# Module AFRANUM #4
# VIH : actualité thérapeutique

jeudi 23 septembre de 17h00 à 19h00 (heure de Paris)

- **Modération : Christine Katlama / Gilles Wandeler**

| | |
|---|---|
| ✓Introduction | *Gilles Wandeler* |
| ✓Les stratégies d'initiation | *Mohamed Chakroun & Charles Kouanfack* |
| ✓Les nouvelles molécules | *Christine Katlama* |
| ✓Les stratégies d'allègement | *Marc-Antoine Valantin* |

*Chaque intervention sera suivie d'une séance de Q&R*

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ALLIANCE FRANCOPHONE DES ACTEURS DE SANTÉ CONTRE LE VIH

# Nouvelles molécules


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SORBONNE UNIVERSITÉ

iPLesp

# Traitement ARV : les « fondamentaux »

## Le traitement ARV :un  traitement à vie

### Objectif principal : Efficacité

Indétectabilité de la charge virale

Plasma Compartiments  CSF /secrétions génitales /Réservoirs

**Objectif  Durée** : maintenir la non réplication **A VIE**

**Objectif Tolérance :** Minimiser les effets secondaires

**Objectif Eco-Thérapeutique :**  minimiser le poids des molécules

**Objectif Pardonnance :** robustesse Pharmaco et virologique

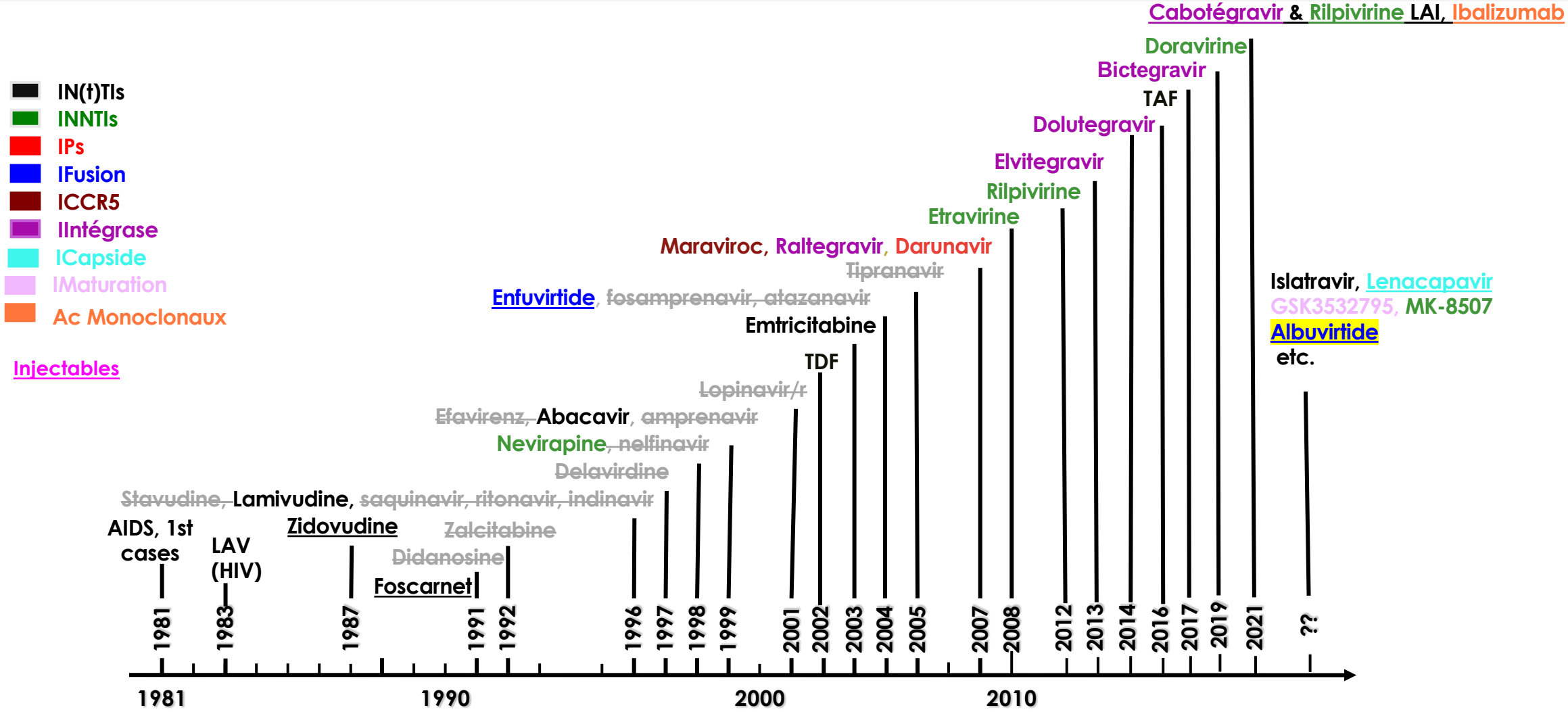
U=U
UNDETECTABLE = UNTRANSMITTABLE

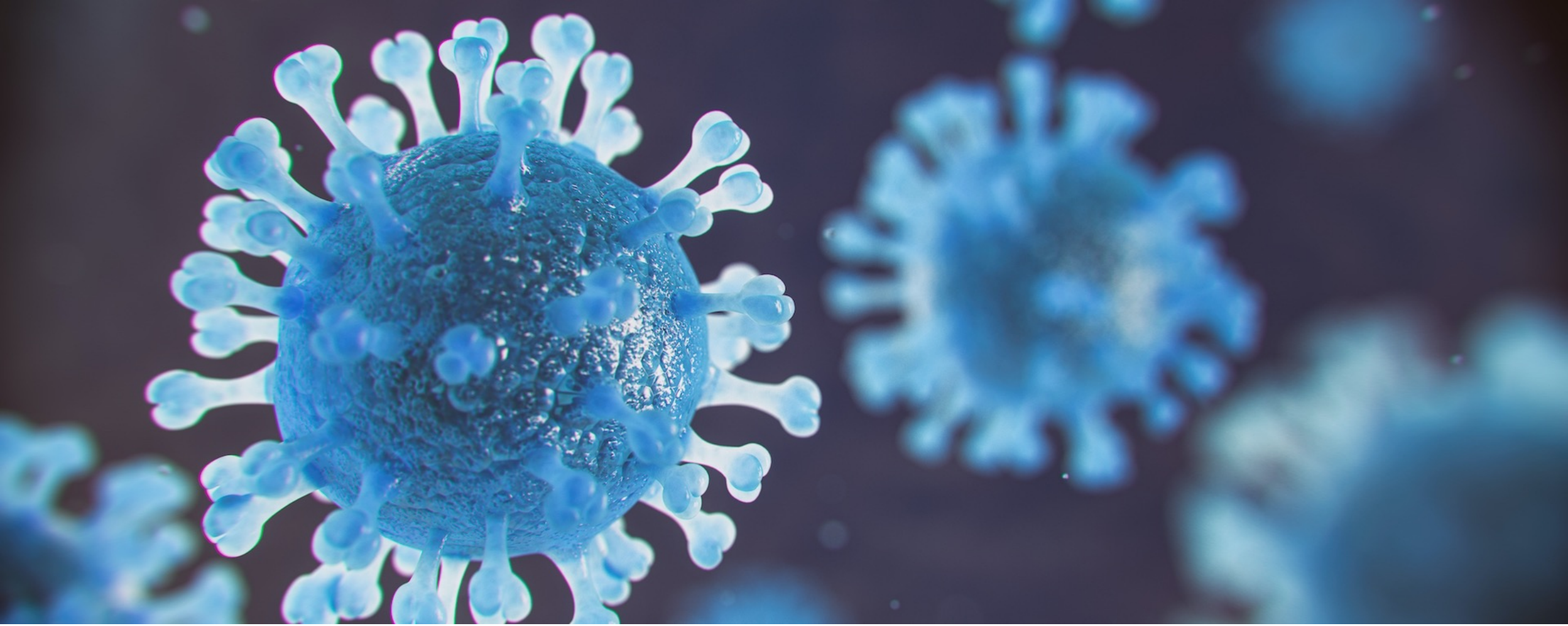
# Définir l'identité d'une molécule ARV

- Spectre activité : VIH1  VIH2  / virus résistants
- Puissance : réduction de CV induite par la molécule seule
- Barriere génétique à la résistance : capacité de « résister à la résistance »  quel niveau de R ; R croisée; « pardonnance »
- Profil pharmacologique

  *- demi vie ; interactions médicamenteuses.*
- Tolérance court / long terme

# Thérapeutique antirétrovirale : un développement dynamique
## > 15 ARVs, > 8 drug classes

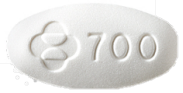




# Les molécules récentes et celles de demain

# Doravine

- **NNRTI 2d generation**
- active on the *most frequent NNRTI mutations* K103N, Y181C , G190A, K103N/Y181C [4]
- once daily; no food constraints
- almost no drug interactions +++ (different from other NNRTI)
- tolerability >>> EFV CNS and lipides ; no metabolic disorders

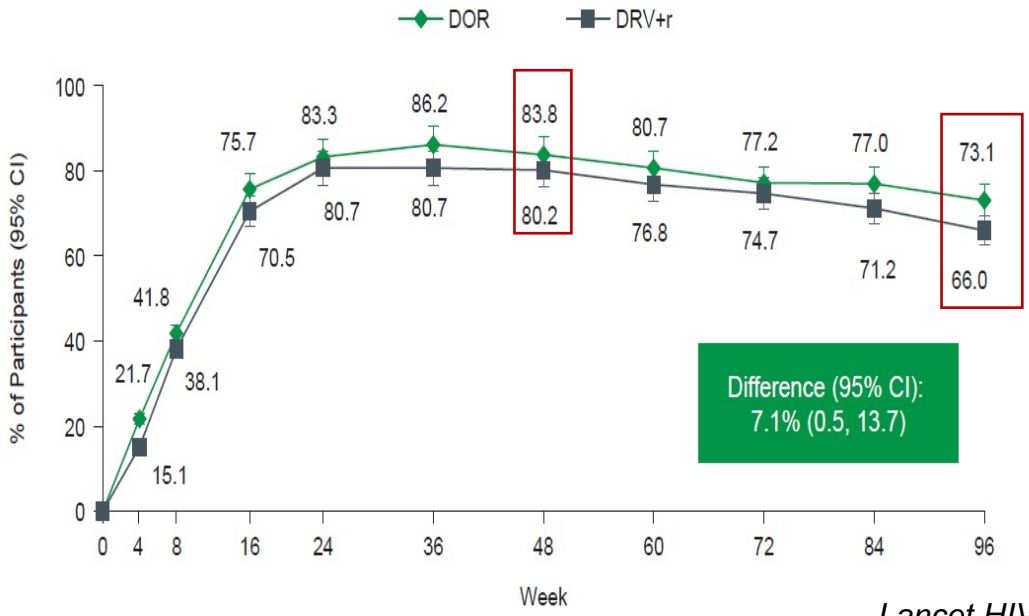



Pifeltro ®


Delstrigo®

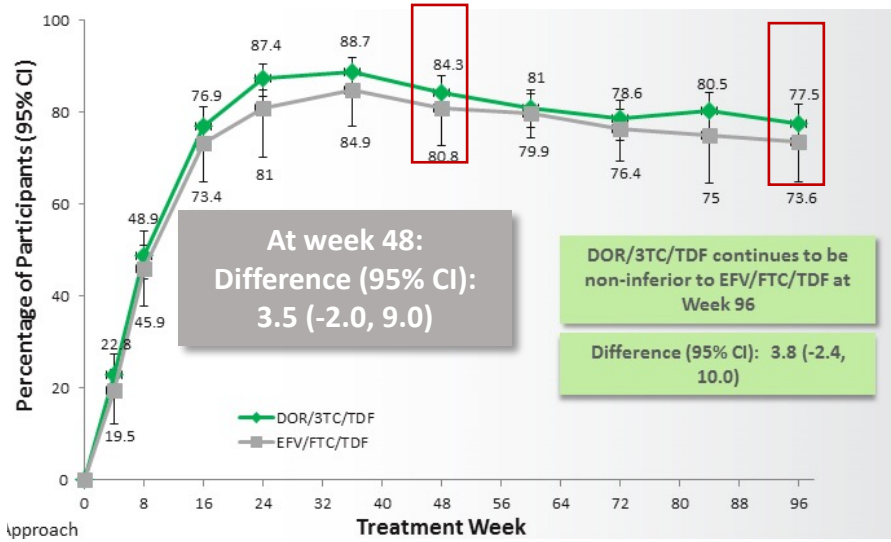
## DRIVE FORWARD DOR vs DRV

766 naive patients CV : 4.35 $log_{10}$ CD4 :435/$mm^3$




## DRIVE AHEAD DOR vs EFV

680 naive patients VL:4.4 $log_{10}$ CD4 : 435/$mm^3$

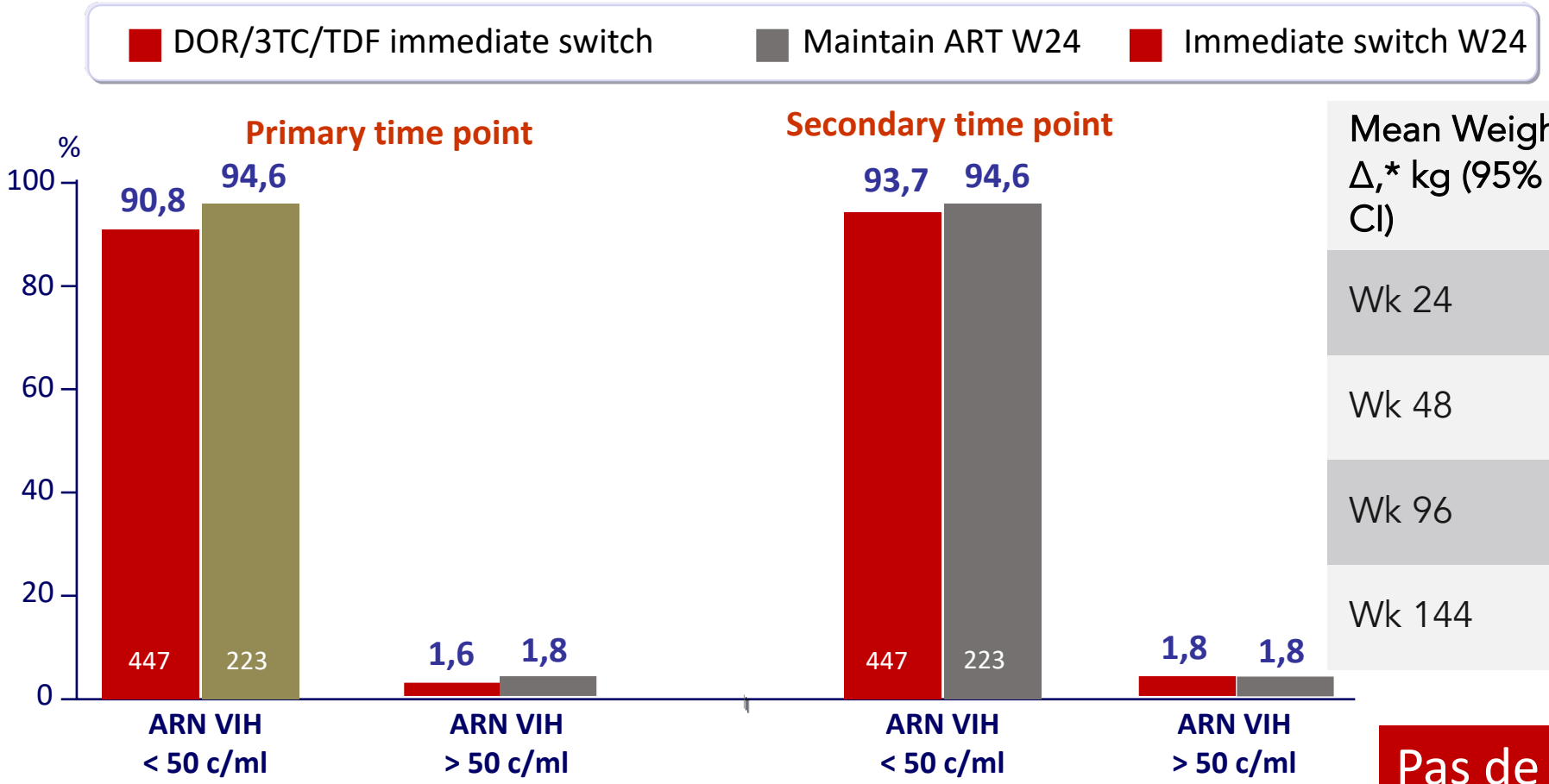



*Lancet HIV 2020; **7**: e16–26.*
*Clin Infect Dis 2019; **68**: 535–44.*

No resistance in the few VF

# Doravine Drive-Shift Switch vers DOR/3TC/TDF

## Efficacy ITT Snapshot




| Mean Weight Δ,* kg (95% CI) | Immediate Switch | Delayed Switch |
|---|---|---|
| Wk 24 | 0.7 (0.4-0.9) | NA |
| Wk 48 | 0.7 (0.4-1.1) | 0.5 (0-1.0) |
| Wk 96 | 1.1 (0.7-1.6) | 0.8 (0.2-1.5) |
| Wk 144 | 1.4 (0.8-1.9) | 1.2 (0.4-2.0) |

Pas de résistance DOR chez les qq échecs

*Johnson M. J Acquir Immune Defic Syndr. 2019 Apr 11. [Epub ahead of print]*

# Long ACTING

## Cabotegravir/Rilpivirine IM ATLAS et FLAIR

*CAB + RPV Long-Acting IM monthly vs 3-DR daily intake*

### ATLAS

Stable ART **PI, NNRTI , INI**
**HIV RNA < 50 c/mL x 2X 12 months**
**N = 616**

***Day 0*** ***Wk 4*** ***Wk 48 Primary Endpoint***

**CAB 30 mg + RPV 25 mg PO QD** (n = 308)

**LA CAB 400 mg + RPV 600 mg** IM Q4W (n = 303)

**Maintain Baseline ART PO** (n = 308)

*Comparator arm patients eligible to receive CAB + RPV in extension phase after Wk 52 (ATLAS-2M study)*

### FLAIR

ART-naive patients
HIV-1 RNA ≥ 1000cp c/mL,
no NNRTI RAMs except K103N
**N = 629**

***Day 0*** ***Wk 4*** ***Wk 48 Primary Endpoint*** ***Wk 96***

***Wk 20***

**DTG/ABC/3TC PO QD**

**CAB 30 mg + RPV 25 mg PO QD** (n = 283)

**LA CAB 400 mg + RPV 600 mg IM Q4W** (n = 278)

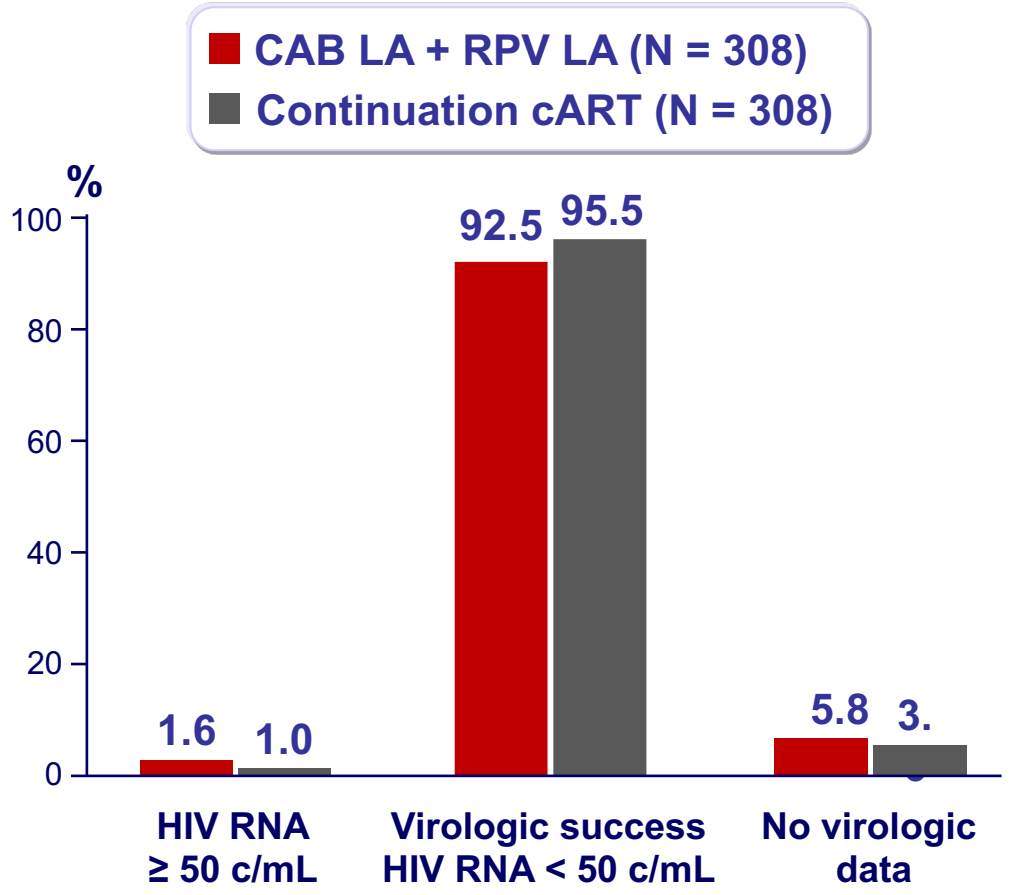
**Continue DTG/ABC/3TC PO QD** (n = 283)

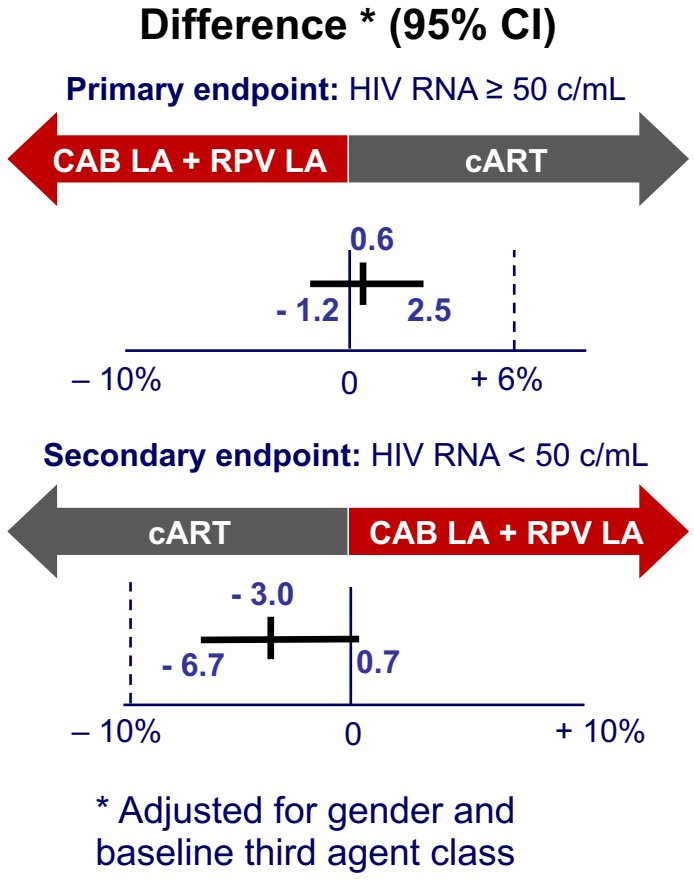
*Overton. IAS 2019. Abstr MOPEB257.*

# Long ACTING

## ATLAS Study: LA cabotegravir/ rilpivirine en switch

### Virologic outcome at W48 (snapshot analysis, ITT-E)



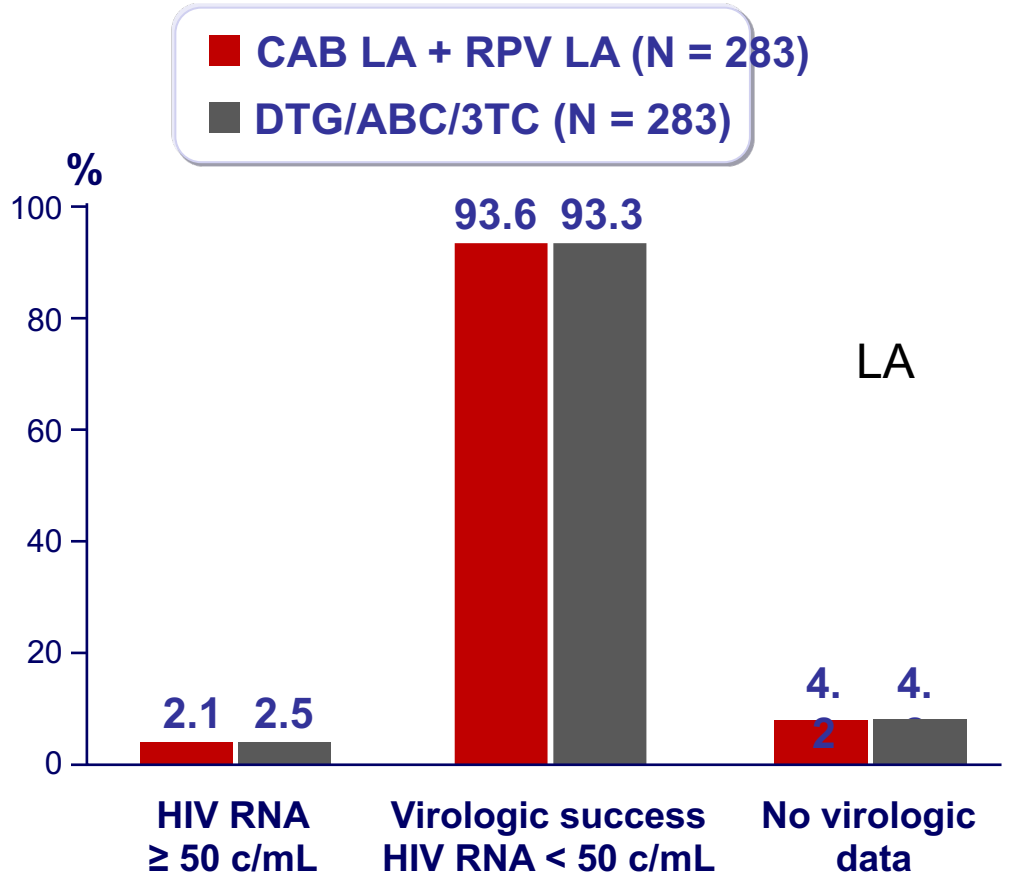

* Adjusted for gender and baseline third agent class

– Non inferiority achieved for primary and secondary endpoints; Resistance ++ in case of failure

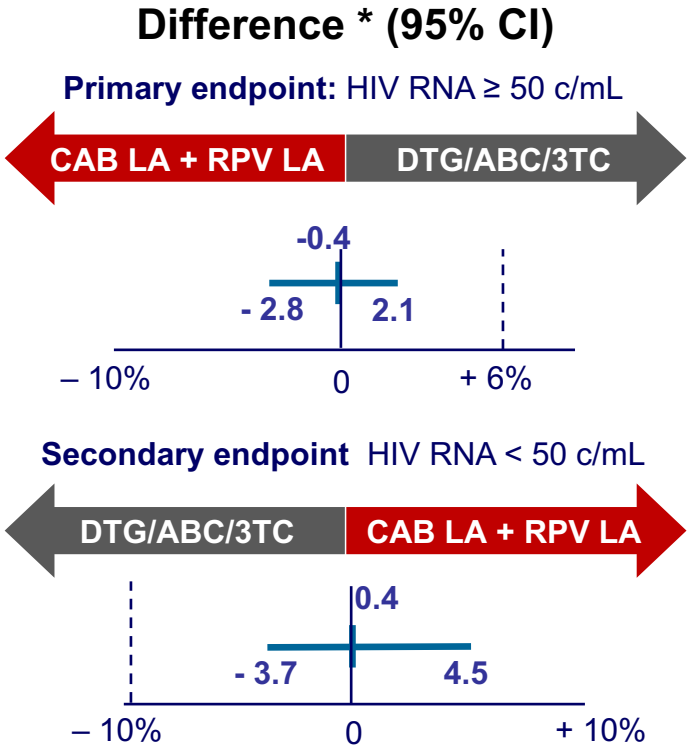
*Swindells S. CROI 2019, Abs. 139*

# Long ACTING
## cabotegravir/rilpivirine FLAIR Study: Patients naifs

### Virologic outcome at W48 (snapshot analysis, ITT-E)




LA




* Adjusted for gender and baseline HIV RNA (< vs ≥ 100 000 c/mL)

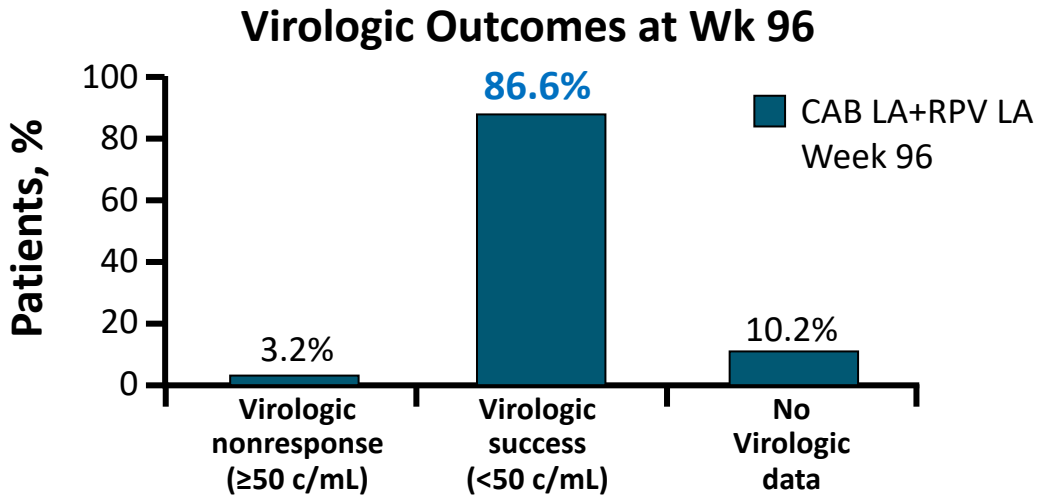
– Non inferiority achieved for primary and secondary endpoints

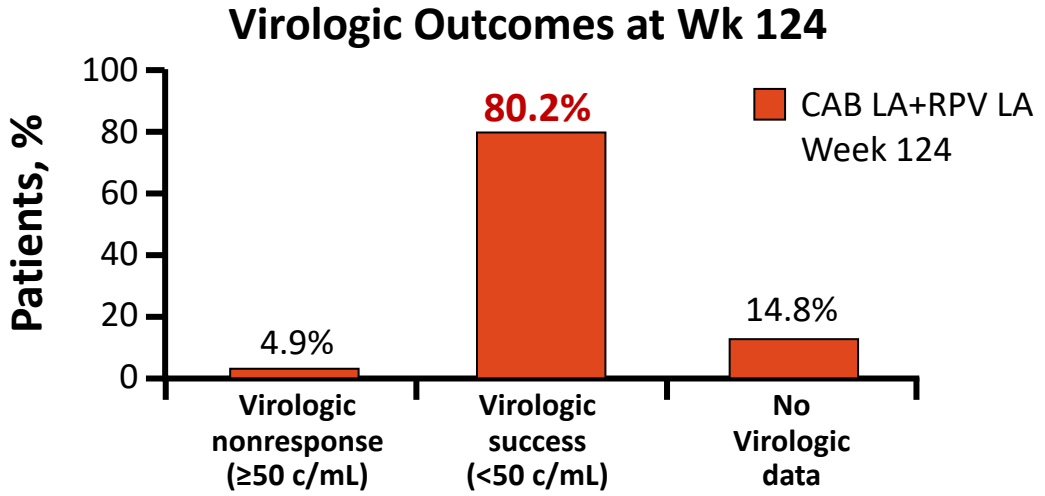
FLAIR

Orkin C. CROI 2019, Abs. 140LB

# Long ACTING Cabotegravir/Rilpivirine IM

## FLAIR: Suppression virologique jusqu'à S144



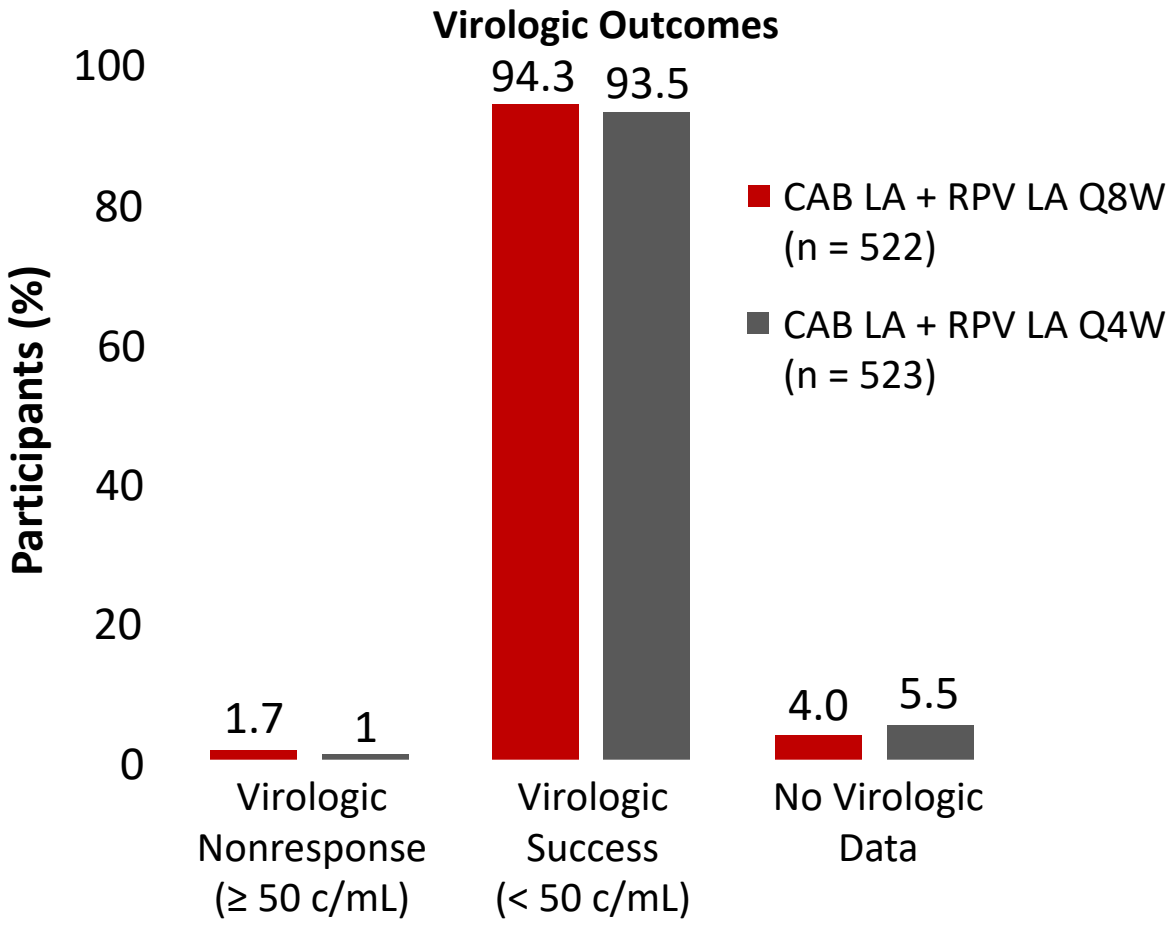

- 5 additional patients had virologic nonresponse between Week 96 and Week 124
- Of the 14.8% not recorded as suppressed at Week 124, this was largely due to nonvirologic reasons (eg, discontinuation due to AEs)
- 1 additional virologic failure at Week 108
  - Treatment-emergent NNRTI RAMs: V106V/A, V108V/I, E138G, M230L
  - Treatment-emergent INSTI RAMs: **N155H, R263K**
  - HIV-1 resuppressed to <50 copies/mL with EFV/TDF/FTC

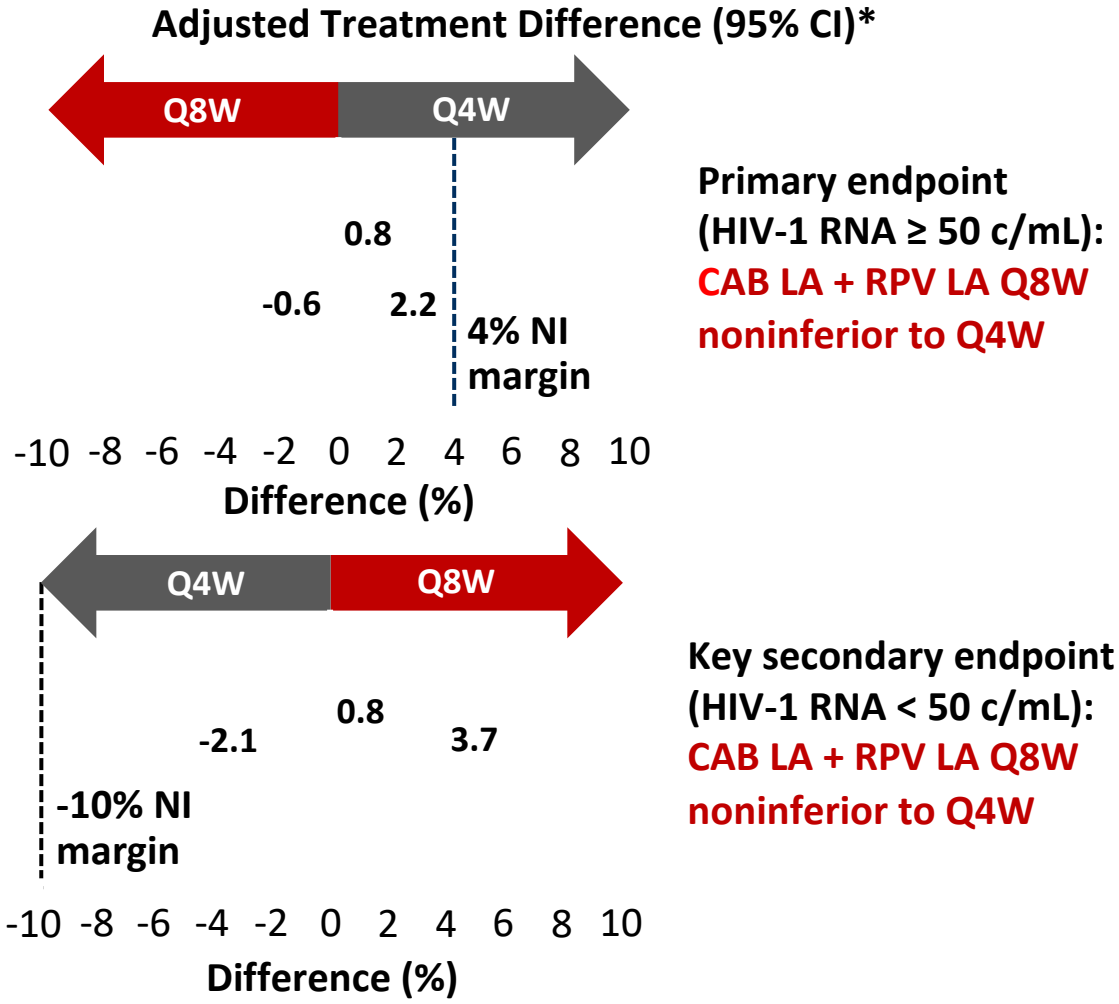
Orkin. IAS 2021. Abstr OAB0302. Reproduced with permission.

# Long ACTING ATLAS-2M

# Cabotegravir/Rilpivirine IM

## IM toutes les 4 sem vs 8 sem




*Based on Cochran-Mantel-Haenszel analysis adjusting for prior CAB + RPV exposure.

Overton. CROI 2020. Abstr 34. Reproduced with permission.

# Cabotegravir/Rilpivirine IM ATLAS-2M:

| Characteristic | CAB LA + RPV LA Q8W (n = 522) | CAB LA + RPV LA Q4W (n = 523) |
|---|---|---|
| CVF, n (%) | 8 (1.5) | 2 (0.4) |
| CVF with RPV RAMs,* n/N | 6/8 | 1/2 |
| Treatment-emergent RPV RAMs | K101E, E138E/K, E138A, Y188L | K101E, M230L |
| CVF with INSTI RAMs,* n/N | 5/8 | 2/2 |
| Treatment-emergent INSTI RAMs | Q148R, N155H† | E138E/K,Q148R, N155N/H |

*Post hoc BL PBMC HIV-1 DNA testing. †Or a mixture.

- **CVF in CAB LA + RPV LA Q8W arm: n = 8**
  - 5 had preexisting major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1 had preexisting major INSTI RAM (G140G/R)
  - 5 had L74I polymorphism (3 subtype A/A1, 1 subtype C, 1 complex subtype)
- Fully active oral ART resulted in viral resuppression in 9/10 patients with CVF
  - 1 patient noncompliant on PI-based ART
- **In all patients with CVF (n = 10), virus maintained phenotypic sensitivity to DTG**

**Facteurs associés à l'échec virologique**

| | OR |
|---|---|
| RPV Résistance (s) at baseline | OR 40.36 |
| Wk 8 RPV concentration résiduelle | OR 5.00 |
| Baseline HIV-1 sous typeA6/A1 | OR 5.92 |
| BMI (kg/m$^2$) at baseline | OR 1.13 |

Overton. CROI 2020. Abstr 34.

# Islatravir EfDA MK-8591

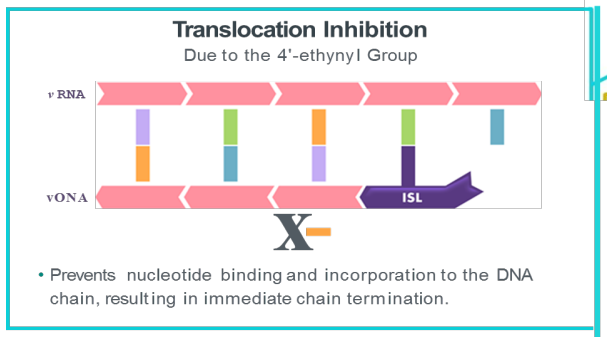
- Inhibiteur de transcription et de translocation NRTTI
- 4 Ethynil fluoro de oxyadenosine

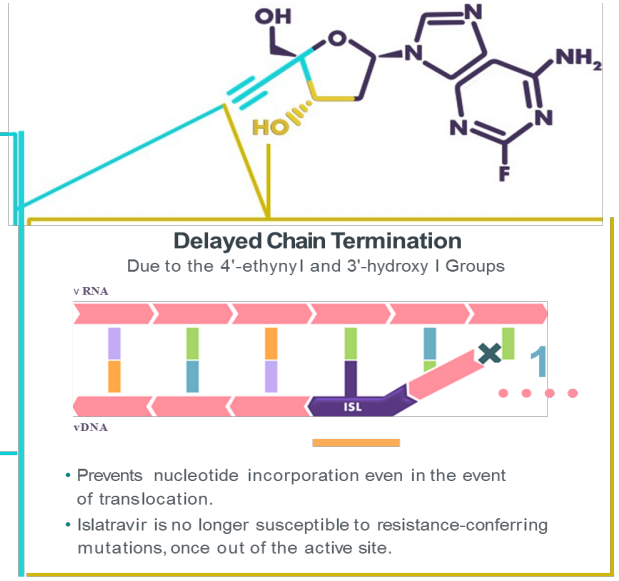
  Fluor : favorise liposolubilité

  et C intracellulaire
- **Puissant antirétroviral ++**

  $CI_{50}$ : 1.5nM soit 0.01 pmol
- Pas d'interactions attendues
- Demi vie longue +++

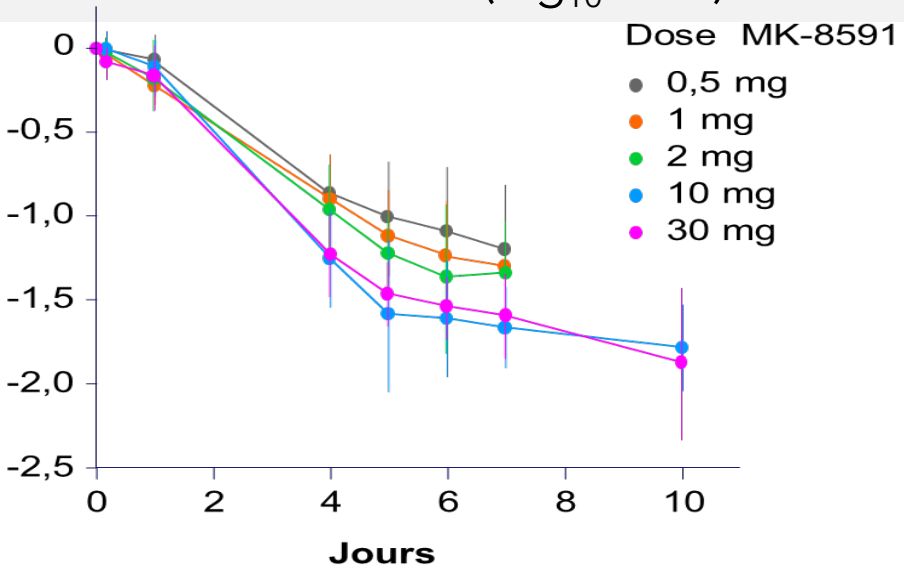
  120 h c/o sujets sains
- Des concentrations élevées tractus génital
- **Un profil pardonnant au plan PK ; objectif traitement et prévention**



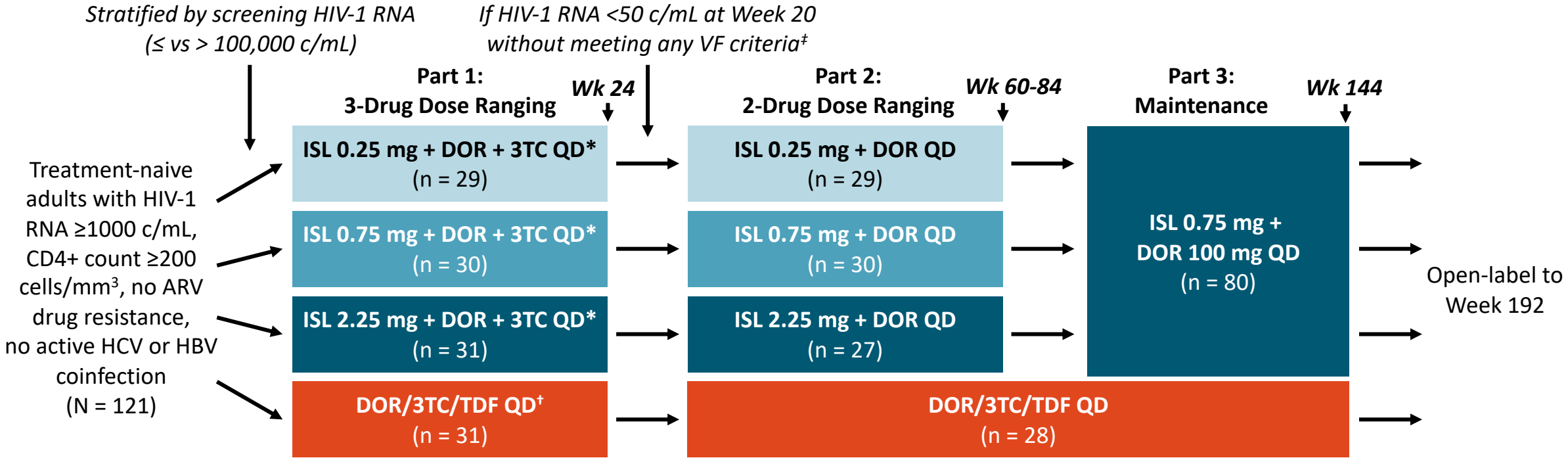

Dose unique MK-8591 n=30

Réduction CV ($log_{10}$ c/ml)



# Islatravir /doravirine : phase 2b patients naïfs

- Analysis of patients participating in an international, randomized, double-blind phase IIb trial




* Received placebo for DOR/3TC/TDF QD. † Received placebo for ISL + DOR + 3TC QD.

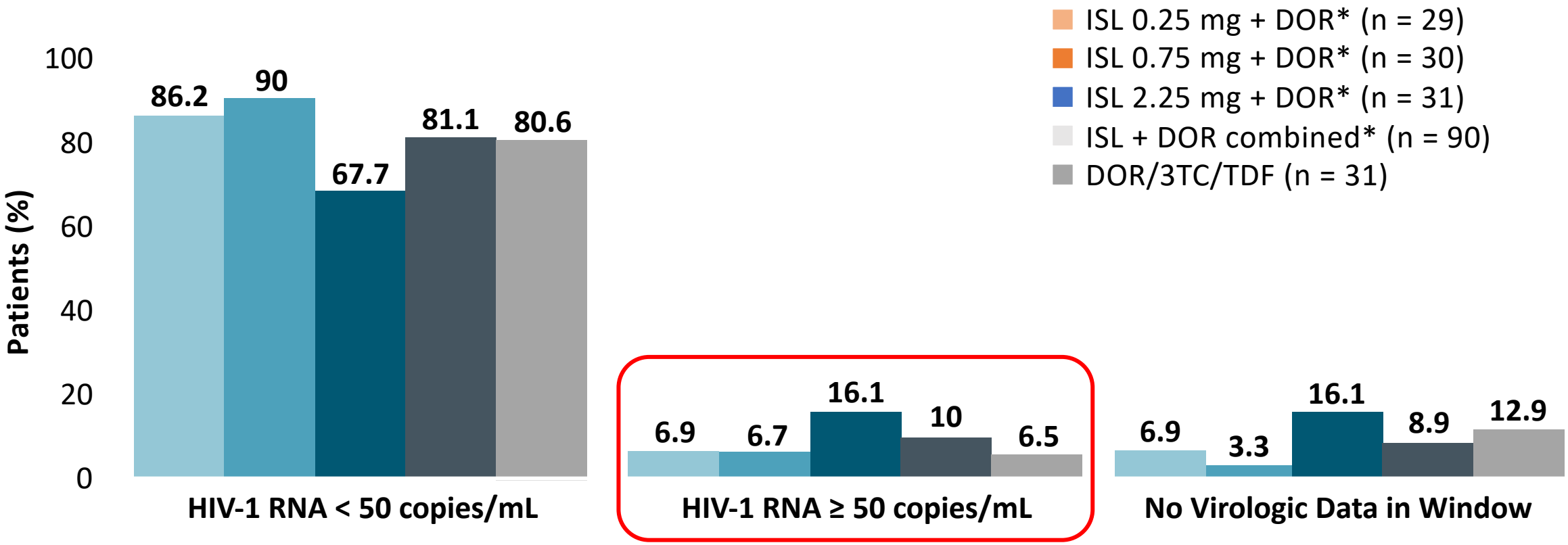
‡ If HIV-1 RNA ≥50 c/mL at Week 20, continued Part 1 until HIV-1 RNA <50 c/mL and, if not meeting any VF criteria, transitioned to Part 2.

Cunningham. IAS 2021. Abstr OAB0304.

Slide credit: clinicaloptions.com

# Islatravir/doravirine

## Phase 2 MK-8591 011 Patients naifs S96




*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR for the Wk 24-96 period of the study.

Molina. HIV Glasgow 2020. Abstr O415.

# Islatravir/doravirine

## Phase 2 MK-8591 011 Patients naifs S96

### *Virologic Failure Through Wk 96*

- Les CV de confirmation étaient toutes < 80 copies/mL chez les patients en échec virologique aucun patient n'avait les critères de résistance testing
- Entre S48 et S96 : 1 rebond additionnel sous ISL 2.25 mg + DOR arm
- Among 7 patients with PDVF, 5 had baseline HIV-1 RNA > 100,000 copies/mL and 5 had HIV-1 RNA < 50 copies/mL preceding ART switch

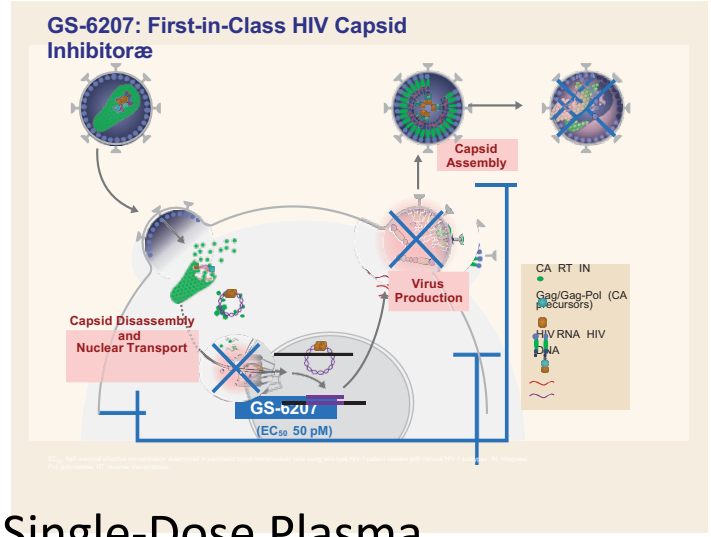
| PDVF at Wk 96, n (%) | ISL 0.25 mg + DOR (n = 29) | ISL 0.75 mg + DOR (n = 30) | ISL 2.25 mg + DOR (n = 31) | ISL + DOR Combined (n = 90) | DOR/ 3TC/TDF (n = 31) |
|---|---|---|---|---|---|
| Nonresponse | 0 | 0 | 1 (3.2) | 1 (1.1) | 0 |
| Rebound with HIV-1 RNA > 50 copies/mL | 2 (6.9) | 2 (6.7) | 1 (3.2) | 5 (5.5) | 1 (3.2) |
| Rebound with HIV-1 RNA > 200 copies/mL | 0 | 0 | 0 | 0 | 0 |

Molina. HIV Glasgow 2020. Abstr O415.

Slide credit: clinicaloptions.com

# Lenacapavir inhibiteur de capside

- **Phase 1b** (dose ranging ), double blind randomised study
- **39 patients**, INSTI naive VL between 5 000 et 400 000 c/ml, CD4 > 200/mm$^3$
- **A single dose** 5 doses : 20 , 50 , 150 , 450 , 750 mg) or placebo 2 pts /arm
  All patients started B/F/TAF à J10

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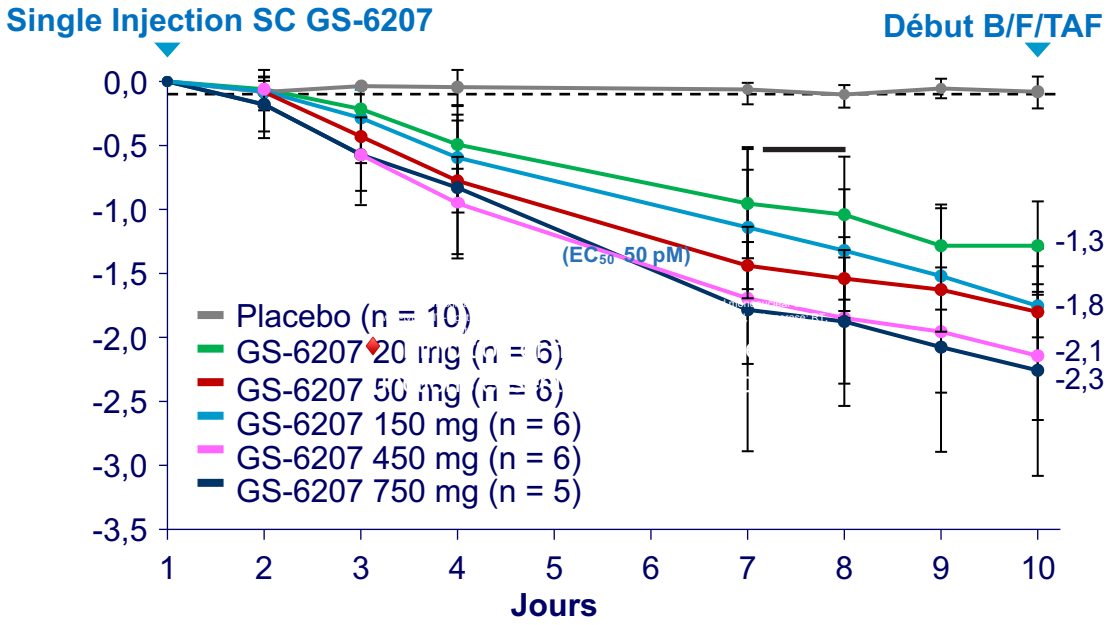
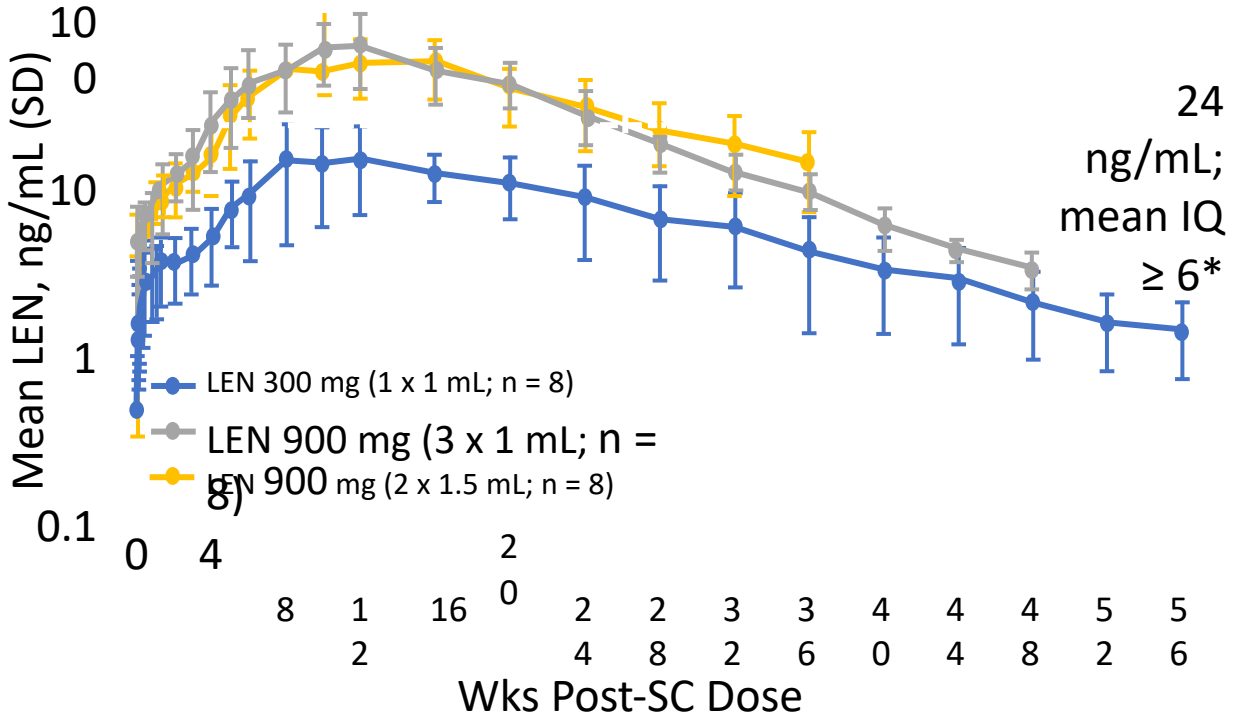



Mean LEN Single-Dose Plasma

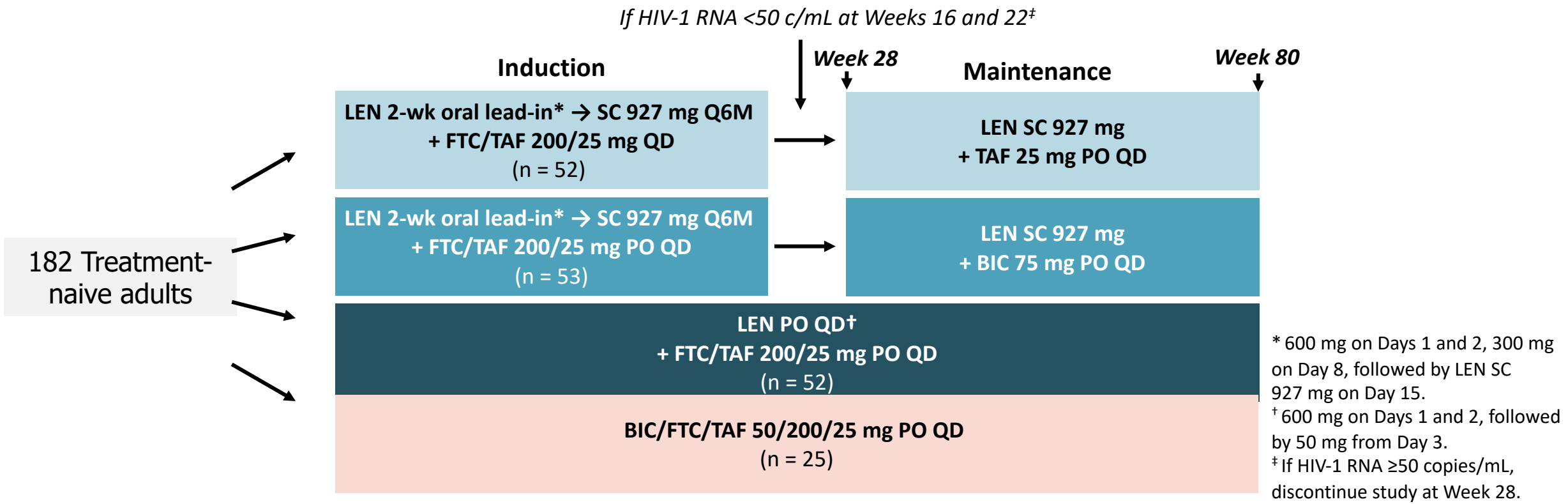



*Daar E, CROI 2020, Abs. 469*

# **Lenacapavir** : Inhibiteur de capside GS-6207

## CALIBRATE : Patients naifs

- Randomized, open-label, active-controlled, phase II induction-maintenance study




* 600 mg on Days 1 and 2, 300 mg on Day 8, followed by LEN SC 927 mg on Day 15.
† 600 mg on Days 1 and 2, followed by 50 mg from Day 3.
‡ If HIV-1 RNA ≥50 copies/mL, discontinue study at Week 28.

- Primary outcome: Patients (%) with HIV-1 RNA <50 copies/mL at Week 54
- Secondary outcomes: Patients (%) with HIV-1 RNA <50 copies/mL at Weeks 28, 38, and 80; change from BL in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Weeks 28, 38, 54, and 80

Gupta. IAS 2021. Abstr OAB0302.

# Lenacapavir

## CALIBRATE Interim Analysis: Virologic Outcomes at Week 28

| | LEN SC + FTC/TAF → TAF n = 5 | LEN SC + FTC/TAF → BIC (n = 53) | LEN Oral + FTC/TAF (n = 52) | BIC/FTC/TAF (n = 25) |
|---|---|---|---|---|
| Virologic Outcome by FDA Snapshot (ITT) | | | | |
| ▪ HIV-1 RNA <50 copies/mL | 94% | 92% | 94% | 100 |
| ▪ HIV-1 RNA ≥50 copies/mL | 0 | 4 | 0 | 0 |
| ▪ No data | 6 | 4 | 6 | 0 |
| Virologic Outcome by Missing = Failure Analysis | | | | |
| ▪ HIV-1 RNA <50 copies/mL at Week 4 | 83 | 79 | 87 | 84 |
| ▪ HIV-1 RNA <50 copies/mL at Week 28 | 94 | 92 | 94 | 100 |

- One patient receiving LEN SC + FTC/TAF → BIC developed resistance mutations at Week 10 conferring a 20-fold change in LEN susceptibility
  - CA: Q67H + K70R; RT: M184M/I
- Plasma concentrations of LEN remained in target range throughout

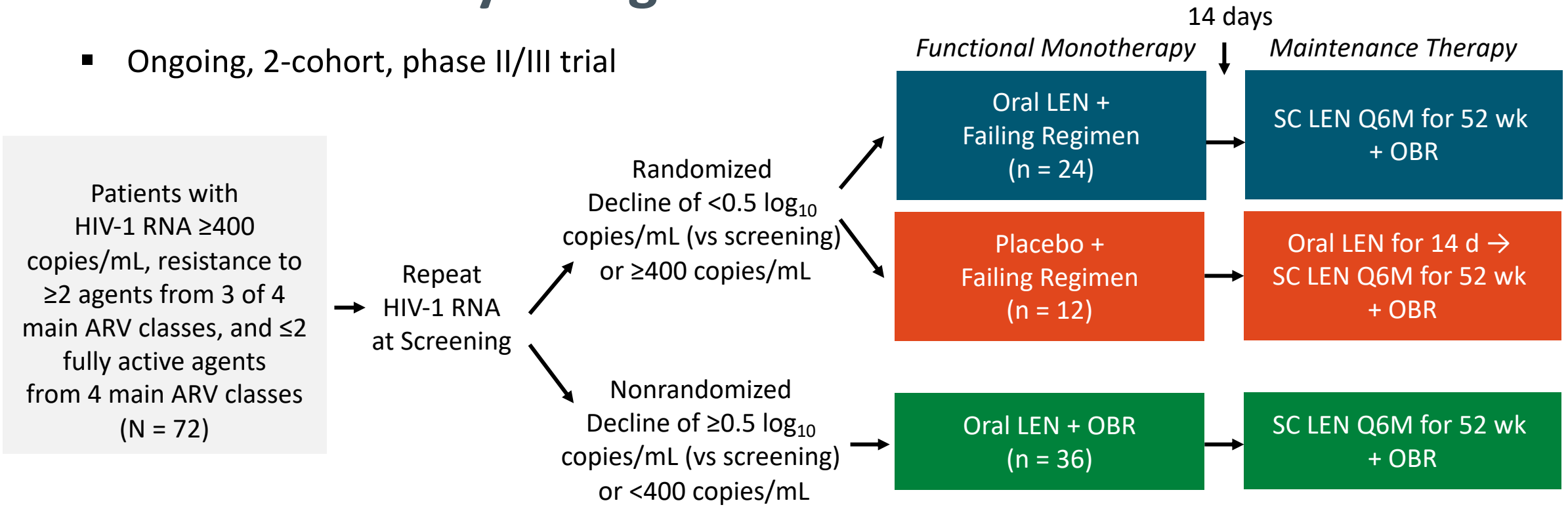
Gupta. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

# Lenacapavir

## CAPELLA : Study Design

- Ongoing, 2-cohort, phase II/III trial




Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

- Primary endpoint achieved in prior analysis: ≥0.5 $\log_{10}$ copies/mL decline in HIV-1 RNA at Day 14 in randomized cohort
- Secondary endpoints: HIV-1 RNA <50 copies/mL, <200 copies/mL at Week 26 in randomized cohort

Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

# Lenacapavir

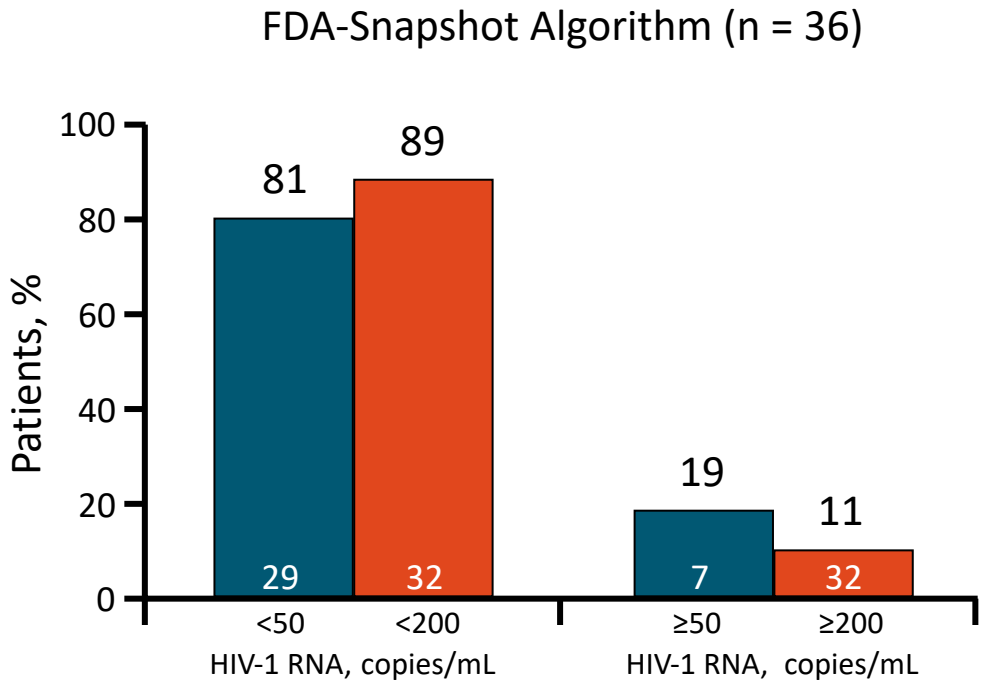
## CAPELLA : Baseline Characteristics

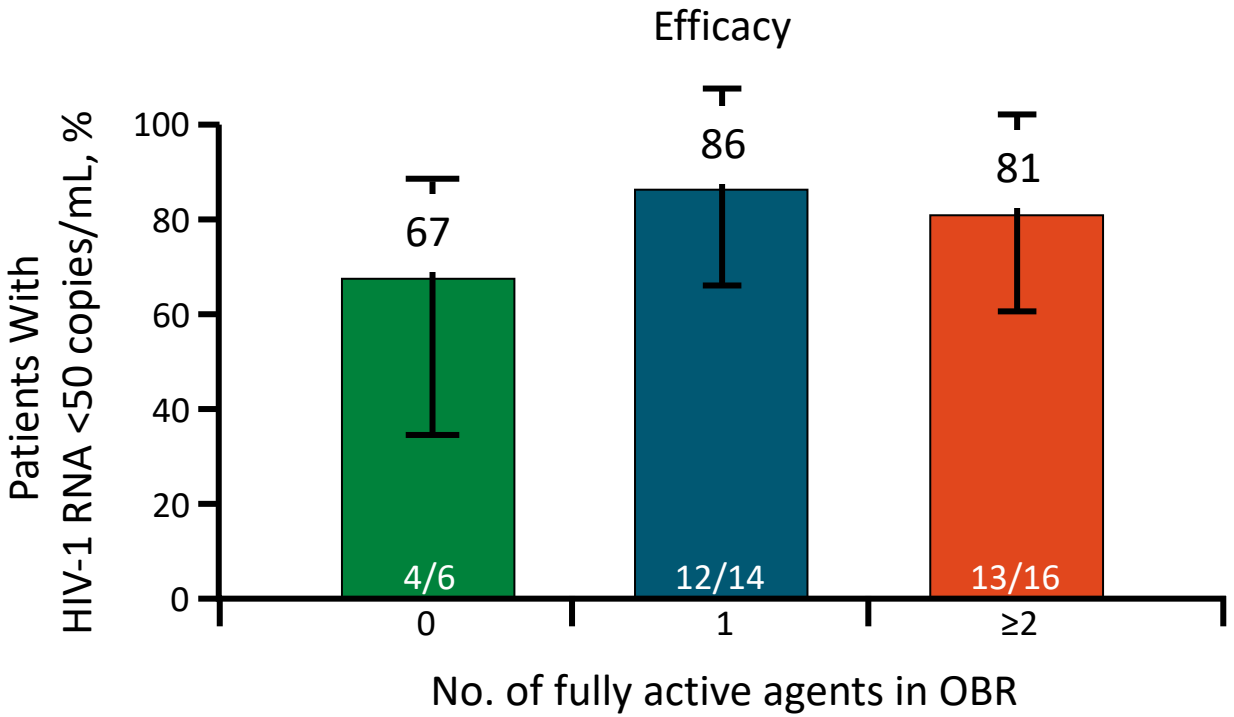
| Characteristic | Randomized | | Nonrandomized | Total (N = 72) |
|---|---|---|---|---|
| | LEN (n = 24) | Placebo (n = 12) | LEN (n = 36) | |
| Median age, yr (range) | 55 (24-71) | 54 (27-59) | 49 (23-78) | 52 (23-78) |
| Female at birth, % | 29 | 25 | 22 | 25 |
| Black, % | 42 | 55 | 31 | 38 |
| Hispanic/Latinx, % | 25 | 36 | 14 | 21 |
| Median HIV-1 RNA, $log_{10}$ copies/ml (range) | 4.2 (2.3-5.4) | 4.9 (4.3-5.3) | 4.5 (1.3-5.7) | 4.5 (1.3-5.7) |
| ▪ >75,000 copies/mL, % | 17 | 50 | 28 | 28 |
| Median CD4+ cell count, cells/$mm^3$ (range) | 172 (16-827) | 85 (6-237) | 195 (3-1296) | 150 (3-1296) |
| ▪ ≤200 cells/$mm^3$, % | 67 | 92 | 53 | 64 |
| Median time since HIV diagnoses, yr (range) | 27 (13-39) | 26 (14-35) | 23 (9-44) | 24 (9-44) |
| Median prior ARVs, No. (range) | 9 (2-24) | 9 (3-22) | 13 (3-25) | 11 (2-25) |
| Median ARVs in failing regimen, No. (range) | 3 (1-7) | 3 (2-6) | 4 (2-7) | 3 (1-7) |
| Resistance to ≥2 drugs in class, % | | | | |
| ▪ NRTI | 96 | 100 | 100 | 99 |
| ▪ NNRT | 92 | 100 | 100 | 97 |
| ▪ PI | 83 | 67 | 83 | 81 |
| ▪ INSTI | 83 | 58 | 64 | 69 |

Molina. IAS 2021. Abstr OALX01LB02.

# Lenacapavir

## CAPELLA Secondary Endpoints: LEN Efficacy at Week 26 in Randomized Cohort




- Mean change in CD4+ cell count: +81 cells/mm$^3$
- Incidence of very low CD4+ cell count (<50 cells/mm$^3$) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26

Molina. IAS 2021. Abstr OALX01LB02. Reproduced with permission.

Slide credit: clinicaloptions.com

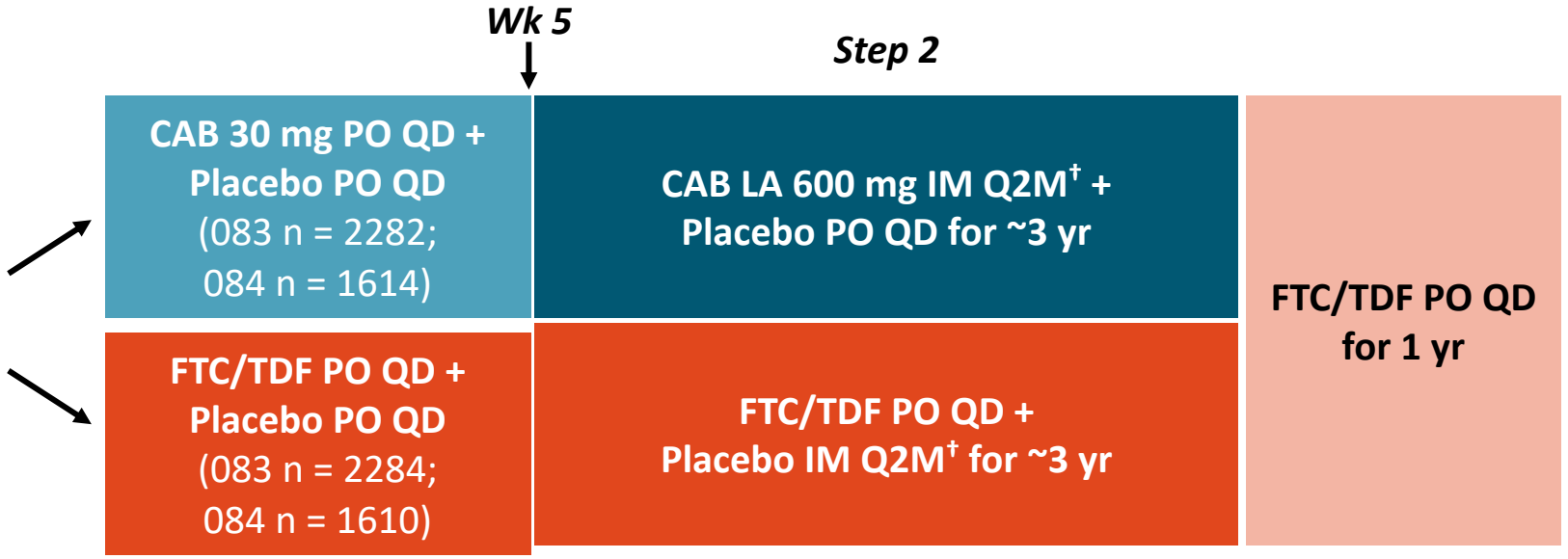
# Long ACTING Cab mono

## HPTN 083 and 084: **LA Injectable CAB vs Daily Oral FTC/TDF for PrEP**

- International, randomized, double-blind phase IIb/III (083) and phase III (084) trials

**083: MSM and TGW** ≥18 yr of age at high risk of HIV infection* (N = 4566)[1]

**084:** Sexually active cisgender **women,** 18-45 yr of age, at high risk of HIV infection (N = 3224)[2]




1. Landovitz. AIDS 2020. Abstr OAXLB0101. 2. Delany-Moretlwe. HIVR4P 2021. Abstr HY01.02.

# Long ACTING

## HPTN 083 and 084: LA Injectable CAB vs Daily Oral FTC/TDF for PREP

# HIV Incidence

LA CAB met criteria for superiority vs FTC/TDF in both 083 and 084[1,2]

| Primary Efficacy Endpoint | HPTN 083[1] | | HPTN 084[2] | |
|---|---|---|---|---|
| | CAB (n = 2244) | FTC/TDF (n = 2247) | CAB (n = 1614) | FTC/TDF (n = 1610) |
| HIV infections, n | 13* | 39 | 3† | 36 |
| PYFU | 3205 | 3187 | 1956 | 1942 |
| HIV incidence per 100 PY | 0.41 | 1.22 | 0.15 | 1.85 |
| **HR for CAB vs FTC/TDF (95% CI)** | **0.34 (0.18-0.62)** | | **0.08 (0.03-0.27)** | |

*Includes 1 case readjudicated post hoc as a baseline infection; revised HIV incidence based on readjudication: 0.37 (95% CI: 0.19-0.65), revised HR: 0.32 (95% CI: 0.16-0.58).
†Includes 1 baseline infection.

1. Landovitz. NEJM. 2021;385:595. 2. Marzinke. IAS 2021. Abstr PECLB25.

# La thérapie antirétrovirale

- Puissance
- Safe
- Barrière génétique R élevée
- Simple
- Pas d interactions

- **Molécules LONG ACTING**

**Un grand challenge pour la décennie à venir**

- administration PO hebdomadaire , mensuelle
- injectable / 2 mois /6 mois

**Nouveaux mode administration**

Injections IM, SCutaneous

Implants ; Patch

**Majeur pour faciliter observance, diminuer stigmatisation**

**ARV new drugs /delivery**

Potentiel pour

**Traitement et prévention**

Le traitement et le « vaccin « de demain