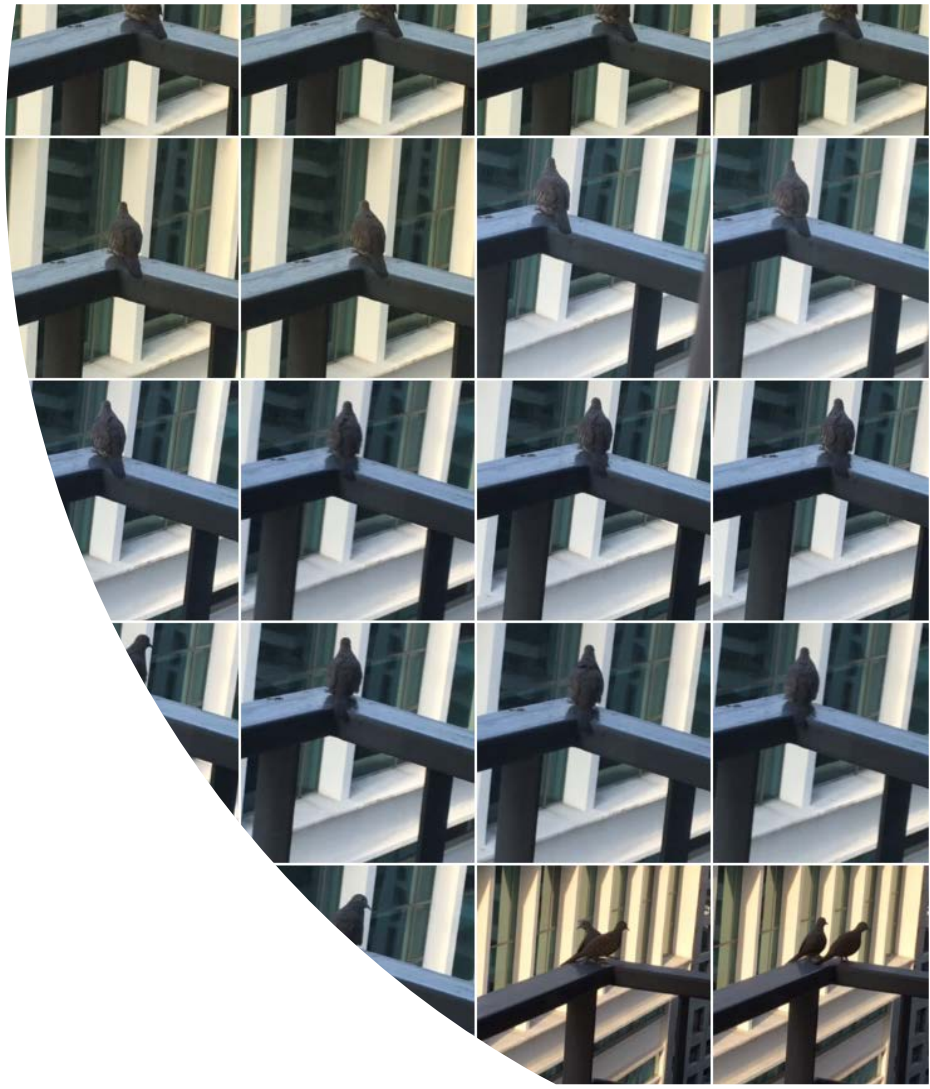
EACS
European
AIDS
Clinical
Society



Optimizing ART in HIV suppressed patients

Pr Christine Katlama

APHP
Hôpital Pitié-Salpêtrière
Sorbonne Université

UPMC PARIS UNIVERSITAS

AFRAVIH
ALLIANCE FRANCOPHONE DES ACTEURS DE SANTÉ CONTRE LE VIH

SORBONNE UNIVERSITÉ

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
  Switching from from TID to BID and QD

- **2015 Individualized optimization**
  To minimize drug exposure
  To adjust ART to comorbidities

HIV and ART
Where are we in 2019 ?

HIV is an integrated virus with limited immune protection

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

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

Long life ART mandatory
up to several decades

The « undetectable Status » to be sustained long life

How to get there ?

- Taking ARV drugs
- Taking the right drugs
- On ART as earlier as possible as lower is
  - HIV RNA and DNA
  - immunity prejudice
  - better will be immune reconstitution

Remain suppressed

- Life-long therapy : a major challenge
- Compliance
- Education
- Patient empowerment
- Empathy

ART has to be a life-long suppressive therapy

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

The Dogma

Viral load undetectable

Rather than the number of drugs

Undetectable = untransmittable

Challenges

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

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

Antiretroviral Drugs 2019

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

Antiretroviral Drugs 2019

3-DR - Single Tablet Regimen

						
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]	3-DR TAF/FTC/BIC Bictarvy[R]	3-DR DOR/TDF/3TC Delestrigo[R]

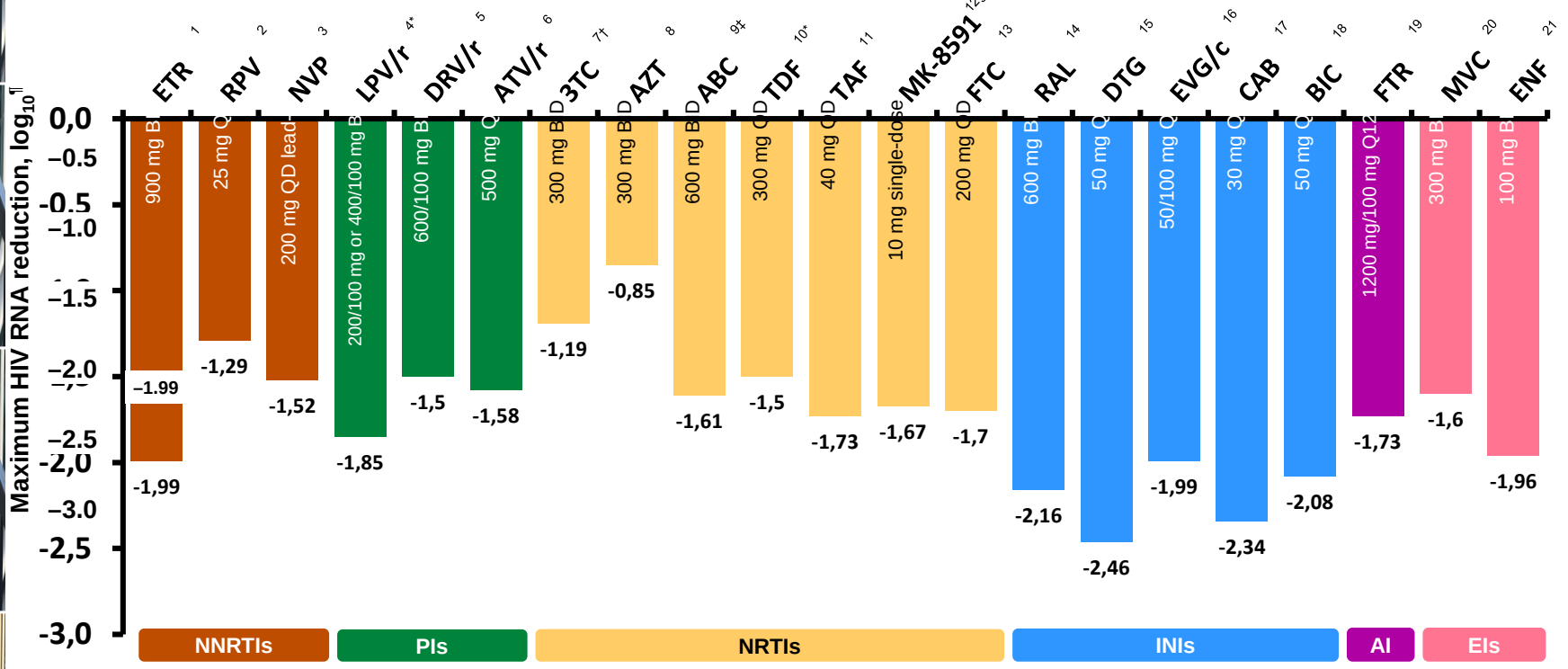
2 DR - Single Tablet Regimen

	
2-DR DTG/RPV Juluca[R]	DTG / 3TC Dovato[R]

ARV viral potency and robustness has improved over years

Potency of ARV in monotherapy

maximum change in HIV RNA (log_{10}) over 7–14 days



References can be found in slide notes

Reasons for switching a suppressive therapy

Improve strategies

1 Simplify regimen pill nb frequency

2 Improve tolerability

3 Prevent toxicity

4 Minimize drug-drug interactions

Long term strategies Reduce drug burden

Why more drugs if we can maintain viral suppression with less

Discard resistant ARV

Optimize cost

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

3-Drug regimen Switch Studies

Within Class

EFV → RPV[1] DOR

RAL → BIC[4] or DTG[3]

PI/r → DRV/c/FTC/TAF[5]

TDF or ABC → TAF[6,7]

Between Class

PI/b → RPV [8], DOR

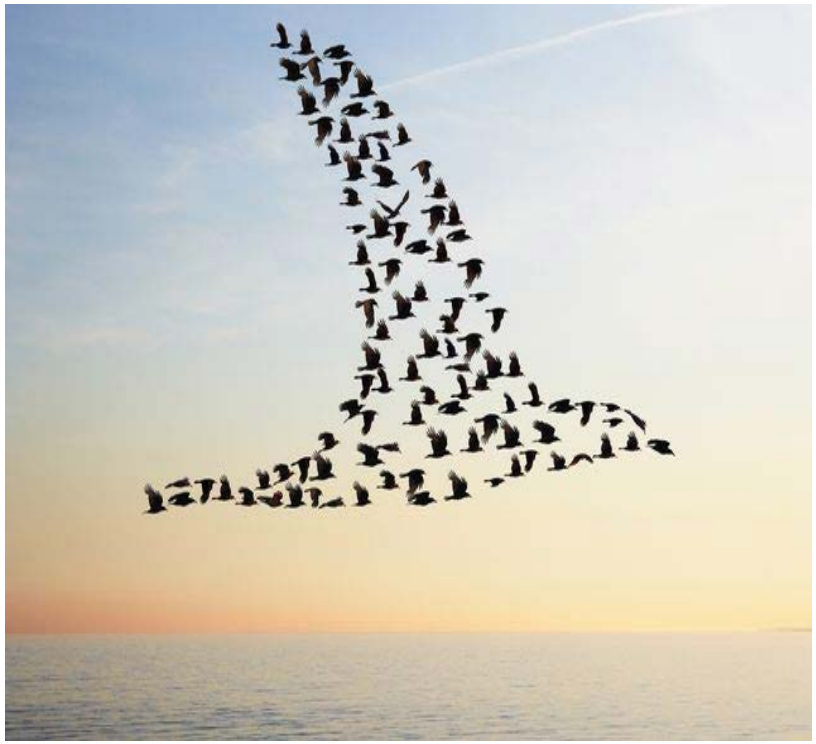
PI/b → INI] DTG,[10] BIC[11]

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 Drug-reduced Strategies



- Adjust ARV to ZERO replication
- Reduce drug burden
- Spare ARV capital

Monotherapy

Dual therapy

Dose reduction

Intermittent therapy

Reduce drug exposure
On which drugs to rely ?

- **Potency**
- **Virologic robustness**
- high genetic barrier to resistance
- **Primary resistance :** low
- **Simplicity QD**
- **PK robustness** ½ life long; no/minimal DDI

NRTI

TDF/FTC TAF/FTC

NNRTI

RPV/DOR

PI

DRV/c

INI

DTG/BIC/**RAL**

Dose Reduction

Drug reduced suppressive ART

Dose reduction in context of 3-DR

- **Dosage reduction**

  Many ARV developped with highest dosage

- **Reduce toxicity**

  - **EFV 400 mg**

  OMS guidelines 2019

  Darunavir

  - **600 or 400 mg**

3-DR dose reduction

Efavirenz 400 mg

Encore *WHO Mexico*

Darunavir/r 400/100 mg

Darulight ANRS

WHHRI 052

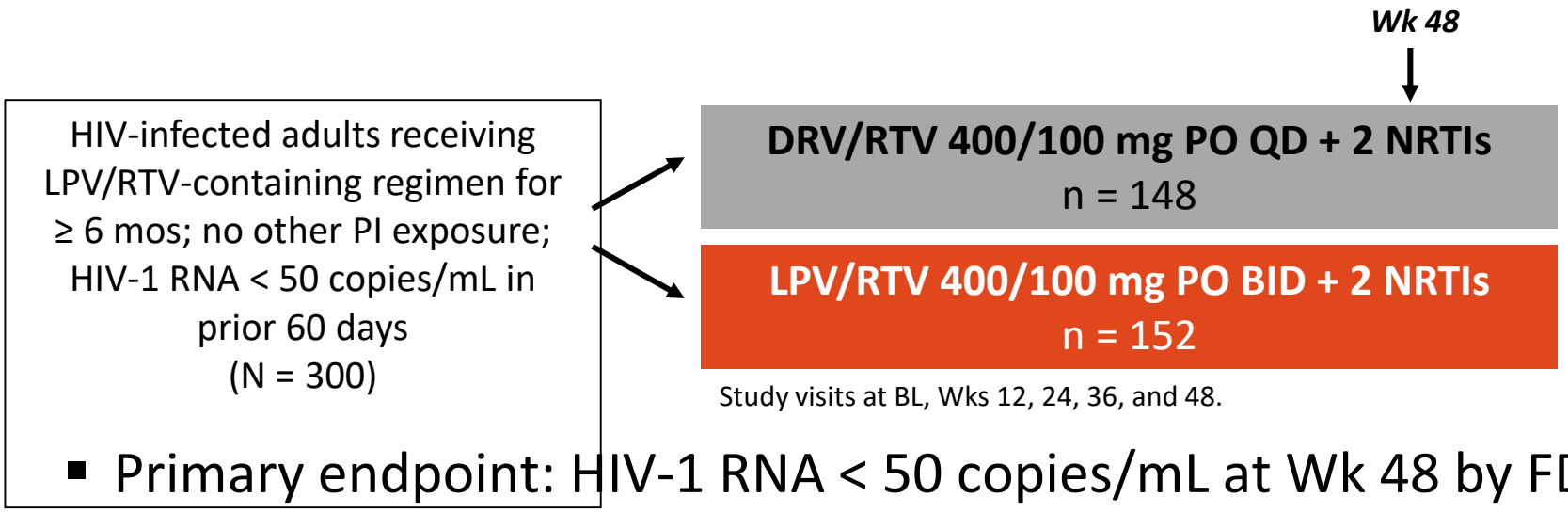
Darunavir/r 600/100

Important to prevent toxicity ; to maintain a class and minimize AE; reduce cost

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

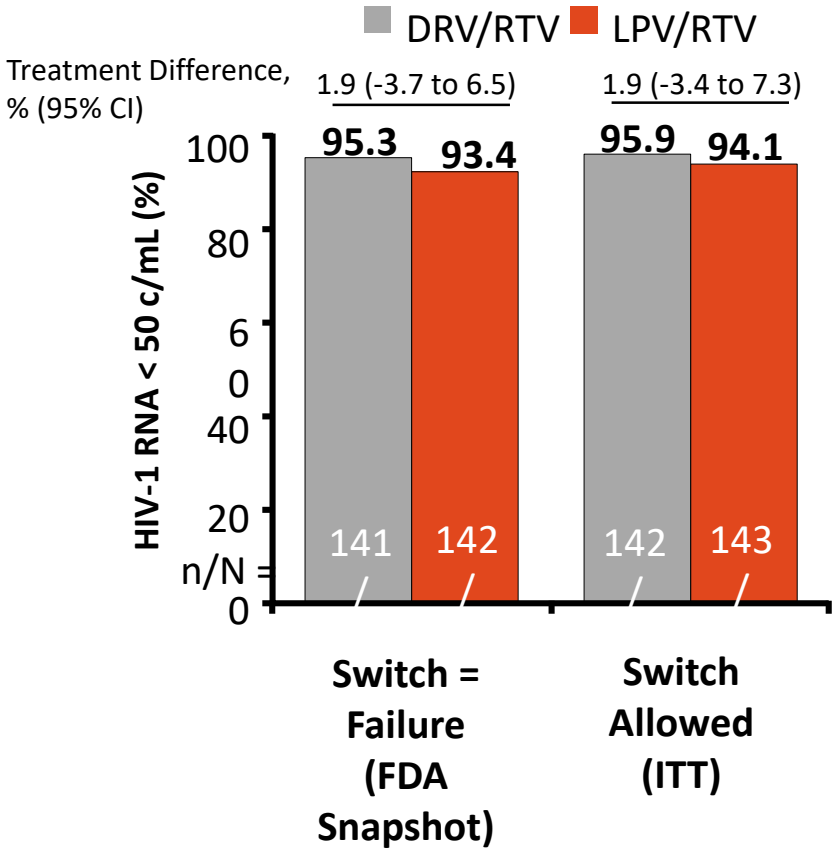


- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA Snapshot, switch = failure analysis

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

Dose Reduction

WRHI 052: Switch to DRV/r 400/100 mg vs LPV/r Virologic Response at Week 48



- 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.

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

MONO

Protease Inhibitor Monotherapy

Switch Studies

Darunavir ++

Monet: *non inferior*

Monoi: *non inferior*

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

Reducing drug burden

Dual Therapies (2-DR)

Initiation

IP / 3TC

LOPI/3TC GARDEL

DRV /3TC ANDES

INI + IP

RAL/DRV NEAT-01

LPV/RAL Progress

DTG / 3TC

PADDLE

ACTG 5353

GEMINI

Long term

PI / 3TC

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

INI + NNRTI

RAL/ETR ETRAL

DTG/RPV SWORD

CAB/RPV LATTE

DTG + 3TC

LAMIDOL TANGO

Switch to Dual Therapy

PI + 3TC

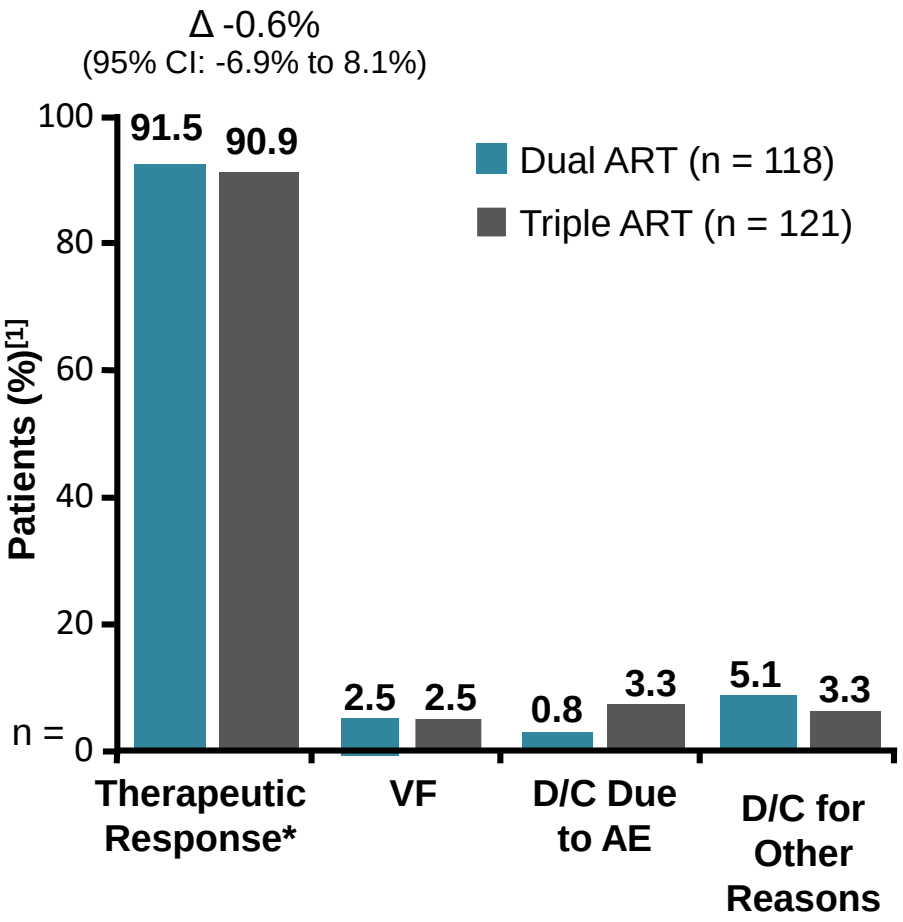
- OLE : LPV/3TC
- SALT : ATV/3TC
- ATLAS : ATV/3TC
- DUAL : DRV/3TC
- Gardel long term LPV+3TC

- Effectif ; Robuste
- Pas de résistance
- Accessible Qd R à NNRTI/INI
- Check for HBV
- Cout raisonnable

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

Switch 2- DR

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

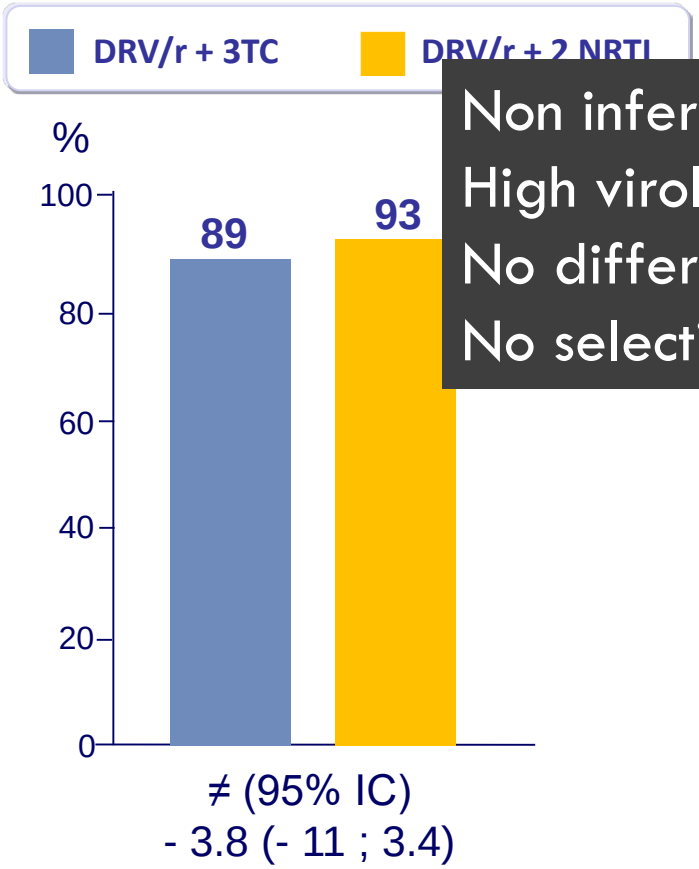
- greater increases in TC (*P* = .02), numerically greater increases in TG (*P* = .09) in dual-ART arm
- May be due to discarding TDF
- Benefit in creatinine in 2-DR

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

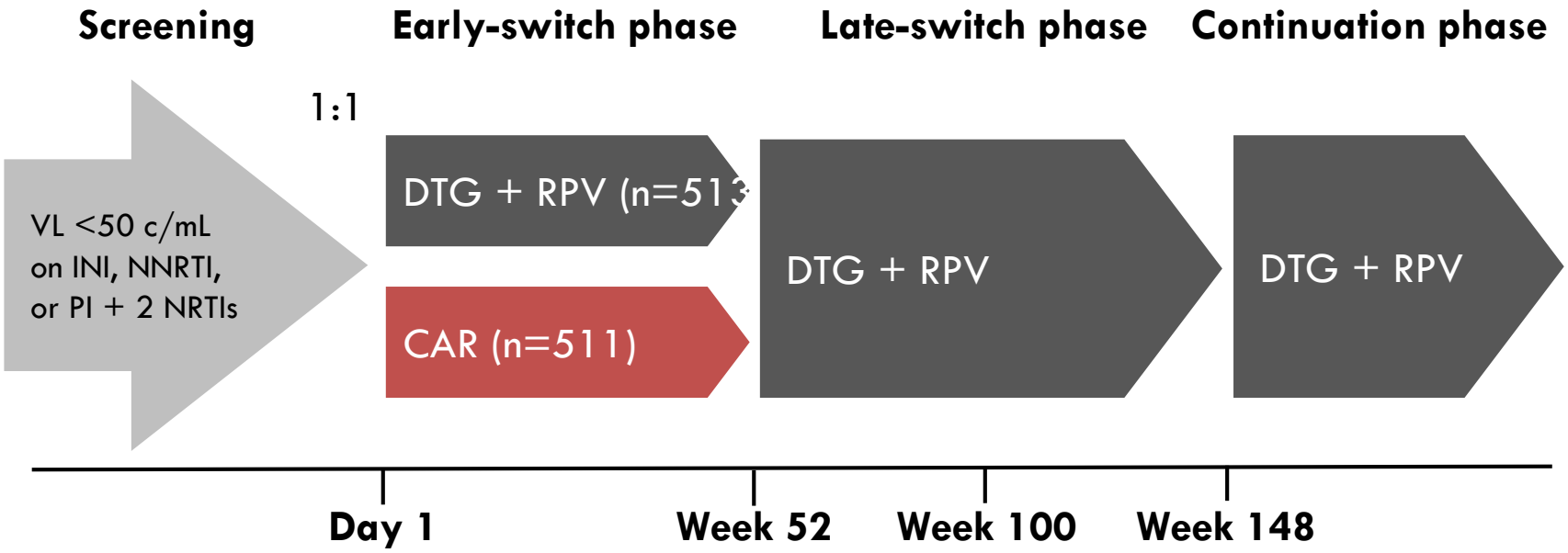
	DRV/r + 3TC	DRV/r + 2 NRTI
		2
		V10I, W71T, D76W in 1 patient

	DRV/r + 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

Switch
2- DR

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



Llibre et al. *Lancet*. 2018;391:839-849.

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

Dual therapy switch

DTG + RPV SWORD-1 et SWORD-2

- **2 RCT**

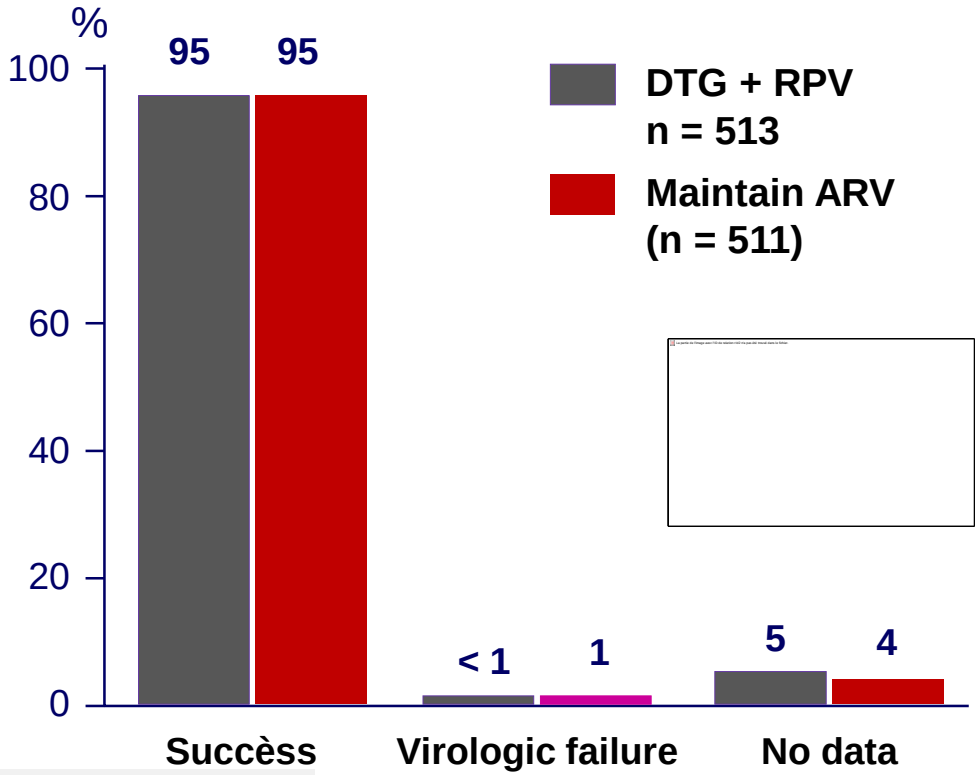
DTG/RPV : 511 pts

Maintain ARV : 513 pts

- **CD4**: 611 /mm3
- **TAR**

TDF : 75% NNRTI:54%

IP: 26% INI:20%



Week 100 : 93 % efficacy

Overall 10/990 VF

Low resistance emergence : 3 with NNRTI RAM

Llibre et al. Lancet. 2018;391:839-849.

1 seul cas resistance K101K
Sensible RPV

Switch
2- DR

SWORD 1&2 DTG/RPV Dual therapy switch
: Low Rates of Confirmed Virologic Withdrawal W100

Week of failure	Previous regimen	Viral loads, copies/mL[b]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[c])	Confirmed virologic withdrawal	
Week 24	EFV/TDF/FTC	88; 466	NNRTI: none INSTI: G193E	NNRTI: none INSTI: G193E	DTG, 1.02
Week 36	EFV/TDF/FTC	1,059,771; 1018; <50	NNRTI: none INSTI: none	NNRTI: K101K/E INSTI: none	RPV, 1.21
Week 64[d]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	INSTI resistance test failed	———
Week 76[d]	ATV, ABC/3TC	79; 162; 217	———	Test not performed[e]	———
Week 88	DTG/ABC/3TC	278; 2571; 55	NNRTI: none INSTI: none	NNRTI: E138E/A INSTI: none	RPV, 1.61 DTG, 0.72
Week 88	RPV/TDF/FTC	147; 289	———	Test not performed[e]	———
Week 100	EFV/TDF/FTC	651; 1105; 300	NNRTI: K101E, E138A INSTI: G193E	NNRTI: K101E, E138A, M230M/L INSTI resistance test failed	RPV, 31
Week 100	ATV, RTV, TDF/FTC	280; 225; 154	NNRTI: none INSTI: none	NNRTI: none INSTI: none	———

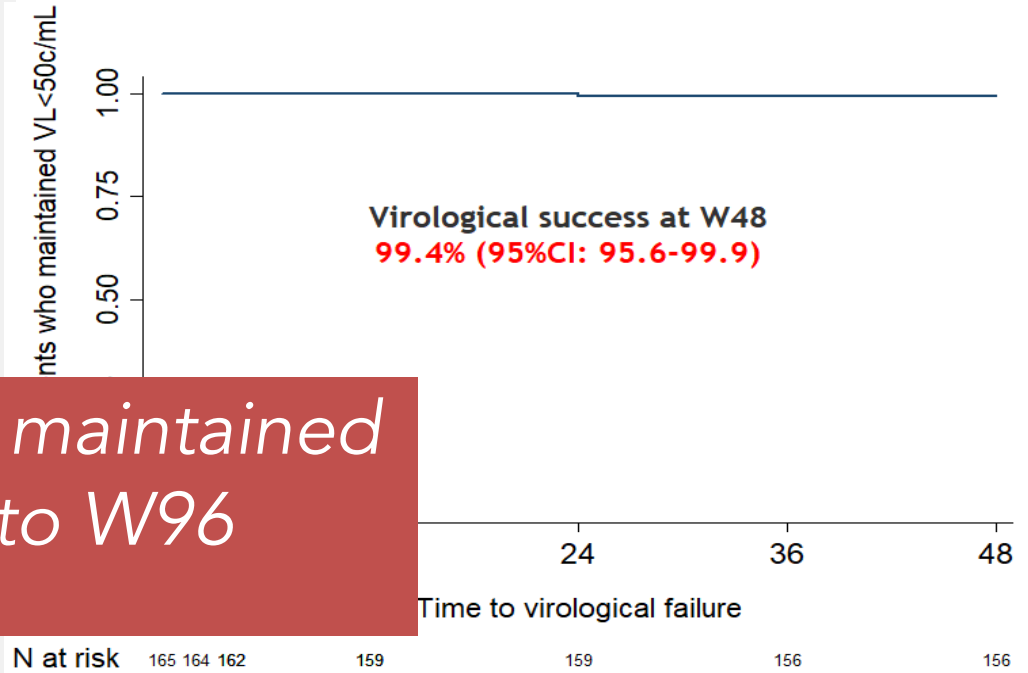
[a]Shading represents participants with treatment-emergent NNRTI resistance–associated mutations. [b]Underlined value denotes viral load when participant met virologic withdrawal. [c]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing. [d]Participants in the late-switch group. [e]Resistance testing not performed because of low viral load.

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

Switch
2- DR

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
  - High Blood Pressure 25%
  - Diabetes 8%
  - Cardiovascular event 3%
- Co-medications med nb 5



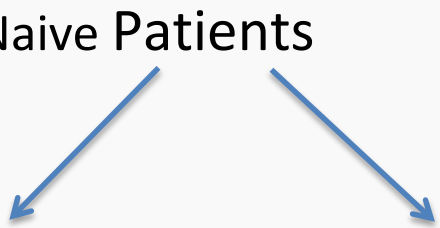
Efficacy maintained up to W96

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

Katlama C et Al IAS Paris 2017 absT MOPEB0314

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



DTG/3TC **DTG+TDF/FTC**

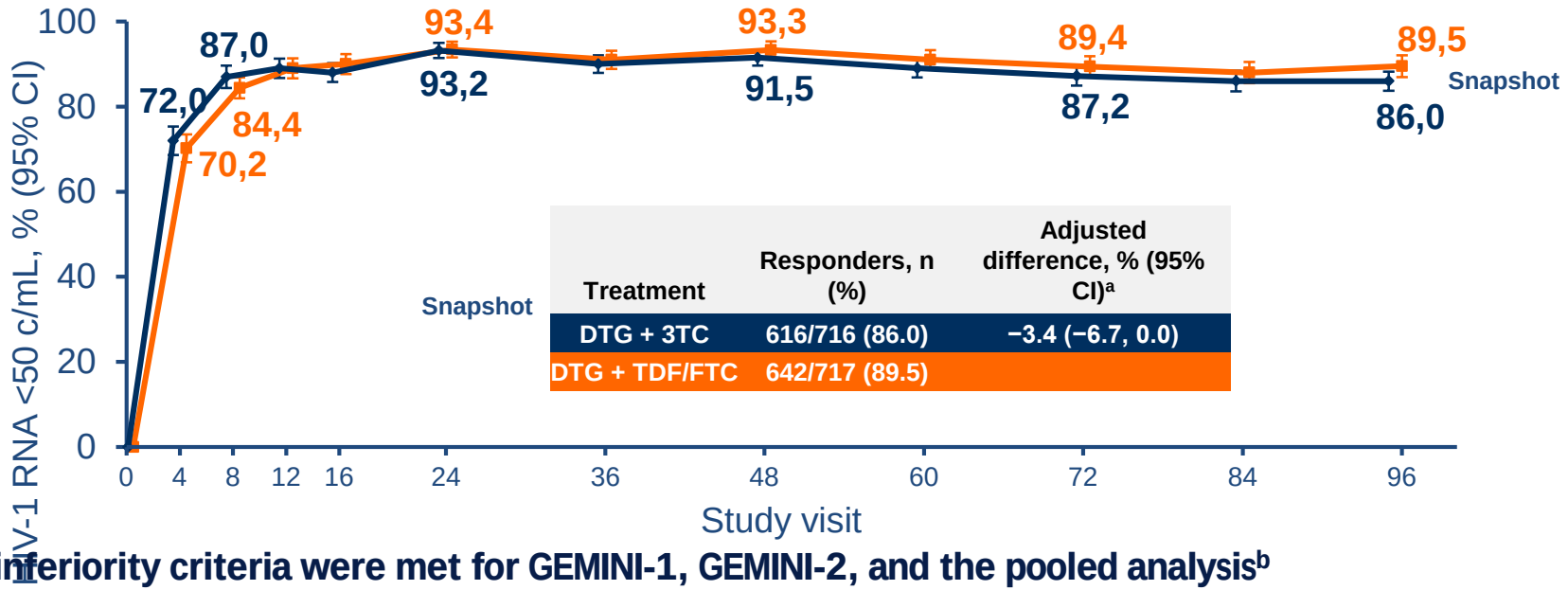
End point : % VS at W48

Follow up : continuation phase for DTG/3TC group

1433 patients

GEMINI Dual Therapy in naive patients

DTG/3TC vs DTG/TDF/FTC



Snapshot

Treatment	Responders, n (%)	Adjusted difference, % (95% CI)[a]
DTG + 3TC	616/716 (86.0)	−3.4 (−6.7, 0.0)
DTG + TDF/FTC	642/717 (89.5)	

Non-inferiority criteria were met for GEMINI-1, GEMINI-2, and the pooled analysis[b]

[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), CD4+ cell count (≤200 vs >200 cells/mm³), and study (GEMINI-1 vs GEMINI-2). The upper limit of the 95% CI for the pooled analysis was 0.0007%.

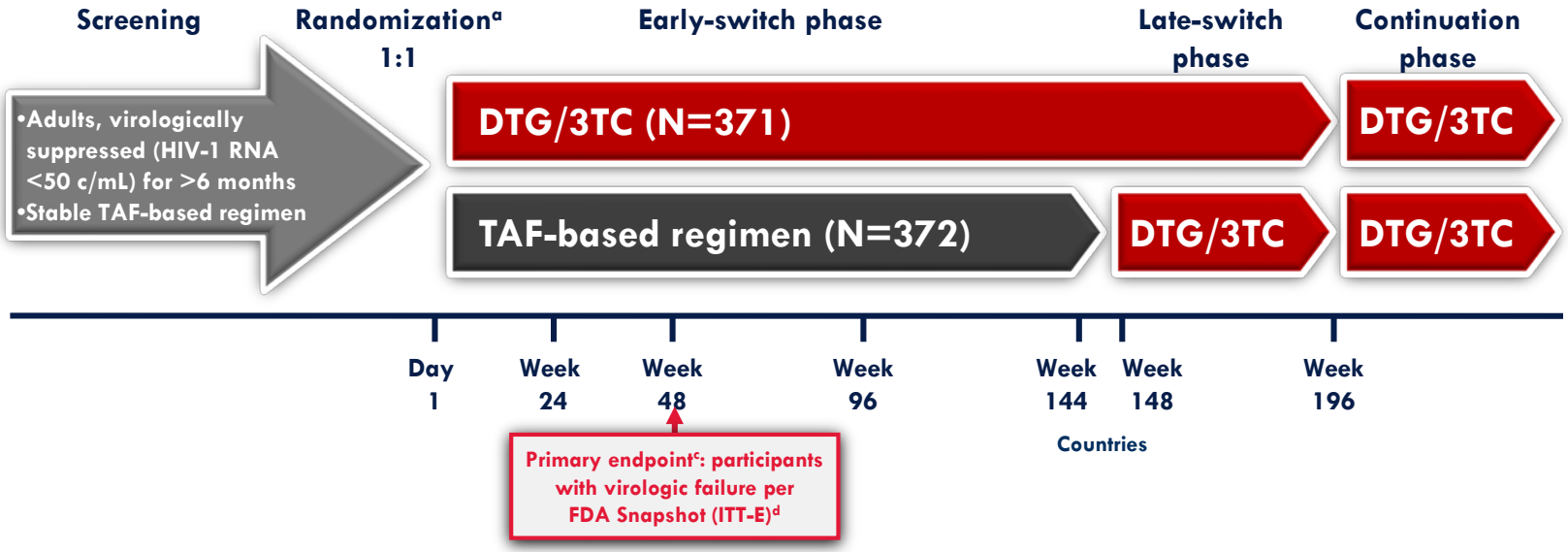
[b]In GEMINI-1, HIV-1 RNA <50 c/mL (95% CI) was achieved in 300/356 participants (84.3% [80.5-88.1]) in the DTG + 3TC group and 320/358 (89.4% [86.2-92.6]) in the DTG + TDF/FTC group (adjusted treatment difference [95% CI], −4.9% [−9.8, 0.03]). In GEMINI-2, the corresponding values were 316/360 (87.8% [84.4-91.2]) and 322/359 (89.7% [86.5-92.8]), respectively (adjusted treatment difference [95% CI], −1.8% [−6.4, 2.7]).

Cahn et al. IAS 2019; Mexico City, Mexico. Slides WEAB0404LB.

Switch
2- DR

Dual therapy switch
DTG/3TC **TANGO**

Randomized, open-label, multicenter, parallel-group, non-inferiority study



[a]Stratified by baseline third agent class (PI, INI, or NNRTI). [b]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [c]4% non-inferiority margin. [d]Includes participants who changed a background therapy component or discontinued study treatment for lack of efficacy before Week 48, or who had HIV-1 RNA ≥50 c/mL in the 48-week window.

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

Switch
2- DR

Dual therapy switch
DTG/3TC **TANGO**
Baseline characteristics

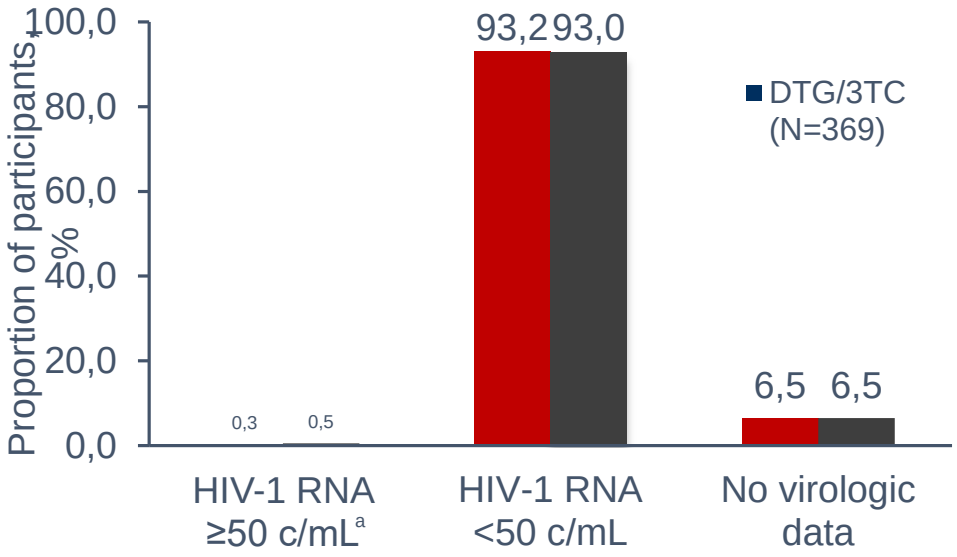
Characteristic, n (%)	DTG/3TC (N=369)	TAF-based regimen (N=372)
Median CD4+ cell count (range), cells/mm³	682.0 (133-1904)	720.0 (119-1810)
CD4+ cell count, cells/mm³		
<350	35 (9)	30 (8)
≥350	334 (91)	342 (92)
Baseline third agent class		
INI	289 (78)	296 (80)
EVG/c	243 (66)	249 (67)
NNRTI	51 (14)	48 (13)
RPV	43 (12)	45 (12)
PI	29 (8)	28 (8)
bDRV	25 (7)	27 (7)
Duration of ART before Day 1, median (range),	33.8 (7.1-201.2)	35.1 (7.0-160.8)

Switch 2 - DR

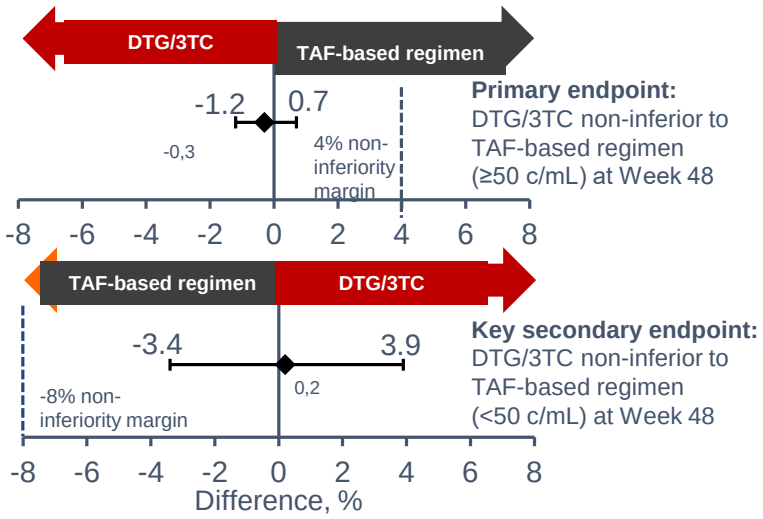
TANGO DTG/3TC *Switch study*

DTG/3TC is non inferior to TAF-based regimen at Week 48

Virologic outcomes



Adjusted treatment difference (95% CI)[b]



0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.6; 95% CI, −1.3 to 0.2)[b]

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

Switch
2- DR

DTG/3TC TANGO Switch study

No virologic withdrawals with DTG/3TC through W48

n (%)	DTG/3TC n=369	TAF-based regimen n=372)
Confirmed virologic withdrawal (CVW)[a]	0	1 (<1)[b]
resistance at failure[c]	0	0

[a]One assessment with HIV-1 RNA ≥200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL.
[b]Treatment interrupted before suspected virologic withdrawal (VL, 38,042 c/mL) and resumed 3 weeks before VL retest (297 c/mL).
[c]Plasma HIV-1 RNA resistance genotype at failure is compared with baseline PBMC pro-viral resistance genotype.

van Wyk et al IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

Switch 2 - DR

DTG/3TC TANGO Switch study
Adverse events

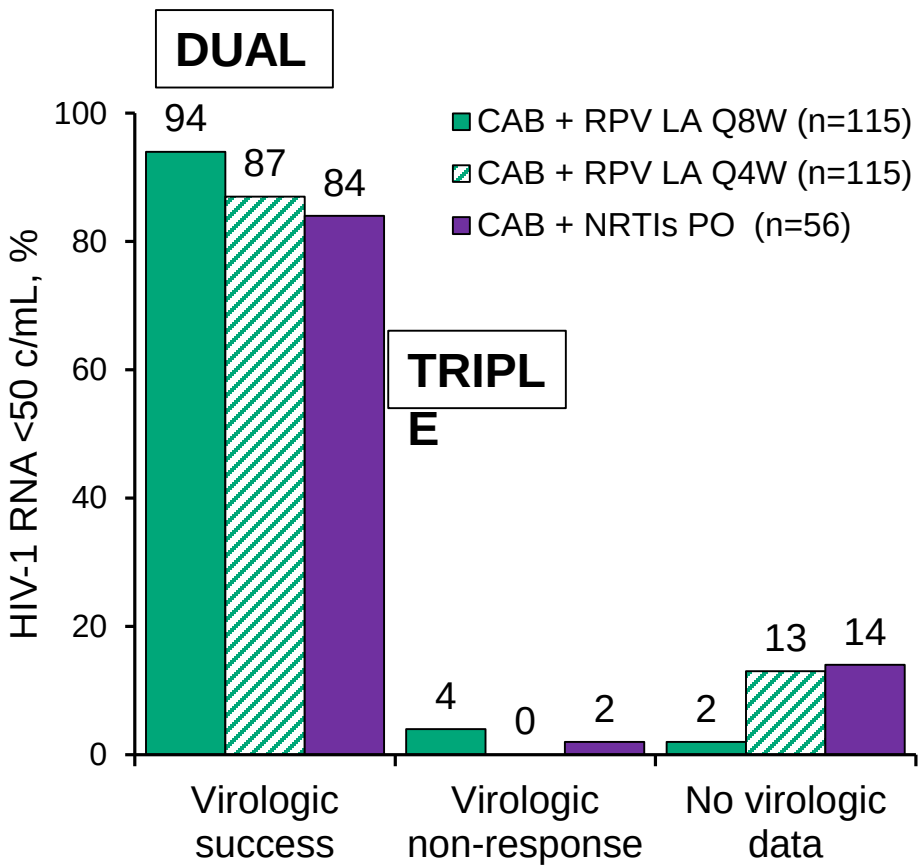
n (%)	DTG/3TC (N=369)	TAF-based regimen (N=371)
Any AE	295 (80)	292 (79)
Nasopharyngitis	43 (12)	41 (11)
Upper respiratory tract infection	31 (8)	32 (9)
Diarrhea	30 (8)	26 (7)
Headache	24 (7)	17 (5)
Syphilis	24 (7)	13 (4)
Back pain	21 (6)	28 (8)
Fatigue	20 (5)	3 (1)
Bronchitis	8 (2)	20 (5)
Any drug-related Grade 2-5 AE	17 (6)	3 (<1)
Drug-related Grade 2-5 AEs occurring in ≥0.5%[a]		
Insomnia	4 (1)	0
Constipation	2 (1)	1 (<1)
Flatulence	2 (1)	0
Headache	2 (1)	0
AEs leading to withdrawal from the study	13 (4)[b]	2 (1)
Any SAE[c]	21 (6)[b]	16 (4)

- At Week 48, a similar mean increase from baseline in weight of 0.8 kg was observed in both treatment groups
- Increased weight was reported as an AE in 3 (1%) participants treated with DTG/3TC and in 6 (2%) treated with a TAF-based regimen

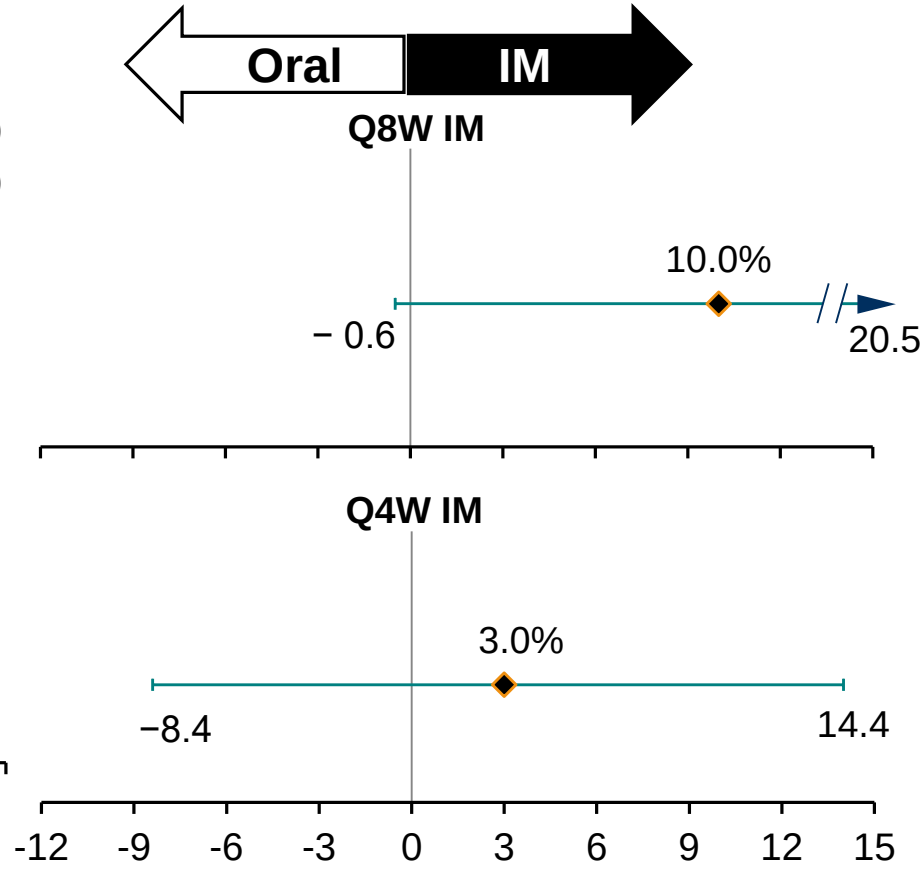
van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

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

Virologic outcomes



Treatment differences (95% CI)

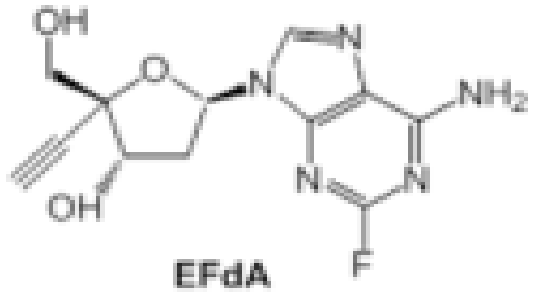


Source: Eron et al. IAS 2017 Paris, France. Abstract MOAX0205LB.

EfDA MK-8591 Islatravir

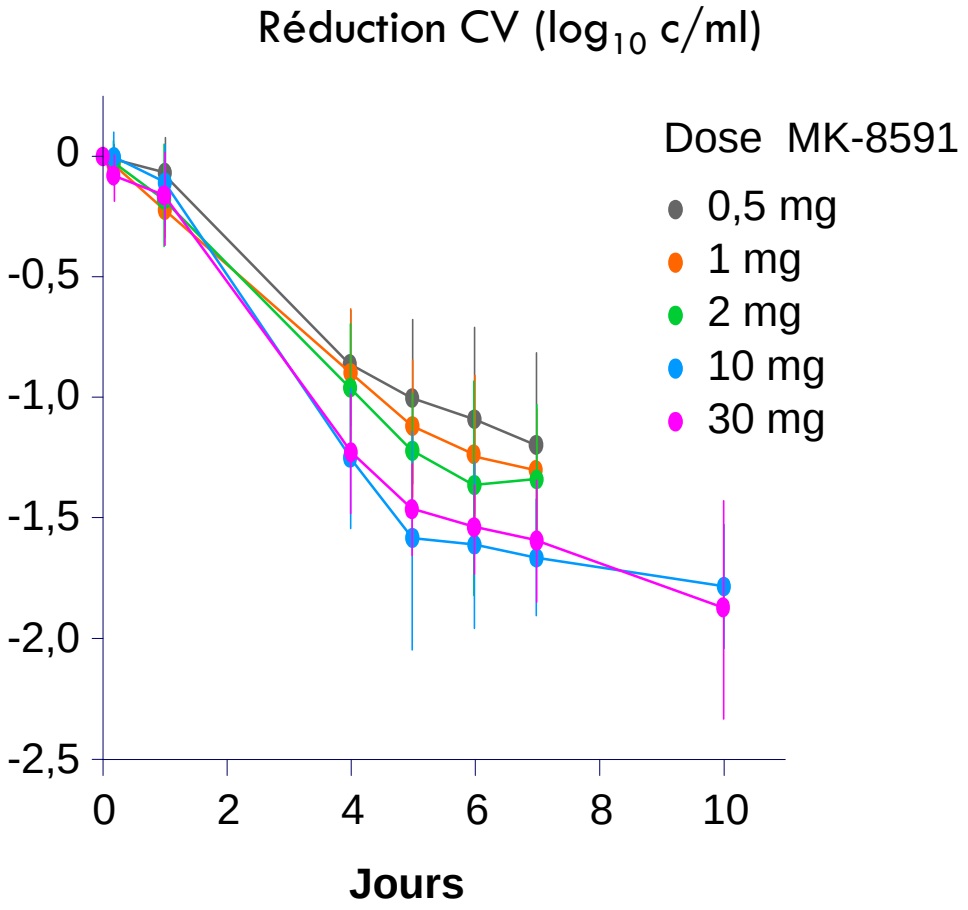
- transcription and translocation NRTTI
- 4 Ethynil fluoro de oxyadenosine
  Fluor : favors liposolubility and
  et intracellular C i
- **Potent antirétroviral ++**
  CI_{50} : 1.5nM
- No drug interactions
- Long halfl life +++ 120 h
- Potential flexible dosing of once daily , once weekly and less
- High concentration in genital tract

Promising drug in treatment and prevention



EFdA

single dose MK-8591 n=30



Switch
2- DR

ISLATRAVIR (ISL , MK-8591) AT Doses of 0.25 TO 2.25 MG QD in combination With Doravirine Maintains Viral Suppression through 48 Weeks IN Adults With HIV-1 Infection

Background

Islatravir (ISL, MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection

- ≥ 10-fold greater potency compared to all other approved antiretroviral agents
- Potent activity against NRTI resistant HIV-1 variants and a high barrier to the development of resistance
- High inhibitory quotients (IQ) achieved with low doses
- Long intracellular half-life (ISL-TP half-life ~120 hours in healthy adults)
- Potential for flexible dosing for once daily, once weekly, and less frequent administration

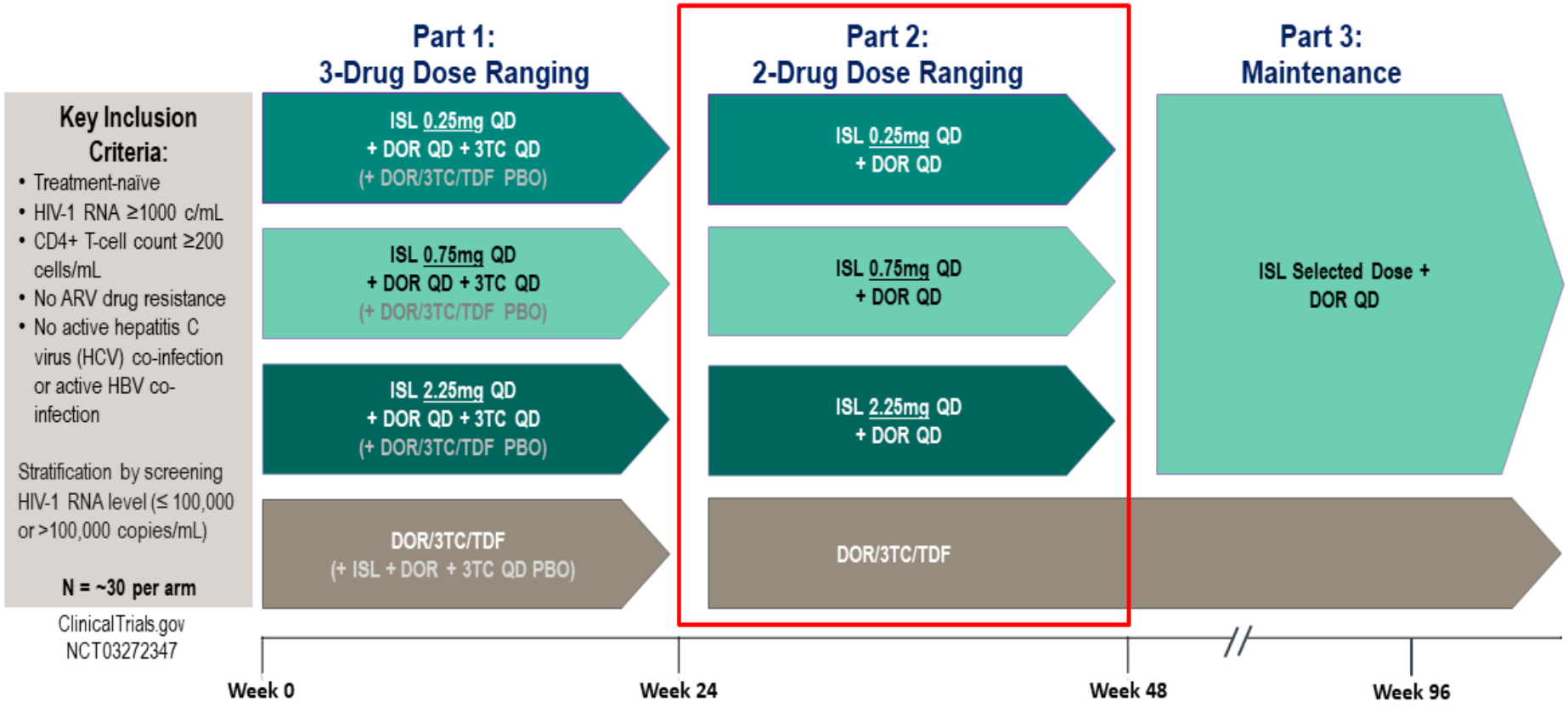
Doravirine (DOR) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1

- Demonstrated in vitro activity against wild-type HIV-1 and the most prevalent NNRTI resistance mutations (RT: K103N, Y181C, G190A, K103N/Y181C, and E138K)
- Dosed once daily, without regard to food and low potential for drug–drug interactions (DDIs)
- Well tolerated with low rates of CNS adverse events and a favorable lipid profile

The combined attributes of ISL+DOR create the potential for a potent, simplified, 2-drug regimen with efficacy comparable to traditional 3-drug regimens

Switch
2- DR

MK-8591 Protocol 011 : Phase 2 Dose Ranging Trial of ISL + DOR

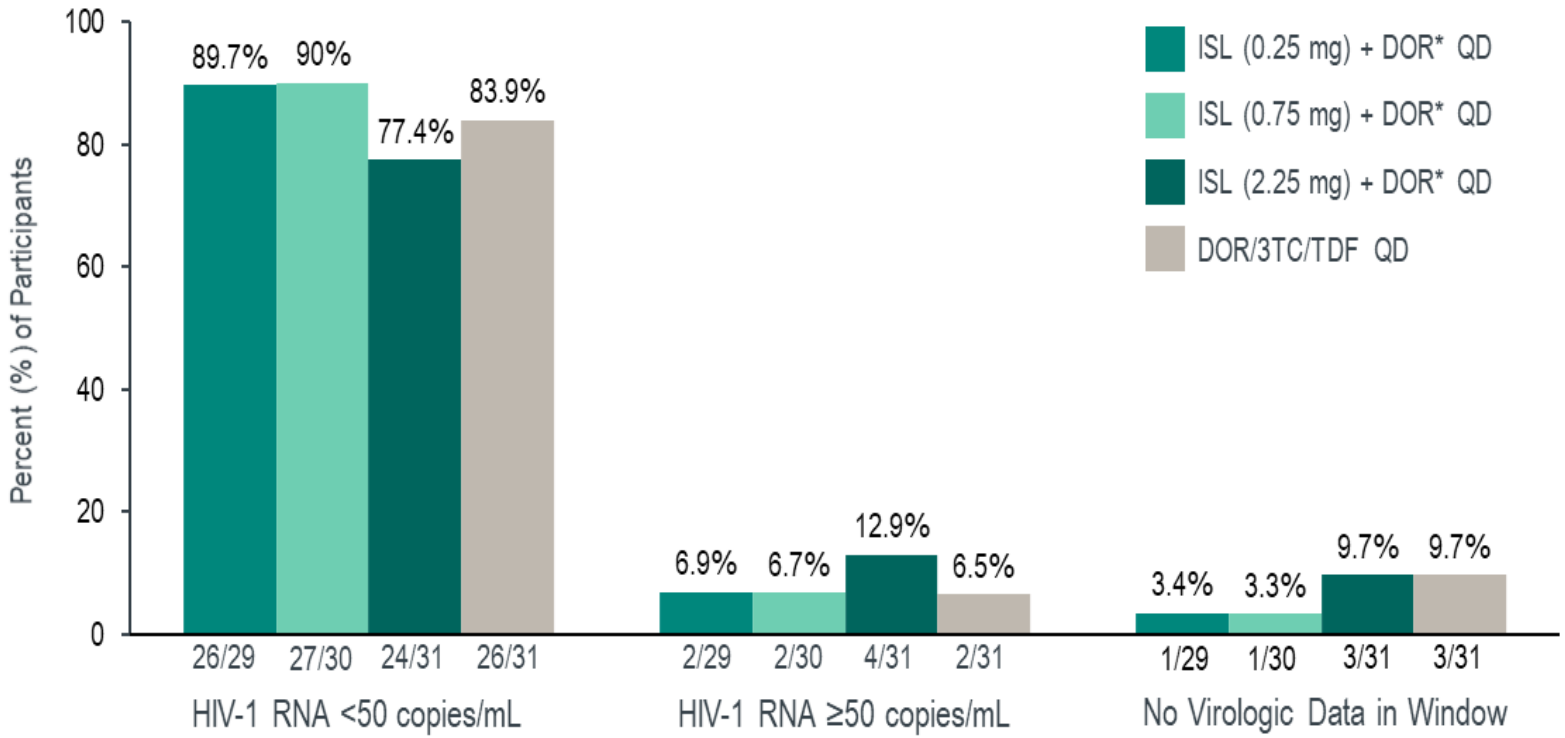


After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at Week 20 will remain in Part 1 until the HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria, at which point they transition to Part 2 at their next visit.

Switch
2- DR

Dual therapy switch
Islatravir / Doravirine

Virologic Outcomes Through Week 48 (FDA Snapshot Approach)



*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

Switch
2- DR

Protocol Defined Virologic Failure (PDVF) at W 48

	ISL (0.25 mg) + DOR* QD	ISL (0.75 mg) + DOR* QD	ISL (2.25 mg) + DOR* QD	DOR/3TC/TDF QD
	N=29	N=30	N=31	N=31
Protocol Defined Virologic Failure				
Non responder[a], n (%)	0 (0)	0 (0)	1 (3.2)	0 (0)
Rebounder with HIV-1 RNA >50 copies/mL, n (%)	2 (6.9)	2 (6.7)	0 (0)	1 (3.2)
Rebounder with HIV-1 RNA >200 copies/mL, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

*Participants initially received ISL+DOR+3TC and switched to ISL +DOR during the week 24-28 period of the study.

[a]Protocol defined virologic failure (PDVF) for this study is defined as one of the followings: 1. Rebounder: confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; or confirmed HIV-1 RNA >1 log (two consecutive measures at least one week apart) increase from the HIV-1 RNA nadir after a >1 log decrease in HIV-1 RNA from baseline at any time during the study; or 2. Non responder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥200 copies/mL at any time from week 24 through week 48; or confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥50 copies/mL at week 48.

- All participants with PDVF had confirmatory HIV-1 RNA levels <80 copies/mL
- No participants met the criteria for resistance testing

Towards a light suppressive ART

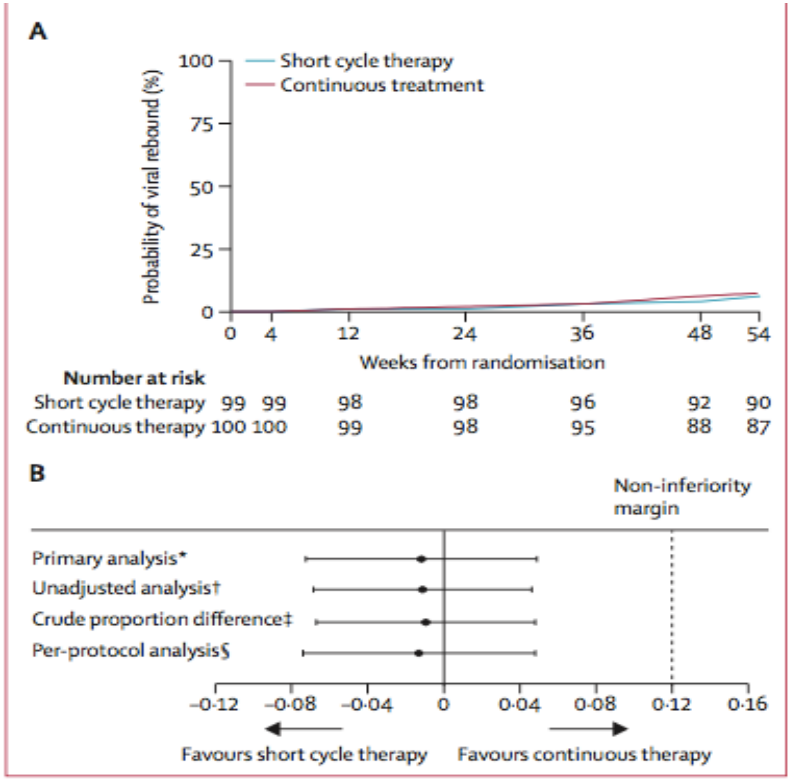
3-DR Intermittent

- 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 3-DR regimen

BREATHER Etude rando.pilote

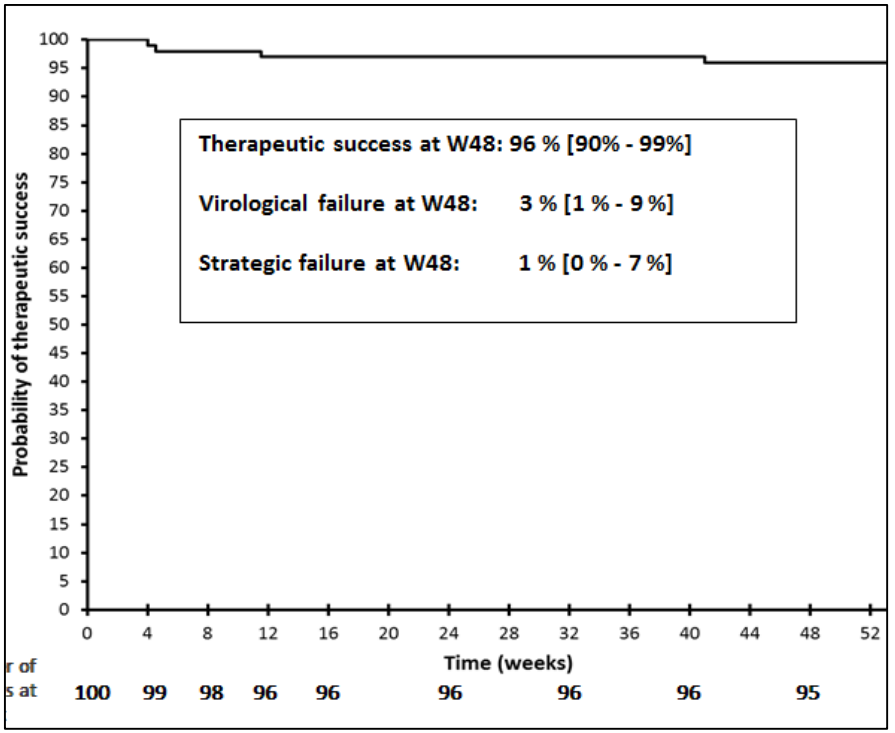
199 enfants /ados TAR:
2NRT/EFV **TAR 5 JOURS /7**



Etude 4D ANRS 162

Etude pilote 100 patients contrôlés

TAR 4 JOURS /7

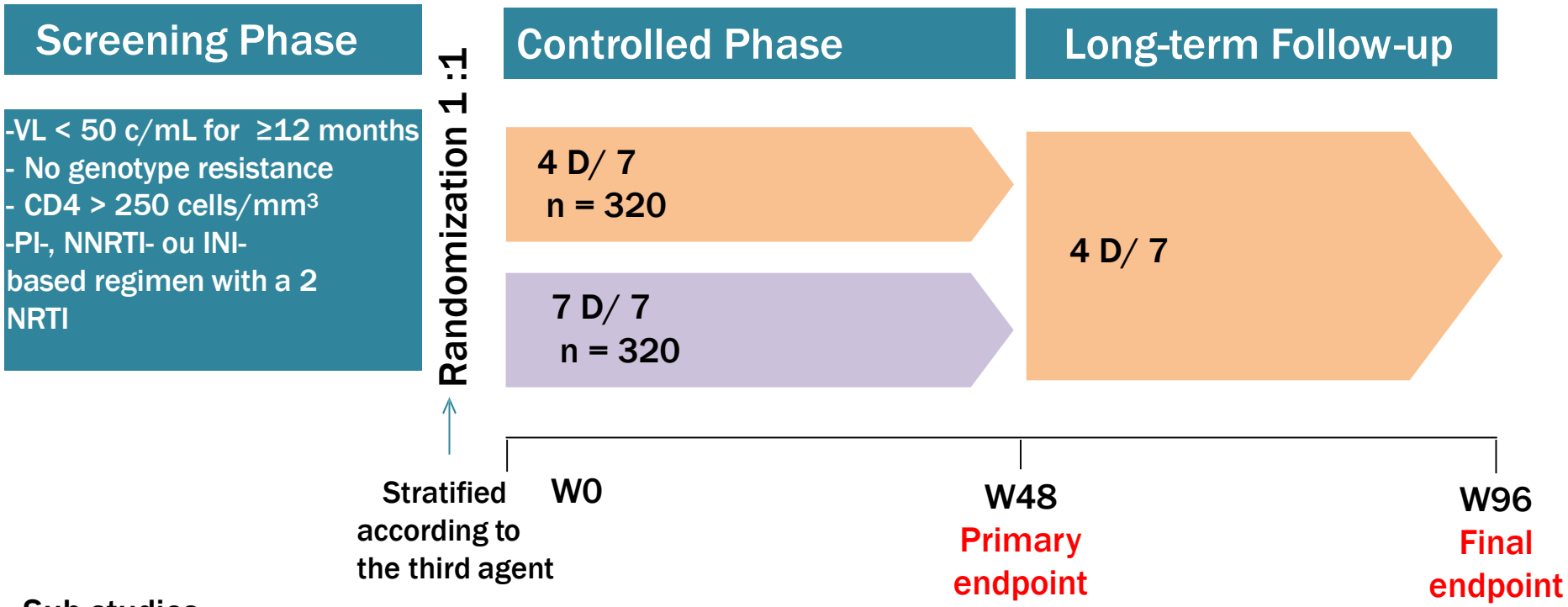


Succès 96% ; 3 échecs ; pas de Résistance

ART
Intermittent

QUATUOR -

randomized, multicenter, national, open-label, non-inferiority study in adults with HIV-1 virological suppression



Sub-studies:

- Treatment adherence: self-reported questionnaire and residual plasma concentrations (TDF and third agent); n = 640
- Hair, intracellular drugs concentrations (third agent); n = 120
- Inflammation and immune activation parameters; n = 120
- Total HIV DNA , HIV viral load in semen; n = 120
- QOL, self-reported patients satisfaction; n = 640

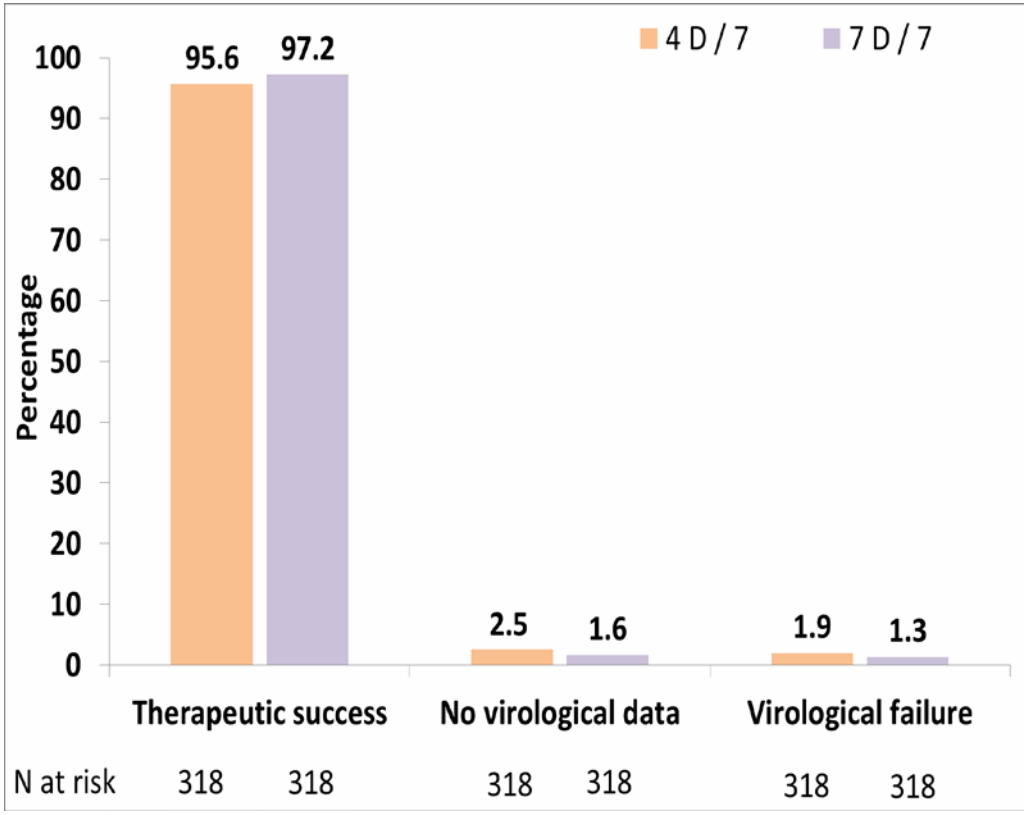
ART Intermittent

QUATUOR - Baseline characteristics

Characteristics	4 D/7 n=318	7 D/7 n=318	Total n=636
Age, year, median (IQR)	50 (41 – 55)	49 (41 – 56)	49 (41 – 55)
Male sex, n (%)	270 (84.9)	269 (84.6)	539 (84.7)
Geographic origin of birth, n (%)			
- Europe	244 (76.7)	254 (79.9)	498 (78.3)
- Sub-Saharan Africa	47 (14.8)	51 (16.0)	98 (15.4)
- Other	27 (8.5)	13 (4.1)	40 (6.3)
MSM, n (%)	211 (66,6)	215 (67.6)	426 (67.1)
CD4 nadir (cells/mm^3), median (IQR)	313 (203 – 422)	289 (189 – 401)	298 (195 – 412)
CD4 at screening (cells/mm^3), median (IQR)	693 (532 – 898)	687 (534 – 861)	689 (533 – 884)
Duration on ARV, year, median (IQR)	6.5 (3.8 – 12.0)	7.4 (4.2 – 12.5)	6.9 (4.0 – 12.4)
Duration of vs (<50 c/mL), year, median median (IQR)	5.1 (3.0 – 8.6)	6.5 (3.5 – 10.3)	5.8 (3.3 – 9.6)
Baseline NRTI, n (%)			
- TDF-TAF/FTC	230 (72.3)	232 (73.0)	460 (72.6)
- ABC/3TC	88 (27.7)	86 (27.0)	174 (27.4)
Baseline third agent class, n (%)			
- INI (DTG/EVG/RAL)	152 (47.8) (73/65/14)	152 (47.8) (76/68/8)	304 (47.8)
- NNRTI (RPV/EFV/ETR)	148 (46.5) (118/24/6)	148 (46.5) (110/32/6)	296 (46.5)
- PI (DRV/ATV/LPV)	18 (5.7) (16/2/0)	18 (5.7) (12/4/2)	36 (5.7)

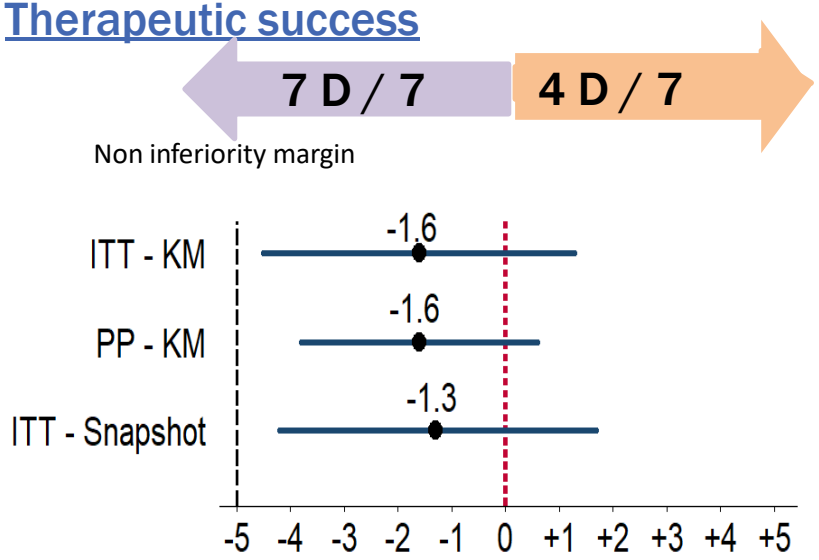
ART Intermittent

QUATUOR - Primary endpoint at W48 (ITT)

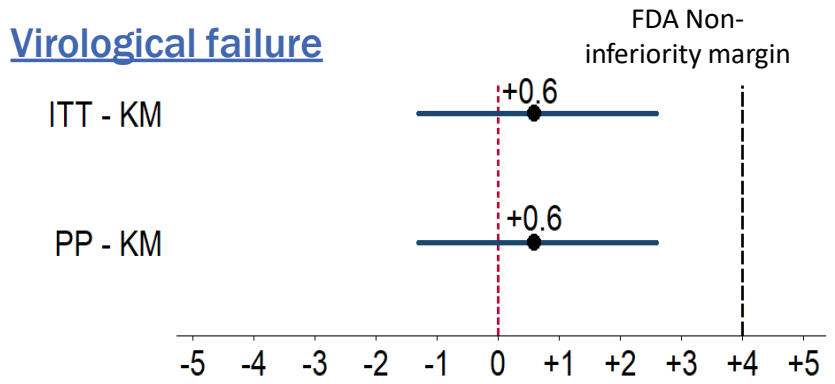


Treatment differences adjusted by third agent stratification using the Cochran-Mantel-Haenszel method

Therapeutic success



Virological failure



Difference (95% CI) of proportion

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..

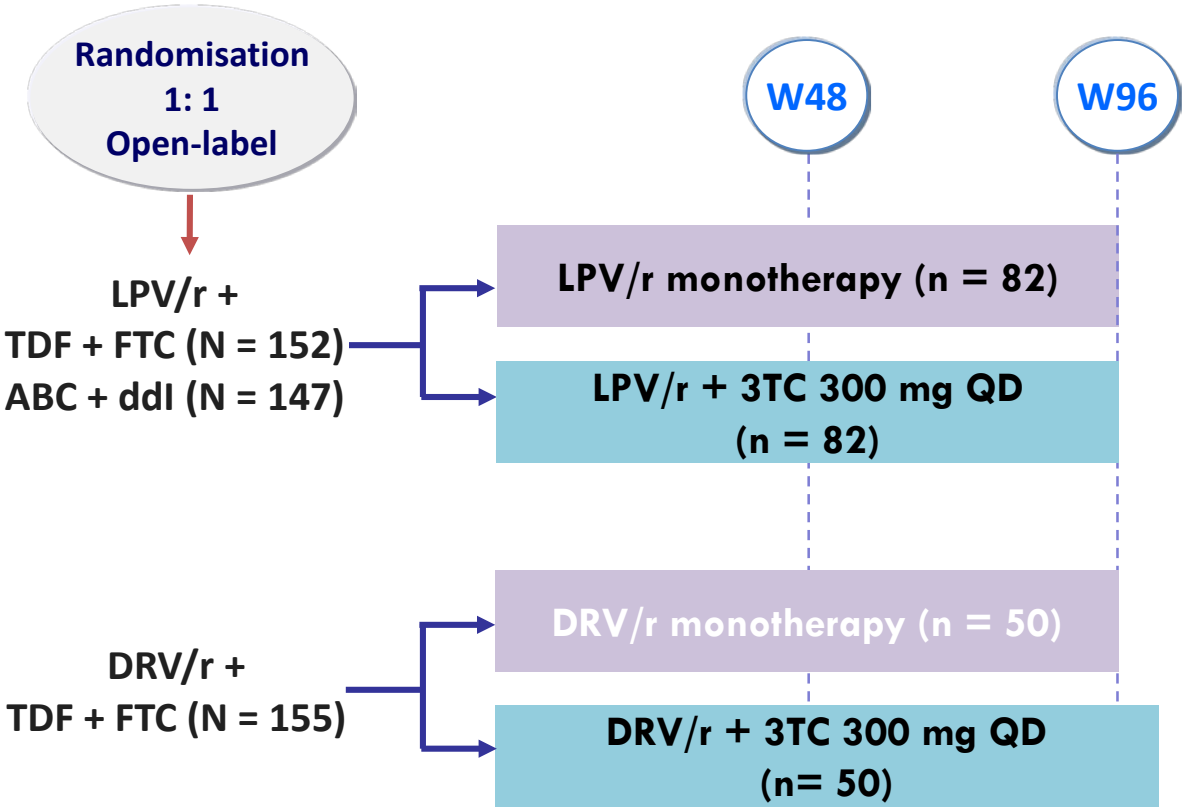
  some failures may be slow to appear

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)
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 resuppressed 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)

2DR dans les recommandations 1ère ligne

Avril 2018

« *peut constituer une alternative lorsque les INTI ne sont pas utilisables* »

DRV + RAL*

Octobre 2018

EACS
European
AIDS
Clinical
Society

« *to be used when none of the preferred regimens are feasible or available, whatever the reason* »

DTG + 3TC
DRV + RAL*

Octobre 2018

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA ·

« *Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal* »

DTG + 3TC
DRV + 3TC
DRV + RAL*

*** Si ARN VIH < 100 000 c/mL et CD4 > 200/mm³**

ART reduced regimen in real life

TAR Allégés
33% en 2017
36% en 2018 des TAR suppressifs

ratégies ART suppressives en 2017/2018
3480 patients avec CV <50 cp/mL

Type TAR	2017 n	%	2018 n	%
	n= 2941 pt		n= 3 480 pt	
Trithérapie	**2026**	**69%**	**2407**	**69,2%**
7 jours /7	**1938**	**66%**	**2187**	**62,8%**
Intermittent	**88**	**3%**	**220**	**6,4%**
4 f/s	**72**	**2,4%**	**137**	**3,9%**
5f/s	**16**	**0,6%**	**83**	**2,4%**
Bithérapie	**713**	**24%**	**874**	**25%**
Monothérapie	**161**	**6%**	**149**	**4,3%**
Multithérapie	**41**	**1,4%**	**50**	**1,4%**

MA Valantin AFRAVIH 2018 Oral sessio

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

Less is more