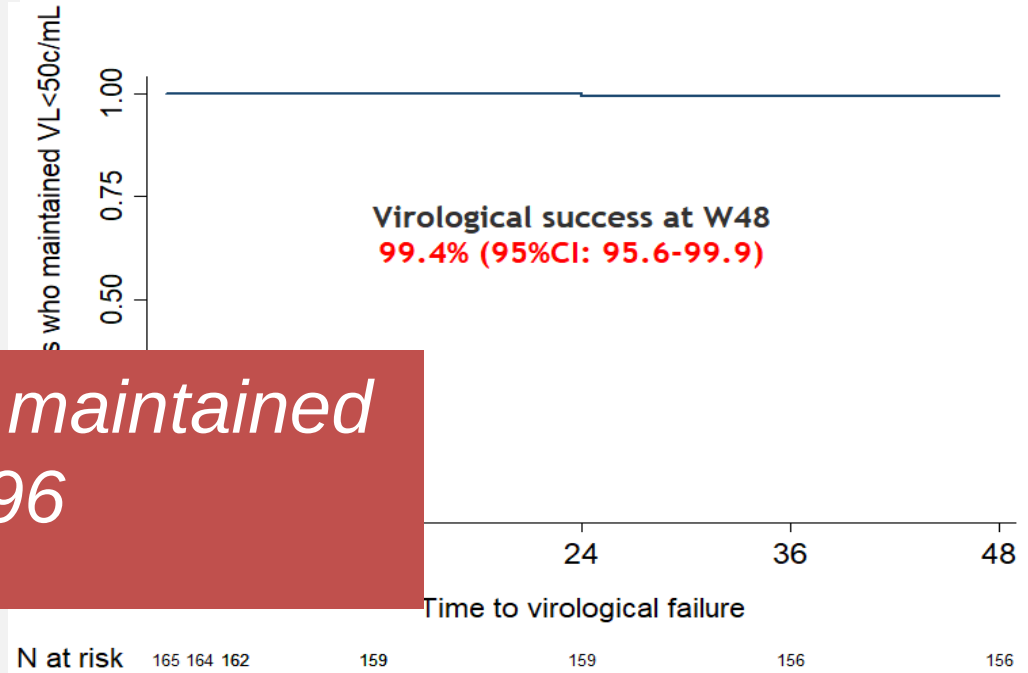


CROI 2017 – from Joly V et al., abstr. 458 actualisé

ETRAL ANRS : 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	
mono PI/r	
Comorbidities	
Dyslipidemia	27%
High Blood Pressure	25%
Diabetes	8%
Cardiovascular event	3%
Co-medications med nb	5



Efficacy maintained up to W96

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

Katlama C et Al IAS Paris 2017 absT MOPEB0314

Switch 2- DR

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*

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

Katlama C et Al IAS Paris 2017
abstract MOPEB0314

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 who ?**

  Avoiding NRTI : NRTI resistance / mito tox

  NNRTI : Resistance

  No major metabolic complications

  Positive interactions : DTG or RAL+ ATV

- **Advantage :** robust
- **Be careful :** drug drug interactions

Towards a light suppressive ART

3-DR Intermittent

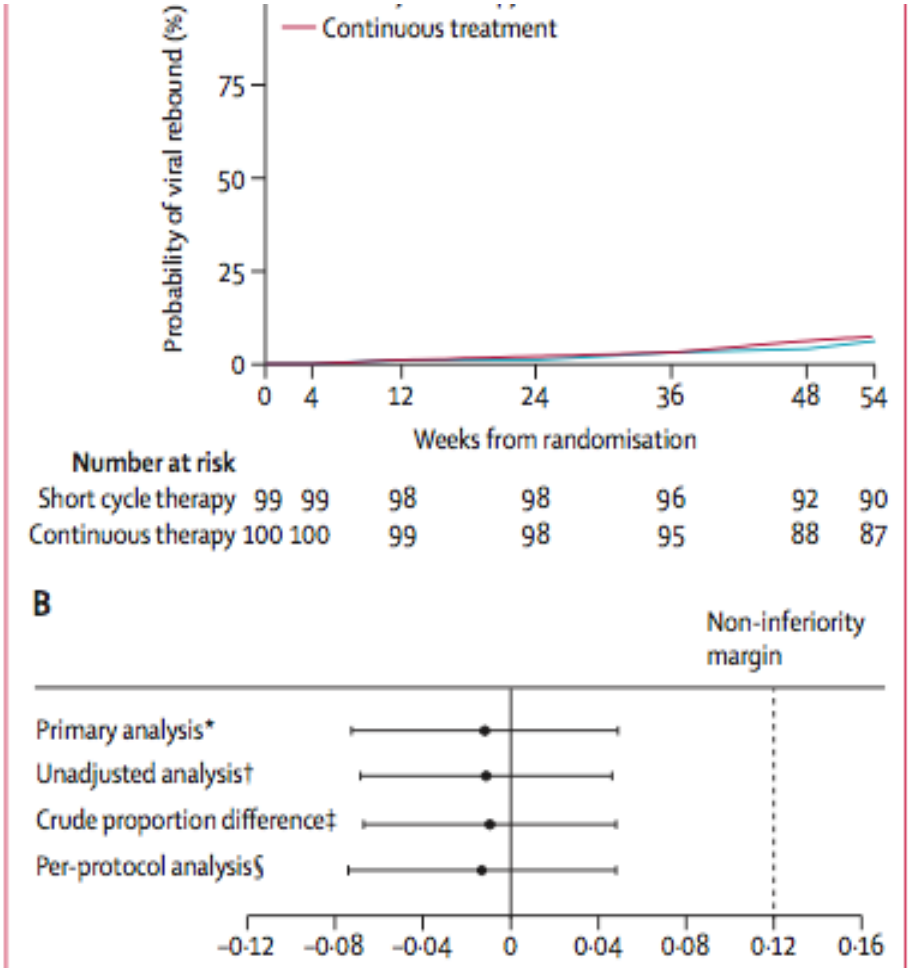
- 3-DR given 4 or 5 days/week
- Keeps Single tablet Regimen
- Higly plebisited by patients ++
- FOTO (2000)
- ICARRE
- BREATHER
- 4D
- QUATUOR on going

Intermittent Therapy
Breather : a week end 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

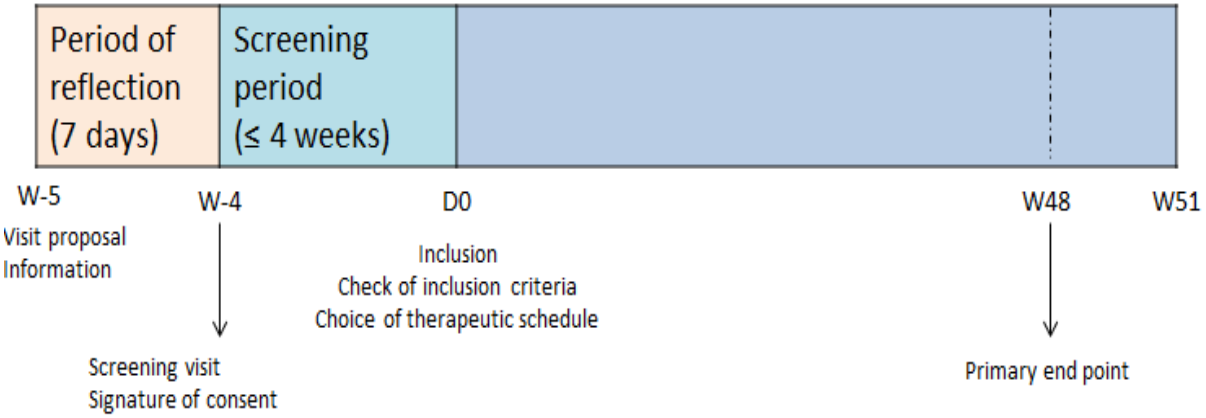
Viral rebound > 50 cp/ml
6 pts Interm ART vs 5 cont ART
difference –1·2%, 90% CI –7·3 to 4·9, test for difference, bootstrap p=0·75; figure 2A). Thus, the 4·9% upper band of the two-sided 90% confidence limit was well within the 12% non-inferiority margin.



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%



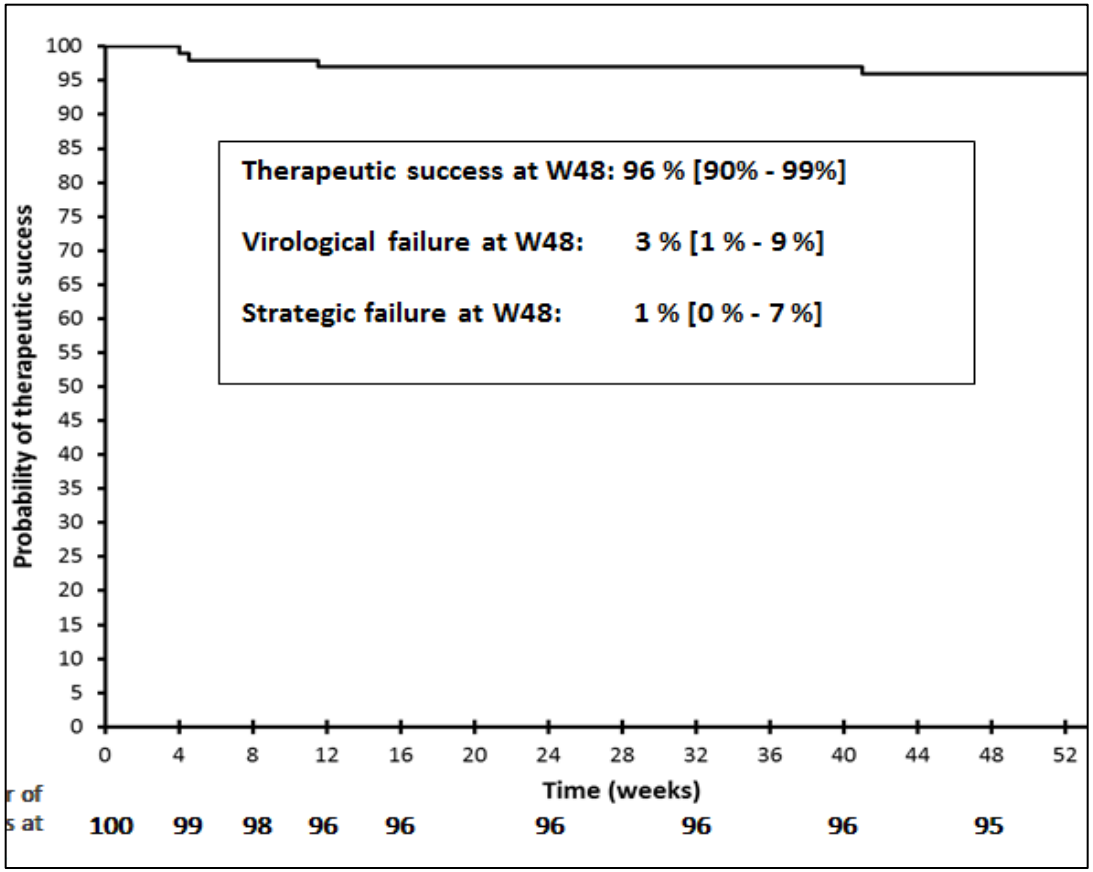
2 weekly modalities of antiretroviral taken

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.



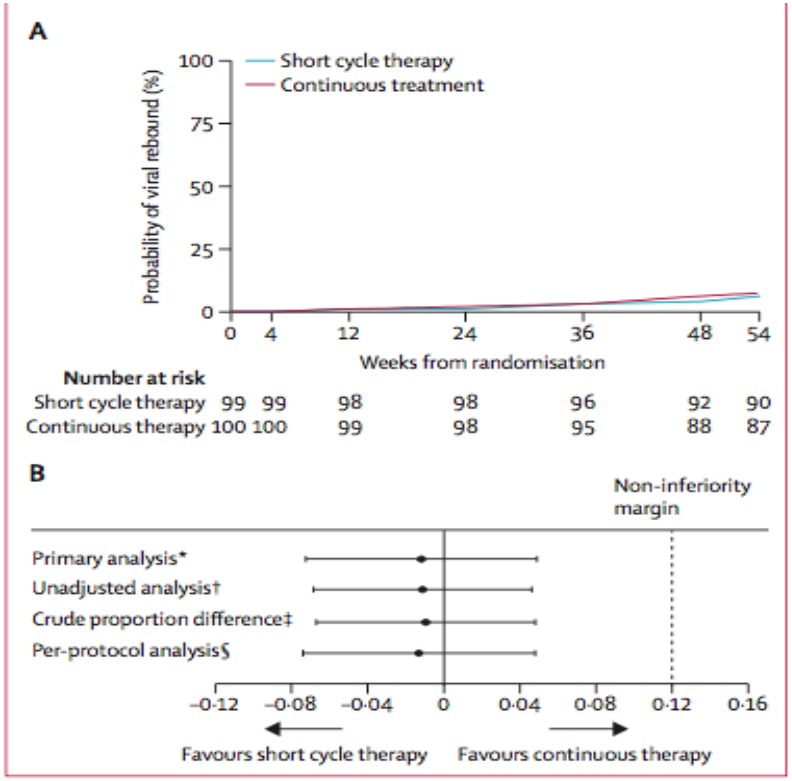
- **3 virological failures**

  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

Intermittent 3-DR regimen

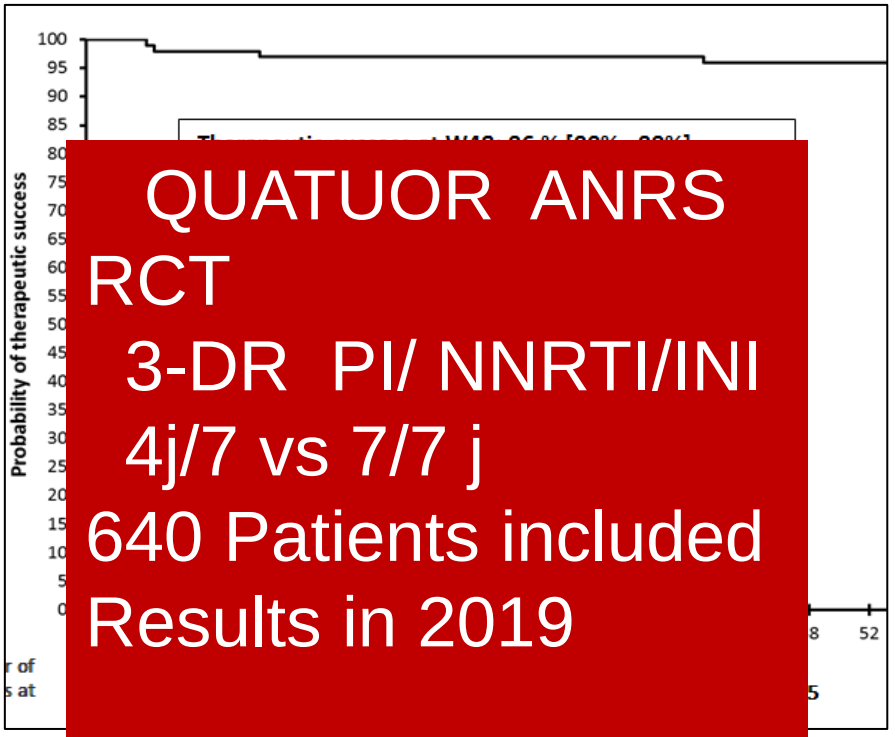
BREATHER Etude rando.pilote

199 enfants /ados TAR :
2NRT/EFV **TAR 5 JOURS /7**



Etude 4D ANRS 162

Etude pilote 100 patients controlés
TAR 4 JOURS /7



QUATUOR ANRS
RCT
3-DR PI/ NNRTI/INI
4j/7 vs 7/7 j
640 Patients included
Results in 2019

Succès 96% ; 3 échecs ; pas de Résistance

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

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)

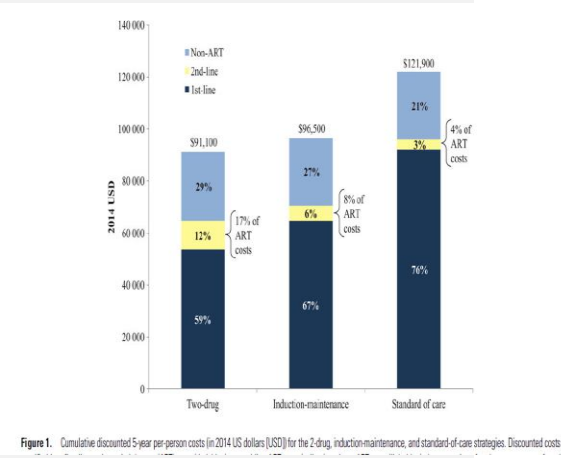


Figure 1. Cumulative discounted 5-year per-person costs (in 2014 US dollars [USD]) for the 2-drug, induction-maintenance, and standard-of-care strategies. Discounted costs

➢ **NAIVE patients**

2-DR prefered strategy if VS > 90%

If 50% uptake

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

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

➢ **SWITCH if 25% of all suppressed patients swicth to DTG/3TC : saving > 3 billion USD**

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

- **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

- *In case of limited access THINK TWICE IT'All RIGHT*

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

  Disccuss within team

- **4 Check** drug drug interactions
  - *between antiretroviral drugs*
  - *with ARV and comedications*

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

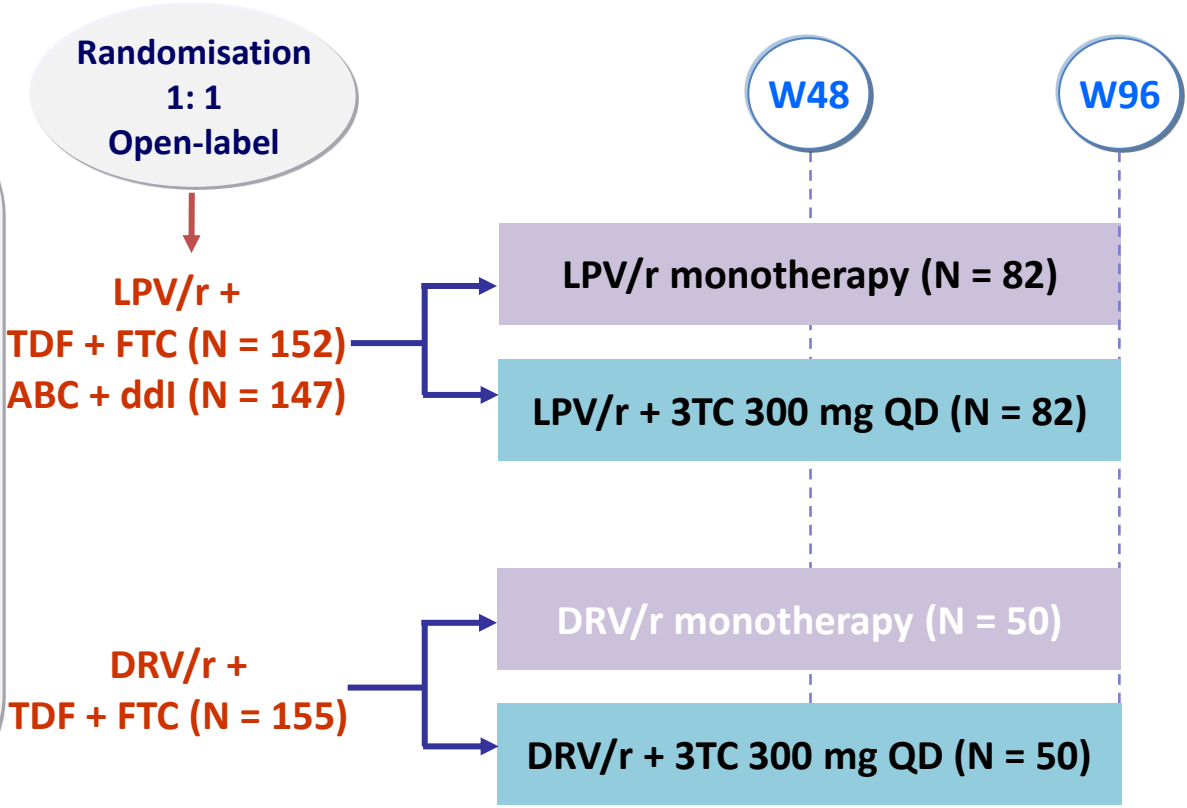
  some failures may be slow to appear

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

	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 suspected to HIV RNA > 200 c/mL a median of 10 weeks after NRTI reintroduction

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

Light ART in real life

Reducied drug strategies in real life

Expérience Pitié-Salpétrière

Drug reduced ART 33%

Suppressive ART in 2017

2941 patients with VL <50 cp/mL

Type TAR	n	%
Triple therapy 3-DR	2026	**69%**
7 days /7	**1938**	**66%**
Intermittent	**88**	**3%**
4d/w	72	
5d /w	16	
Dual therapy 2-DR	713	**24%**
Monotherapy	161	**6%**
Multitherapy	41	**1,39%**

MA Valantin AFRAVIH 2018 Oral session ARV

Suppressive ART in 2017

2-drug regimen in 713 patients

Regimen	Nb patients	
INI + NNRTI	405	56%
INI+ NRTI	120	17%
2 NRTI	82	12%
PI+NRTI	79	11%
INI + PI	66	9%
NNRTI + PI	38	
INI + MVC	21	
NRTI + NNRTI	19	
MVC + IP	5	
MVC + NNRTI	4	
2IP	2	

RAL/ETR : 129 pts
DTG+RPV : 115 pts

DTG/3TC : 83
DTG/TDF: 18

TDF/FTC : 75

From ID department
C. Katlama personnal data

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**

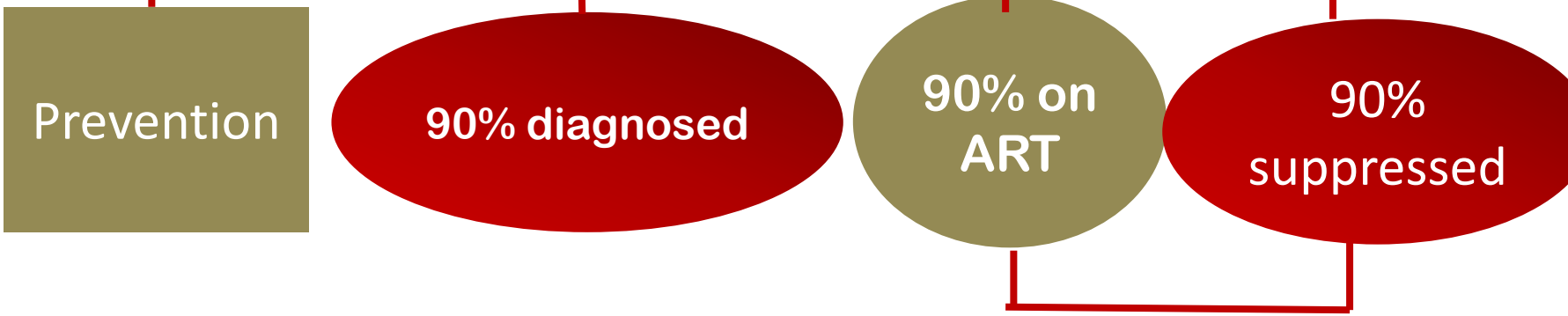
- **SWITCH 25% of all suppressed patients : saving > 3 billion USD**

Antiretroviral Strategies

Innovation for duration

- Ajust ART to patient
- Adjust drug dispensiation to context
- Adjust follow up
- Empower patient

Differentiated care



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

BACK UP SLIDES

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

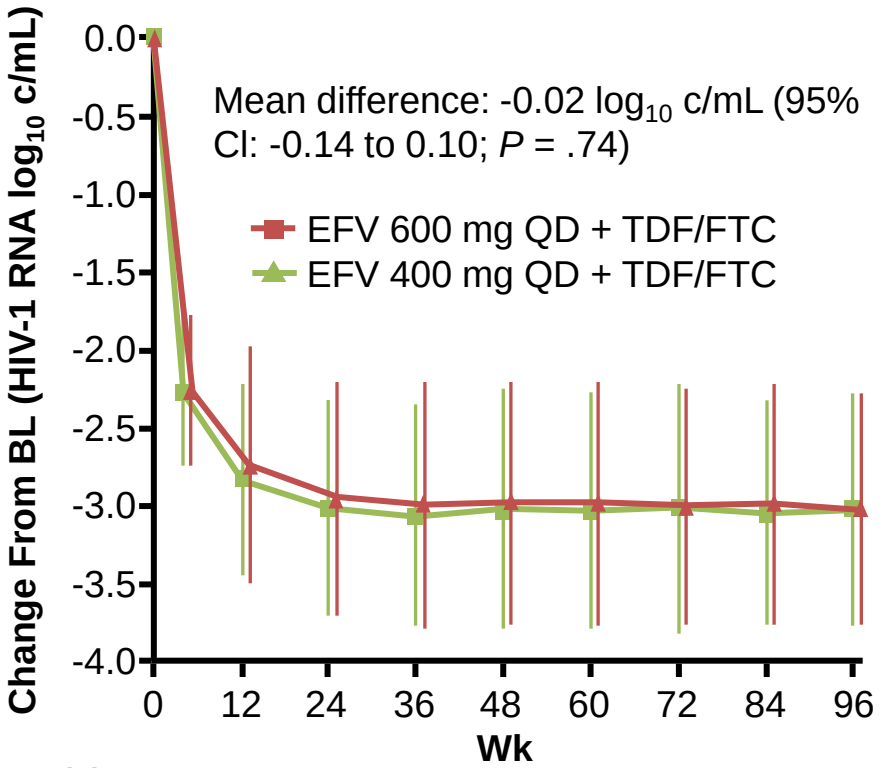
	HIV-1 RNA < 200 cp/ml W48		
	NC=F	**ITT**	**PP**
EFV* 400 mg + Placebo + TDF/FTC n = 324	90.0 %	94.1 %	98.3 %
EFV* 600 mg + TDF/FTC n = 312	85.8 %	92.2 %	97. 4 %

- 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

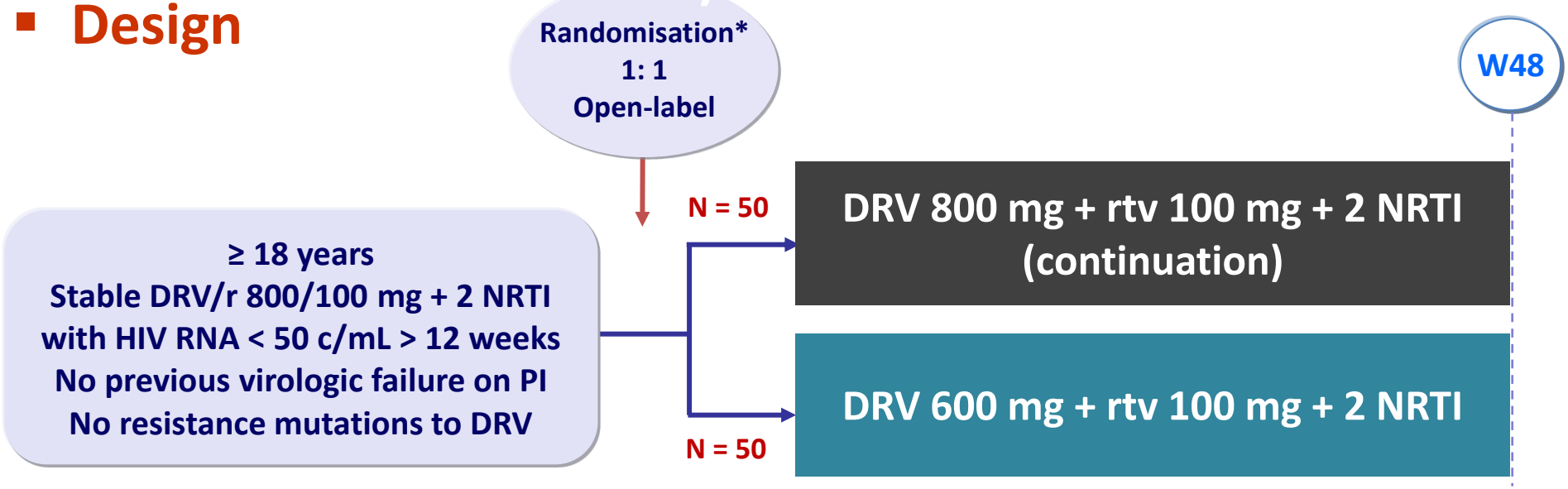
- Mean change in CD4+ cell count from BL greater with 400-mg vs 600-mg EFV (P = .03)
- Rate of EFV-related AEs lower with 400-mg vs 600-mg dose: 37.7% vs 47.9% (P = .01)
- Trend toward lower rate of discontinuation for EFV-related AEs with 400-mg vs 600-mg dose: 8.3% vs 15.5% (P = .07)
- Frequency of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



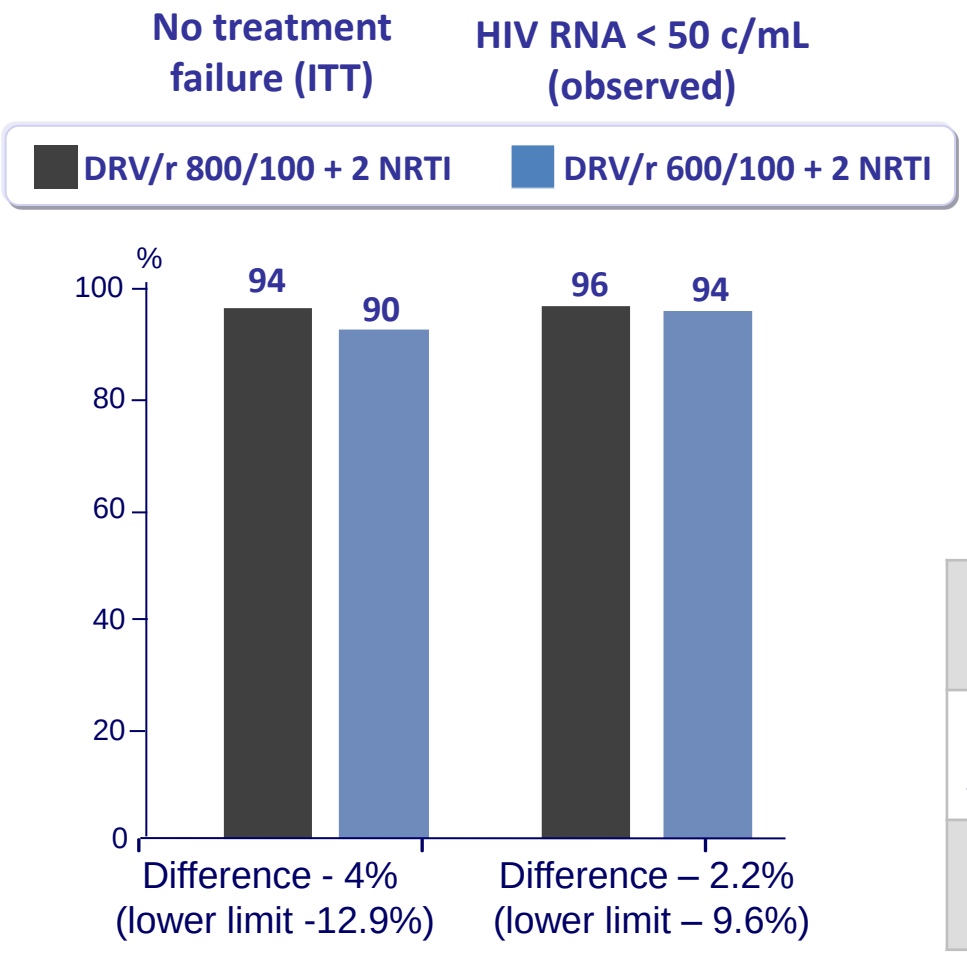
* Randomisation was stratified on HIV RNA (≤ or > 100,000 c/mL) prior to ART start

- **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

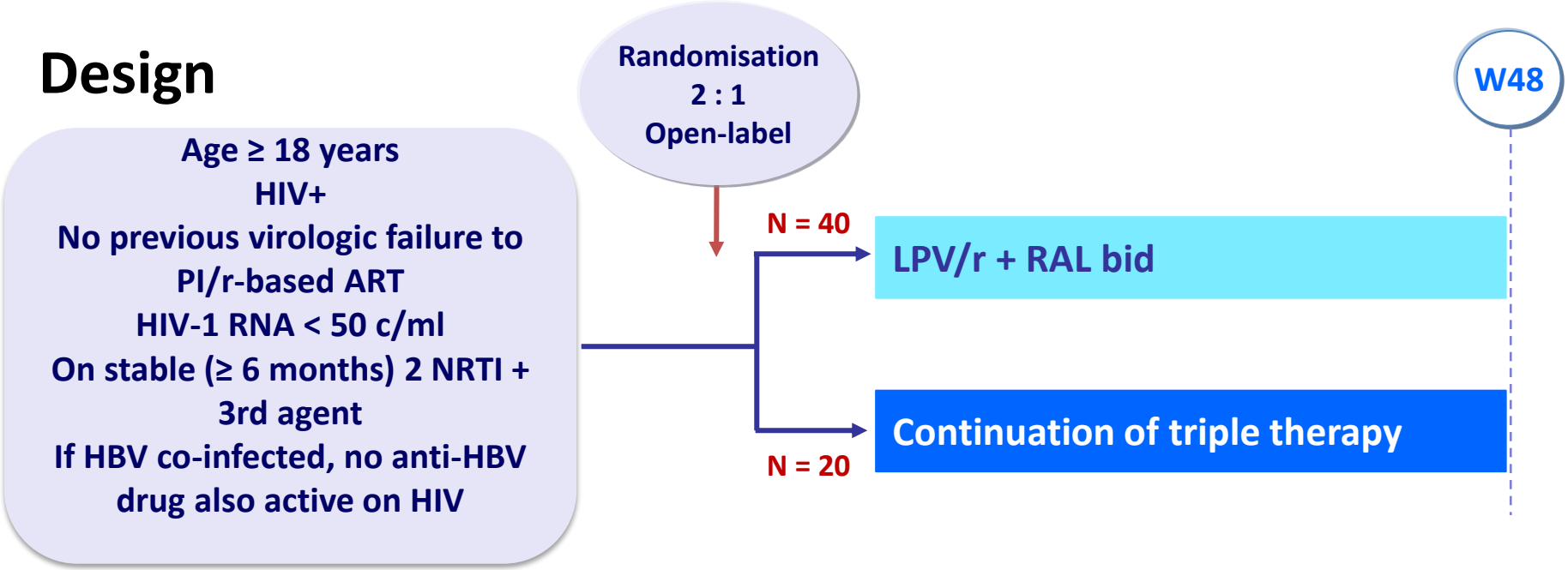
Full PK analysis

	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

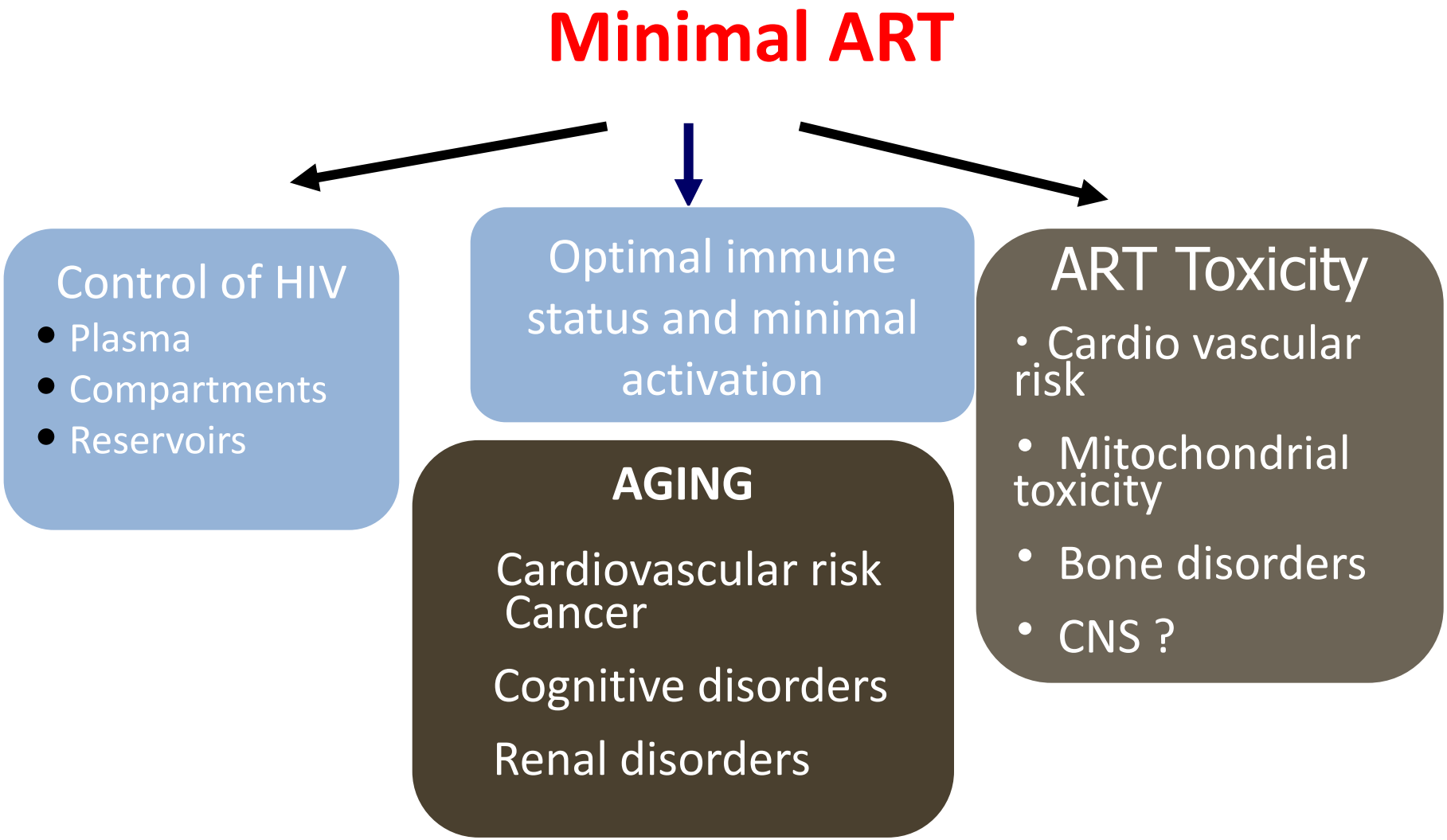
Outcome - Efficacy

	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

Need for individualized therapy in Long-term virological suppression



3-Drug regimen Switch Studies

Simplification : STR

TDF/FTC/EVG
TAF /FTC/EVG

TAF/FTC/ BIC

Alternate NRTI

TDF or ABC to TAF

Toxicity Prevention

Alternate drug class

++ Check whether 3d agent is not in a functonnal mono therapy situation

3DR regimen with TDF/3TC + DRV or LPV

Switch to TDF/FTC/EVG stribild or Genvoya

But missed K65R TAMS from the past ; PI was doing the job

1. Mills AM, et al. HIV Clin Trials. 2013;14:216-223.
2. Mills A, et al. HIV Clin Trials. 2014;15:51-56.
3. Trottier B, et al. Antivir Ther. 2017;22:295-305.
4. Sax PE, et al. IDWeek 2017. Abstract 1380.
5. Orkin C, et al. Lancet HIV. 2018;5:e23-e34.
6. Gallant JE, et al. Lancet HIV. 2016;3:e158-e165.

7. Winston A, et al. Lancet HIV. 2018;5:e162-e171.
8. Palella FJ Jr, et al. AIDS. 2014;28:335-344.
9. Arribas JR, et al. Lancet Infect Dis. 2014;14:581-589.
10. Gatell JM, et al. AIDS. 2017;31:2503-2514.
11. Daar E, et al. IDWeek 2017. Abstract LB-4.
12. Pozniak A, et al. Lancet Infect Dis. 2014;14:590-599.

Principles of regimen switching in virologically suppressed patients

Explain

why you propose switching

ART history

- AIDS related event ; CNS event which may require adequate CSF drug penetration
- CD4 nadir and VL
- **Patient adherence to ART**
- ART history for possible VF
- **HIV education**

Drug Resistance:

- Review all available resistance test results
- If prior resistance uncertain: only consider switch if new regimen likely to maintain suppression of resistant virus
- Caution when switching from boosted PI to another class if full treatment/resistance history not known
- Consult an expert when switching if resistance to ≥ 1 class
- Within class switches usually maintain virologic suppression if no resistance to drugs in that class are present

Principles of regimen switching in virologically suppressed patients

Safety:

- Review ART history for intolerance
- Must be HLA-B*5701 negative if considering ABC
- Drug–drug interactions with comedications

Comorbidity:

- HBV coinfection
- Cardiovascular disease or risk
- Renal function
- Bone mineral density
- Other coinfections

90% Suppression virologique Optimiser le soin durablement

MEDICAL

- Faciliter le travail médical

Privilégier dossier médical informatisé

- Repérer les échecs
- Repérer les PDV

Poster A Balde n° XX

PATIENT

Mettre le patient au coeur de son su , TAR

MÏDOC

- Simplifier accès TAR
- Soins adaptés

Differentiated Care

rapport OMS ;session samedi 7/04

Le défi : un traitement suppressif à vie
une dispensation individualisée

Reducing drug burden

- Initiation Therapy