Les nouveaux antirétroviraux

Gwenaël LE MOAL

Service de Maladies infectieuses

CHU Poitiers
CENTRE HOSPITALIER UNIVERSITAIRE

Géricco
GROUPE D'ÉPIDÉMIOLOGIE ET RECHERCHE EN INFECTIOLOGIE CLINIQUE CENTRE OUEST

JOURNEES MEDICALES 2023

LES GRENETTES, SAINTE-MARIE-DE-RE

Liens d'intérêt

- Gilead : invitation congrès

  Sophie Poupon
- MSD : invitation congrès

  Christophe Lheritier
- ViiV : invitation congrès

  Richard Durdilly
- Autres : LH, le meilleur de….

Traitement ARV où en est on en 2023?

- Les étapes antérieures importantes
  - Efficacité (1996-aujourd'hui) : trithérapie
  - Tolérance (2000-aujourd'hui) : sélection de la molécule la mieux tolérée
  - Simplicité (2008-aujourd'hui) : SingleTabletRegimen
  - Treatment as Prevention (2011-aujourd'hui) : U=U
  - Prévention (2015-aujourd'hui) : PreP
- Les prochaines étapes
  - Meilleure tolérance et commodité
  - Moins de toxicité, d'interactions médicamenteuses, de stigmatisation
  - Guérison ?

Nouveaux?

- Molécules de demain?
- Molécules ayant eu une ATU en 2022?
- Molécules ayant eu une AMM en 2022?
- Molécules utilisées autrement?

- Nouvelles molécules, nouvelles stratégies……

Nouvelles stratégies

Allègement

Nouveaux modes d’administration

Allègement

Bithérapie

Traitement intermittent

Les bithérapies

- Questions
  - Efficacité ?notamment sur réservoir ?
  - Tolérance ?
  - Effets sur l'activation immunitaire et inflammation?

Attention VHB

3TC-DGV

- Evaluée
  - Instauration de traitement (GEMINI)
  - Maintenance de traitement (TANGO et SALSA)

Clinical Infectious Diseases
MAJOR ARTICLE

Efficacy and Safety of Switching to Dolutegravir/Lamivudine Versus Continuing a Tenofovir Alafenamide–Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults With Human Immunodeficiency Virus Type 1: Results Through Week 144 From the Phase 3, Noninferiority TANGO Randomized Trial

Olayemi Osiyemi,[1] Stéphane De Wit,[2] Faïza Ajana,[3] Fiona Bisshop,[4] Joaquín Portilla,[5] Jean-Pierre Routy,[6] Christoph Wyen,[7] Mounir Ait-Khaled,[8] Peter Leone,[9] Keith A. Pappa,[9] Ruolan Wang,[9] Jonathan Wright,[10] Nisha George,[11] Brian Wynne,[9] Michael Aboud,[8] Jean van Wyk,[8] and Kimberly Y. Smith[9]

[1]Triple O Research Institute PA, West Palm Beach, Florida, USA; [2]CHU Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium; [3]Centre Hospitalier de Tourcoing, Tourcoing, France; [4]Holdsworth House Medical Brisbane, Queensland, Australia; [5]Hospital General Universitario de Alicante, Alicante, Spain; [6]McGill University Health Centre, Montreal, Quebec, Canada; [7]Praxis am Ebertplatz, Cologne, Germany; [8]ViiV Healthcare, Brentford, United Kingdom; [9]ViiV Healthcare, Research Triangle Park, North Carolina, USA; [10]GlaxoSmithKline, Brentford, United Kingdom; and [11]GlaxoSmithKline, Bangalore, India

- Essai randomisé chez des patients avec CV < 50 c/ml sous ARV : DTG/3TC (n = 369) vs poursuite de la trithérapie à base de TAF en cours (n = 372)

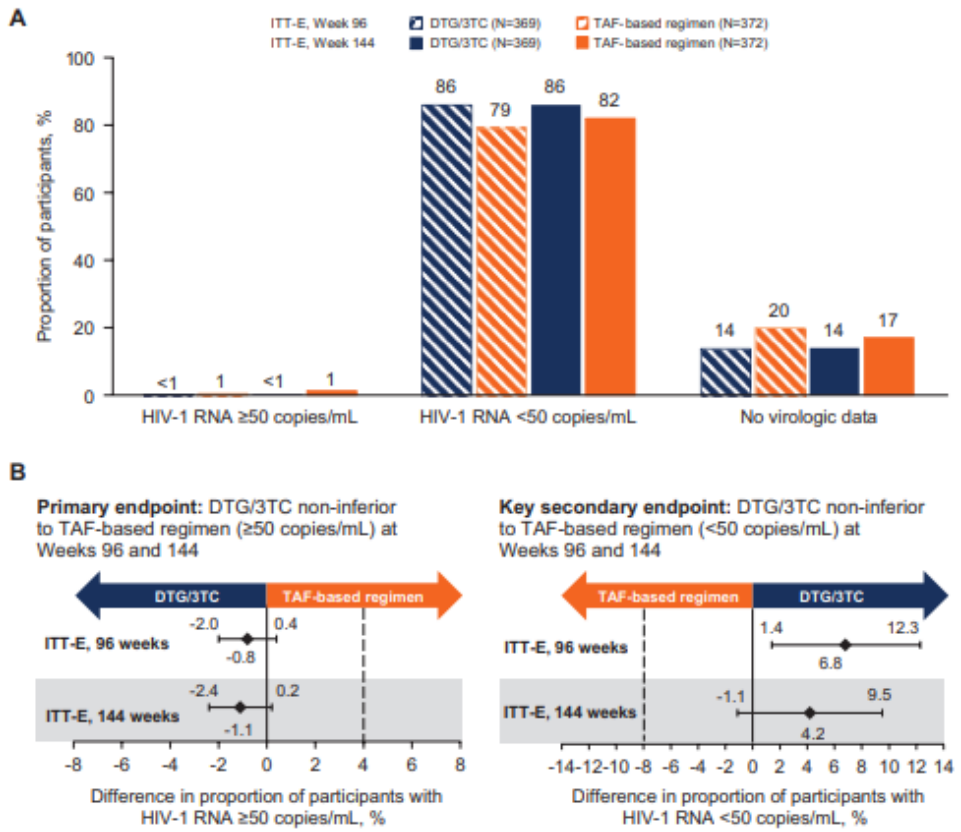


Figure 2. *A*, Virologic outcomes at weeks 96 and 144 in the intention-to-treat–exposed (ITT-E) population by the US Food and Drug Administration Snapshot algorithm. *B*, Adjusted treatment differences (dolutegravir/lamivudine [DTG/3TC] group value – tenofovir alafenamide [TAF] group value), based on Cochran-Mantel-Haenszel stratified analysis, with adjustment for baseline third agent class. Abbreviation: HIV-1, human immunodeficiency virus type 1.

C’est bien toléré

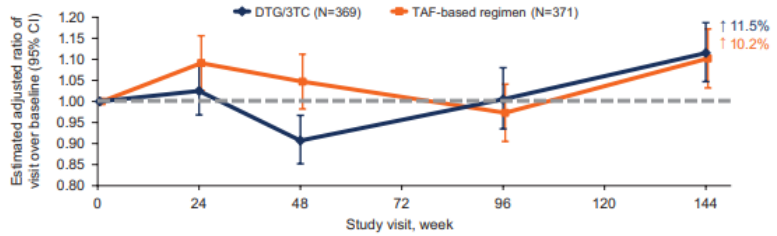


Figure 5. Change from baseline in homeostasis model of assessment–insulin resistance (HOMA-IR) in the safety population through week 144. The change from baseline was calculated using mixed-model repeated measures adjusting for treatment, visit, baseline third agent class, CD4$^+$ cell count (continuous), age (continuous), sex, race, body mass index (continuous), presence of hypertension, $\log_e$-transformed baseline HOMA-IR (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. Abbreviations: CI, confidence interval; DTG/3TC, dolutegravir/lamivudine; TAF, tenofovir alafenamide.

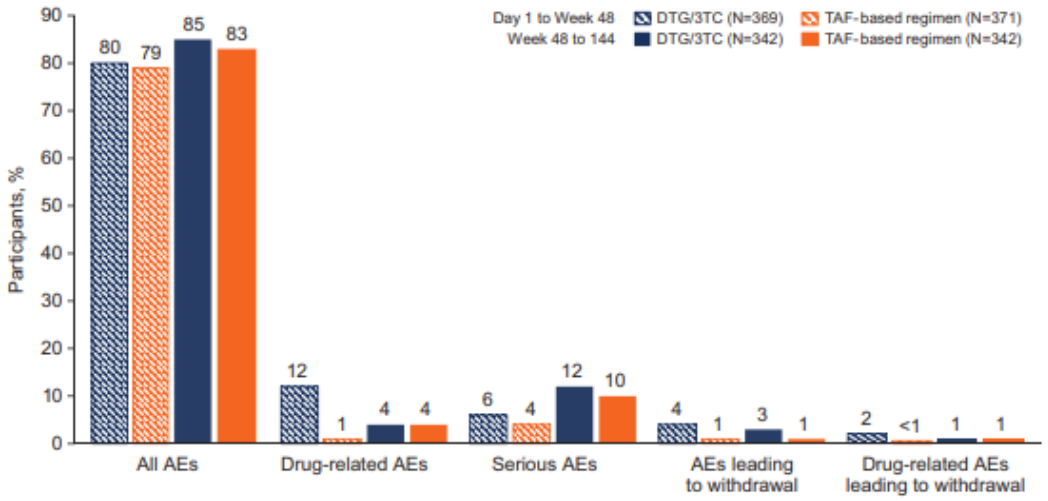


Figure 4. Summary of adverse events (AEs) after week 48. Abbreviations: DTG/3TC, dolutegravir/lamivudine; TAF, tenofovir alafenamide.

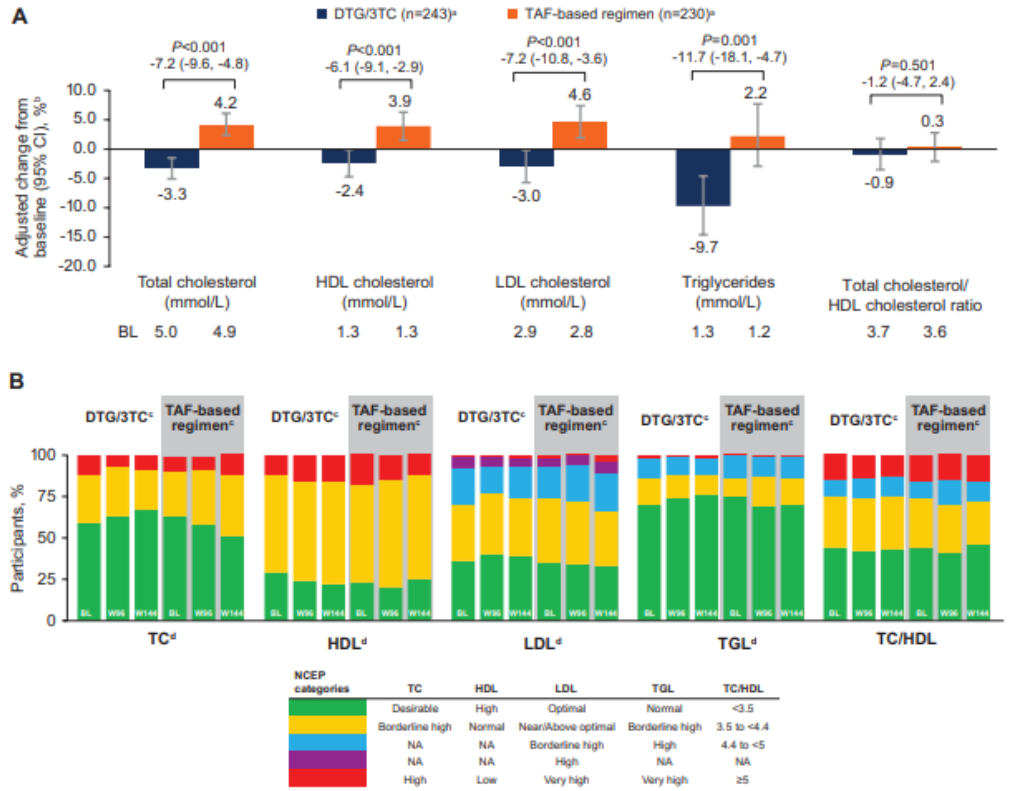


Figure 6. Change from baseline in fasting lipids at week 144 (*A*) and at weeks 96 and 144 (*B*) by National Cholesterol Education Program (NCEP) category. [a]Number of participants with nonmissing fasting lipid data at baseline and week 144, excluding those with lipid-modifying agent administered at baseline (lipid data collected after initiation of a lipid-modifying agent were censored and a last observation carried forward method was applied). Use of lipid-modifying agents at baseline was similar between treatment groups (dolutegravir/lamivudine [DTG/3TC], 13%; tenofovir alafenamide [TAF]–based regimen, 15%). [b]Percentage change from baseline based on adjusted ratio (week 144 to baseline) in each group calculated from mixed-model repeated measures applied to change from baseline in $\log_e$-transformed data adjusting for treatment, visit, baseline third agent class, age (continuous), body mass index (continuous), race, CD4$^+$ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [c]Numbers of participants with nonmissing fasting lipid data at baseline and study week (week 96: DTG/3TC, n = 238; TAF- based regimen, n = 213; week 144: DTG/3TC, n = 243; TAF-based regimen, n = 230), excluding participants with lipid-modifying agent administered at baseline (lipid data collected after initiation of a lipid-modifying agent were censored and a last observation carried forward method was applied so that the last available fasted, on-treatment lipid value before initiation of a lipid-modifying agent was used). [d]NCEP categories at weeks 96 and 144 versus baseline. Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; TC, total cholesterol; TGL, triglycerides.

CHU Poitiers

Osiyemi O, Clin Infect Dis 2022Sep 29;75(6):975-986

Quantification des provirus intacts dans le réservoir après un switch vers DTG/3TC vs BIC/FTC/TAF (1)

- Etude Rumba : étude prospective ouverte randomisée, monocentrique de switch vers DTG/3TC
- **Critère principal :** non infériorité de la bithérapie DTG/3TC vs trithérapie BIC/F/TAF à S48 en termes de % de génomes proviraux intacts (marge : 12 %)
- 134 patients inclus, CHU Gand, Belgique, avec CV < 50 c/ml depuis plus de 3 mois sous trithérapie à base d'INI de 2ème génération, pas de résistance
- Technique de quantification des provirus intacts et défectifs : IPDA

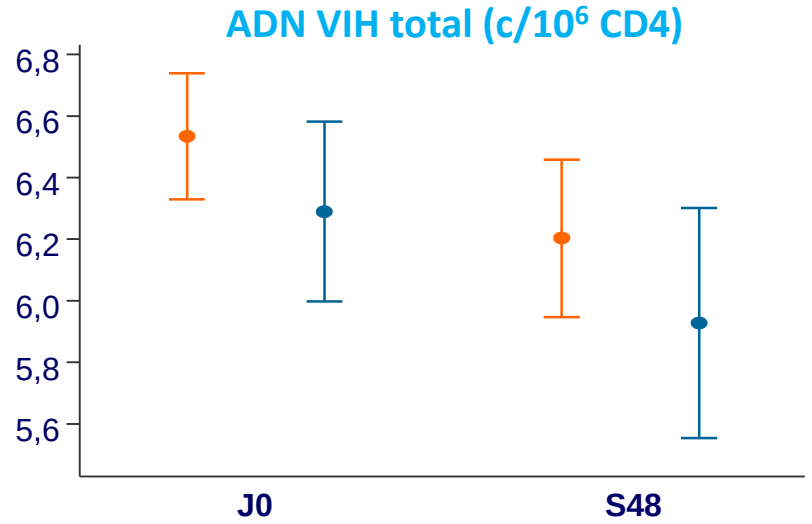
Caractéristiques des patients à J0

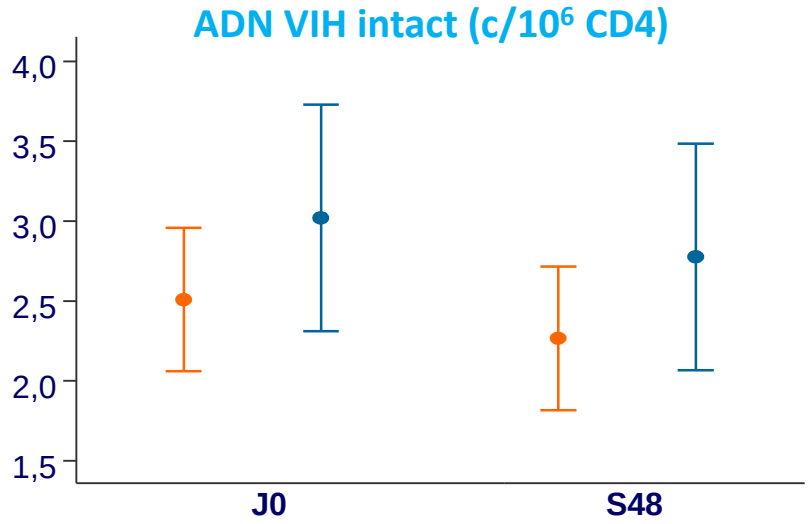
	DTG/3TC (n = 89)	BIC/F/TAF (n = 45)
Homme, n	79	39
Age, ans, médiane (IQR)	46 (36-53)	45 (50-56)
CD4 à J0, /mm^3, médiane (IQR)	691 (558-933)	677 (527-872)
Zénith de CV, c/ml, médiane (IQR)	122 563 (32 292-405 527)	62 448 (12 097-192 502)
Temps sous ARV, ans, médiane (IQR)	8,1 (4,8-11,2)	6,0 (4,4-9,0)
ADN VIH total, c/10^6 CD4, médiane (IQR)	773 (420-1 388)	511 (283-1 483)
ADN VIH intact, c/10^6 CD4, médiane (IQR)	21 (2-42)	26 (0-109)

- 79/81 (97 %) et 39/40 (98 %) des participants dans les bras DTG/3TC et BIC/F/TAF, respectivement, gardent CV < 50 c/ml à S48

Blomme E, HIV Glasgow 2022, Abs. M042

Quantification des provirus intacts dans le réservoir après un switch vers DTG/3TC vs BIC/FTC/TAF (2)

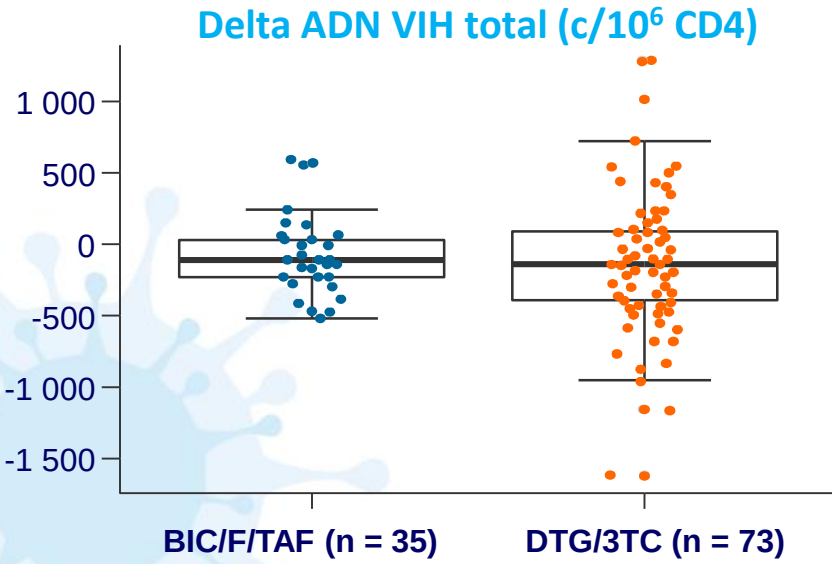


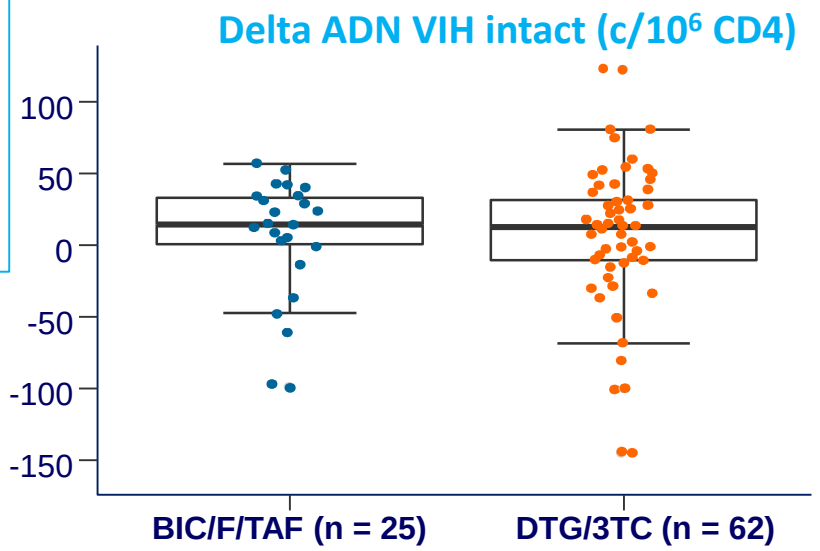


DTG/3TC — BIC/FTC/TAF

Pas de différence d'ADN total VIH et d'ADN intact VIH à S48 après un switch vers DTG/3TC vs BIC/FTC/TAF

Pas de différence dans la dynamique de changement





Blomme E, HIV Glasgow 2022, Abs. M042

Essais TANGO et SALSA (switch pour DTG/3TC) : étude des biomarqueurs inflammatoires à S48 (2)

Moyennes géométriques (IC 95 %) des marqueurs inflammatoires et du rapport CD4/CD8 à J0 et S48

		DTG/3TC n = 615	Poursuite trithérapie n = 619
CD14s, x 10^6 ng/ml	J0 S48	1,58 (1,56 - 1,61) 1,27 (1,19 - 1,35)	1,53 (1,51 - 1,56) 1,35 (1,27 - 1,43)
CD163s, ng/ml	J0 S48	611,1 (590 - 632,9) 570,5 (540,1 - 602,6)	602,1 (582,5 - 622,3) 561 (530,9 - 592,9)
IL-6, ng/l	J0 S48	1,67 (1,58 - 1,78) 1,63 (1,4 - 1,9)	1,67 (1,57 - 1,78) 1,51 (1,29 - 1,76)
CRPus, mg/l	J0 S48	1,36 (1,25 - 1,49) 1,13 (0,90 - 1,42)	1,29 (1,18 - 1,41) 1,30 (1,03 - 1,63)
Rapport CD4/CD8, %	J0 S48	0,94 (0,90 - 0,98) 1,00 (0,96 - 1,03)	0,95 (0,91 - 0,99) 1,01 (0,97 - 1,05)

- Moyenne S48 ajustée sur le traitement, sexe, ethnie, IMC, groupe CDC, tabagisme, co-infection VHC, âge, rapport CD4/CD8, étude, et nature du 3ème agent
- Pour IL-6 et rapport CD4/CD8, ajustement également sur CRPus à J0
- Pour CRPus, ajustement également sur triglycérides, utilisation hypolipidémiant, cholestérol total, LDL-cholestérol, HDL-cholestérol

Llibre JM, AIDS 2022, Abs. EPB165

3TC-DOR

P094

Doravirine plus lamivudine (DOR/3TC) two-drug regimen as a maintenance antiretroviral therapy in virally suppressed persons living with HIV

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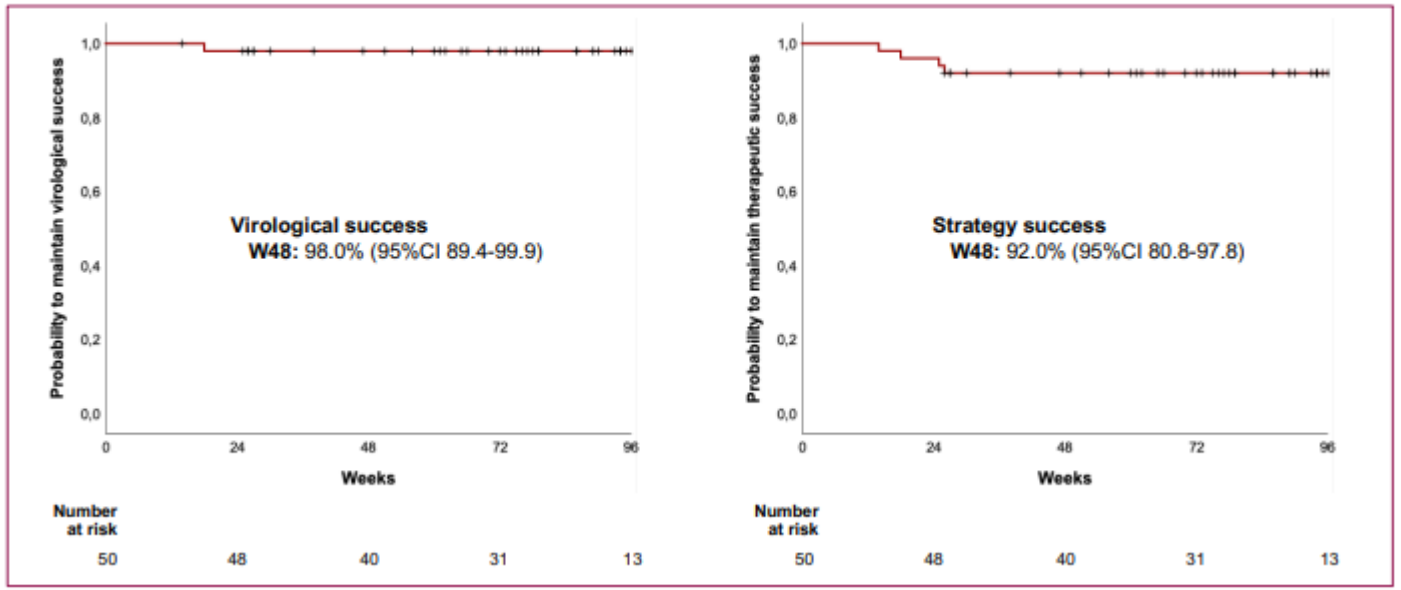
1. Public Health Center, Quimper Hospital, Quimper, France
2. Sorbonne University, Virology Department, Pitié-Salpêtrière Hospital, AP-HP, Pierre Louis Epidemiology and Public Health Institute (iPLESP), INSERM 1136, Paris, France
3. Sorbonne University, Infectious Diseases Department, Pitié-Salpêtrière Hospital, AP-HP, Pierre Louis Epidemiology and Public Health Institute (iPLESP), INSERM 1136, Paris, France

Table. Baseline patients' characteristics (N=50).

Age, years, median (IQR)	58 (51-62)
Gender, n (%)	
- Male	34 (68)
- Female	16 (32)
Birth Country, n (%)	
- France	44 (88)
- Other	6 (12)
Transmission group, n (%)	
- Heterosexual	23 (46)
- MSM	21 (42)
- Other	6 (12)
CDC stage C, n (%)	11 (22)
CD4 nadir, cells/mm^3, median (IQR)	258 (145-385)
HIV-RNA zenith, log$_{10}$ copies/mL, median (IQR)	4.79 (3.67-5.32)
Time from HIV diagnosis, years, median (IQR)	24 (16-29)
Time from ART initiation, years, median (IQR)	20 (13-23)
Genotypic sensitivity score, n (%)[a]	
- 2	18/20 (90)
- 1	2[b]/20 (10)
Duration of viral suppression, years, median (IQR)	14 (8-19)
CD4 count, cells/mm^3, median (IQR)	784 (636-889)
CD4/CD8 ratio, median (IQR)	1.16 (0.96-1.50)
Antiretroviral strategy prior to DOR/3TC, n (%)	
- NNRTI-based 3-DR	25 (50)
- INSTI-based 3-DR	11 (22)
- Dolutegravir/lamivudine	6 (12)
- Darunavir/ritonavir/lamivudine	3 (6)
- Other 2-DR	3 (6)
- Boosted PI monotherapy	2 (4)

NOTES. 3-DR: three-drug regimen. 2-DR: two-drug regimen. a. Calculated from cumulative historical HIV-RNA and HIV-DNA genotypes with reverse transcriptase available sequences (N=20). b. These two patients had a documented M184V mutation in past genotypes.

Figure. Virological and therapeutic success rate under DOR/3TC.



Perfezou P, HIV Glasgow 2022, Abs. P094

Les traitements intermittents

- Quatuor

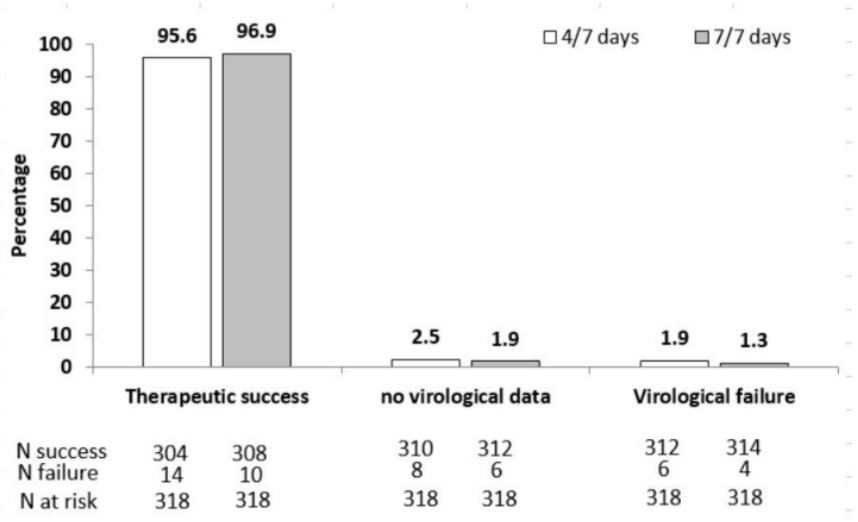
Version of Record: https://www.sciencedirect.com/science/article/pii/S2352301821003003
Manuscript_444ac8a2584ec3217e27da39863bc687

Title: ANRS 170 QUATUOR 4/7-days maintenance strategy in HIV-1treated patients: a randomised open-label parallel non-inferiority trial.

Authors:

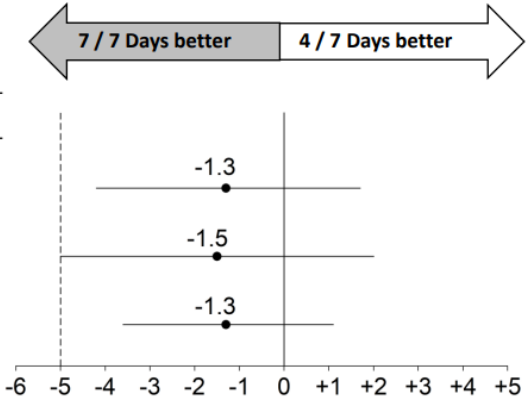
Roland Landman[1,6], Pierre de Truchis[2], Lambert Assoumou[3], Sidonie Lambert[4], Jonathan Bellet[5], Karine Amat[6], Bénédicte Lefebvre[7], Clotilde Allavena[8], Christine Katlama[9], Yazdan Yazdanpanah[1], Jean M Molina[10], Ventzislava Petrov-Sanchez[11], Séverine Gibowski[11], Jean C Alvarez[12], Jacques Leibowitch[2]†, Jacqueline Capeau[13], Soraya Fellahi[13], Martin Duracinsky[14], Laurence Morand-Joubert[4], Dominique Costagliola[3], Pierre M Girard[7] and ANRS 170 QUATUOR study group*

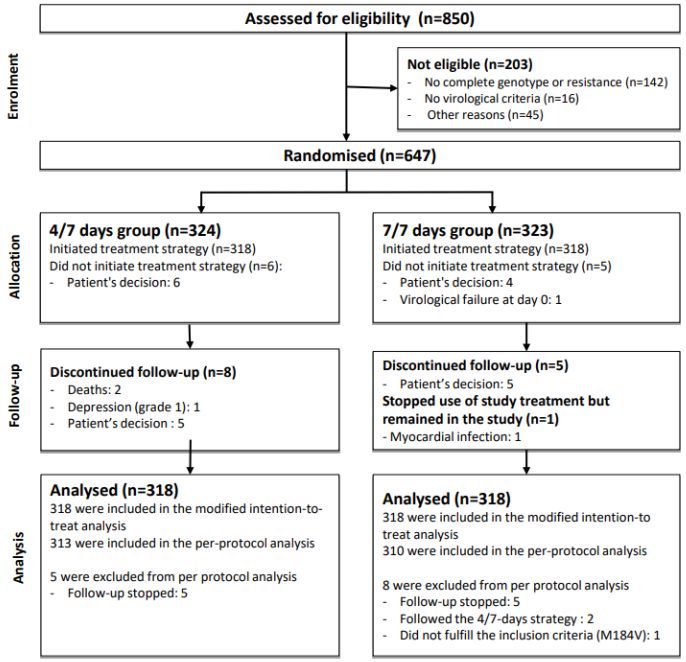
A) Primary endpoint (FDA Snapshot method)



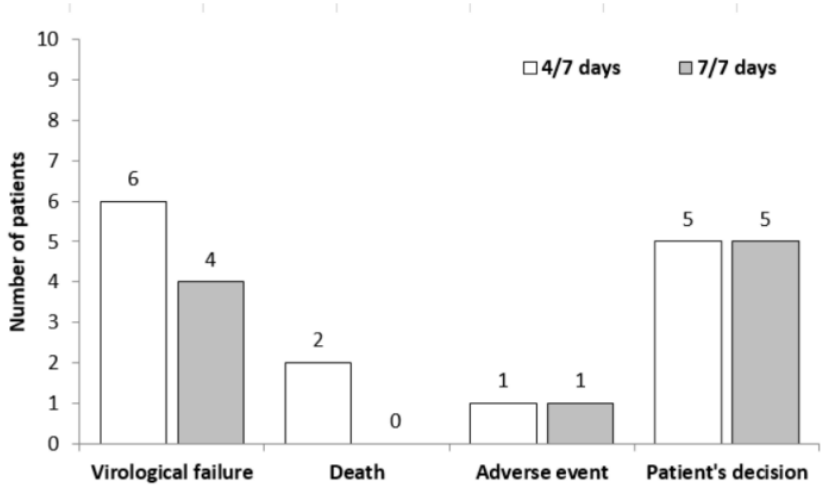
B) Therapeutic success (FDA Snapshot method)

	4 / 7 Days	7 /7 Days
mITT	95.6 % (304/318)	96.9 % (308/318)
ITT	93.8 % (304/324)	95.4% (308/323)
PP	97.1 % (304/313)	98.4 % (305/310)



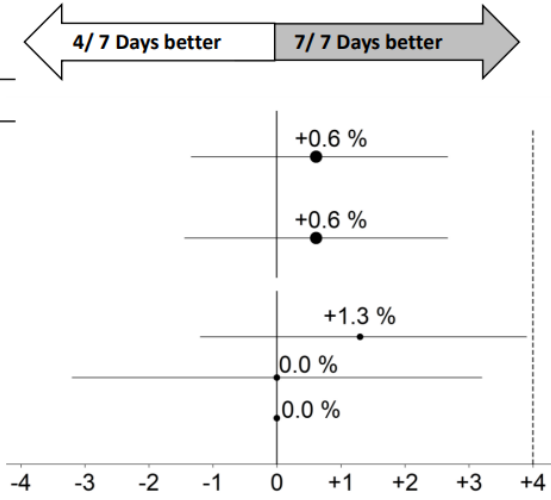


C) Reasons of Failure



D) Virological failure (VF) – FDA Snapshot method

	4 / 7 Days	7 /7 Days
mITT	1.9 % (6/318)	1.3 % (4/318)
PP	1.9 % (6/313)	1.3 % (4/310)
INsTI	2.0 % (3/152)	0.7 % (1/152)
NNRTI	2.0 % (3/148)	2.0 % (3/148)
PI	0.0 % (0/18)	0.0 % (0/18)



QUATUOR

- Réservoir
  - CV us : pas de changement significatif
  - DNA proviral stable et similaire dans les 2 groupes
- Activation immunitaire : pas de différence significative
  - CD4
  - CD4/CD8
  - Marqueurs inflammatoires
- Satisfaction
  - 59% de patients avec amélioration de la qualité de vie contre 8% 7j/7
- Coût : économie de 3 000 euros/patient/an

Landman R, Lancet HIV 2022 Feb;9(2):e79-e90

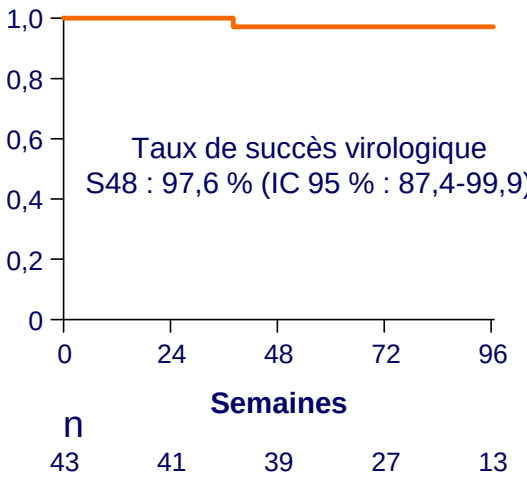
TDF/3TC/DOR en schéma intermittent 4 ou 5 jours/7 de switch : étude observationnelle

- Etude rétrospective, non comparative, bicentrique
  - Adultes VIH+, contrôlés virologiquement (CV < 50 c/ml) ayant changé de traitement ARV entre octobre 2019 et janvier 2021 pour la trithérapie TDF/3TC/DOR prise 4 ou 5 jours sur 7
  - Critère succès virologique : absence d'échec virologique (défini comme 2 CV ≥ 50 c/ml, ou 1 CV ≥ 200 c/ml ou 1 CV ≥ 50 c/ml avec modification du traitement ARV) à S48
  - Critère succès thérapeutique (CV < 50 c/ml sans changement de traitement) à S48

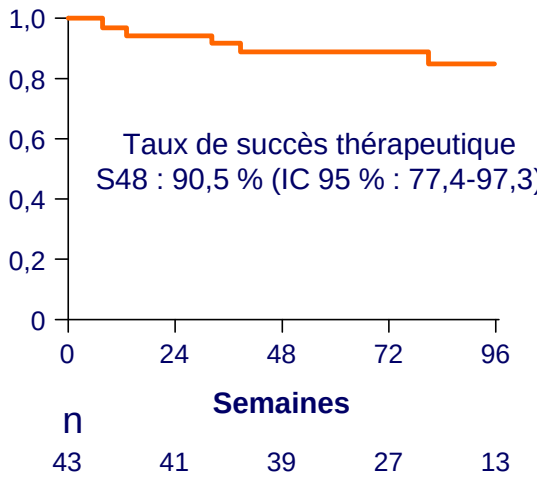
Caractéristiques des patients (n = 43)	
Age médian (IQR), ans	53 (48-58)
Genre masculin, HSH, naissance France	42 %, 56 %, 60 %
Nadir CD4 médian (IQR)	236/mm^3 (102-433)
Durée ARV, durée suppression médiane (IQR)	15 ans (8-23), 6 ans (2-9)
GSS = 3, GSS = 2, n (%)	25 (86), 4* (14)
Virémie résiduelle détectable (1-20 c/ml), n (%)	16 (42)
CD4/mm^3 (IQR), CD4/CD8 (IQR)	607 (485-875), 0,91 (0,72-1,36)
Tt précédent : 3DR 7j/7, 3DR 4 ou 5 j/7, 2DR 7j/7	33 %, 60 %, 7 %
Fréquence intermittence 4 j/7, 5 j/7; n (%)	36 (84), 7(16)

* Ces 4 patients avaient un antécédent de mutation M184V/I

Probabilité de maintenir le succès virologique



Probabilité de maintenir le succès thérapeutique



- **Suivi médian** : 78 semaines (IQR = 62-97)
- **Un échec virologique** à S38 (CV 61 et 76 c/ml sans notion de mauvaise observance, sans résistance sur TI à l'inclusion, sans émergence de résistance et CV < 50 c/ml après reprise BIC/FTC/TAF
- **5 arrêts de la stratégie pour EI** (hépatite cytolytique n = 2, troubles neuropsychiques n = 2, ostéoporose n = 1), 2 décès (COVID-19, IdM) et 1 perdu de vue (prison)
- **Pas de changement significatif des CD4, du rapport CD4/CD8, des virémies résiduelles** au cours du suivi

Palich R, AIDS 2022, Abs. EPB167

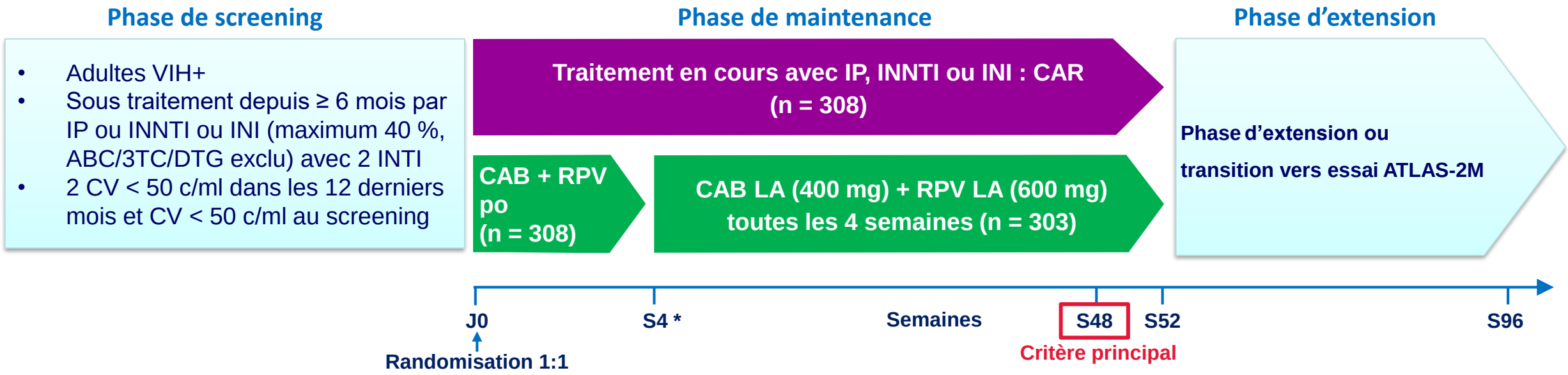
Nouveau mode d’administration

Le Long acting

- CAB-RPV
  - Efficacité? Réservoir?
  - Tolérance?
  - Etude de vraie vie, ressenti des patients et des docteurs

Essai ATLAS : CAB LA + RPV LA en maintenance - Résultats à S48 (1)

- Essai international de phase 3, randomisé en ouvert, de non infériorité



* S4 dose de charge CAB LA 600 mg + RPV LA 900 mg

- **Critère principal de jugement**
  - % CV ≥ 50 c/ml à S48 (Snapshot), borne de non infériorité : 6 %

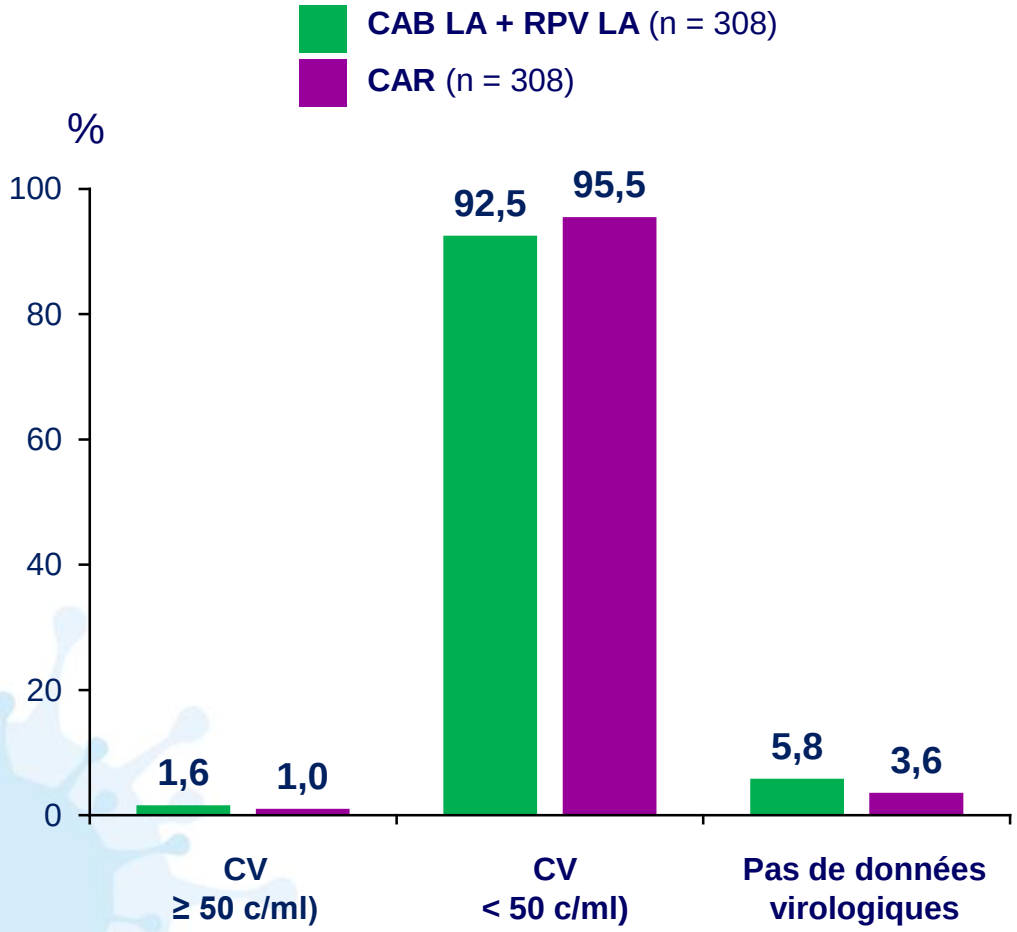
- **Critères secondaires**
  - % CV < 50 c/ml à S48 (Snapshot)
  - Tolérance
  - Résistance associée à échec virologique confirmé (2 CV consécutives ≥ 200 c/ml)
  - Questionnaire de satisfaction et préférence

Swindells S, CROI 2019, Abs. 139

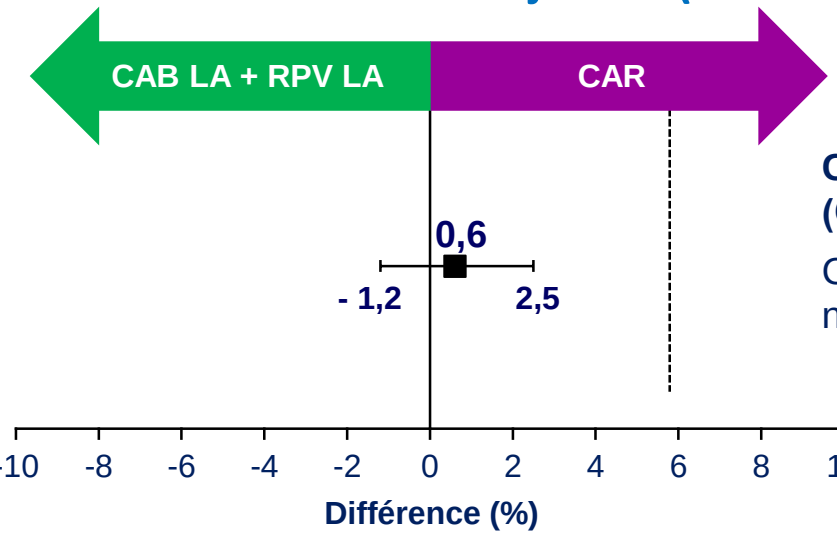
le meilleur ...de CROI 2019

Essai ATLAS : CAB LA + RPV LA en maintenance - Résultats à S48 (3)

CV à S48 (analyse ITT, snapshot)

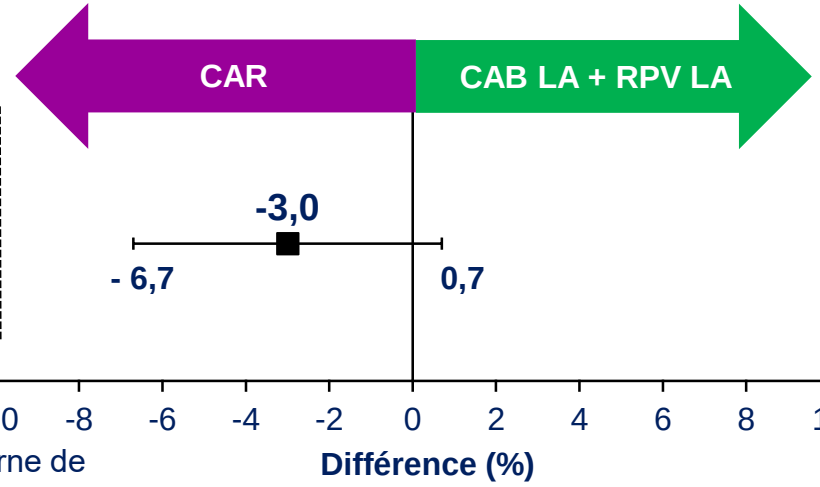


Différence ajustée (IC 95 %)



Critère principal (CV ≥ 50 c/ml à S48)

CAB LA + RPV LA non inférieur à CAR



Critère secondaire (CV< 50 c/ml à S48)

CAB LA + RPV LA non inférieur à CAR

−10 % borne de non infériorité

Swindells S, CROI 2019, Abs. 139

JOURNAL ARTICLE CORRECTED PROOF

Human Immunodeficiency Virus Type 1 RNA Levels in Rectal and Seminal Compartments After Switching to Long-Acting Cabotegravir Plus Rilpivirine: A Longitudinal Study

Get access

Mar Masiá, Marta Fernández-González, Vanesa Agulló, Paula Mascarell, Sergio Padilla, Javier García-Abellán, Félix Gutiérrez

Clinical Infectious Diseases, ciac676, https://doi.org/10.1093/cid/ciac676

Published: 20 August 2022 **Article history**

- Inclusion de 12 patients contrôlés switch vers CAB-RPV ou poursuite ABC-3TC-DGV
- Mesure de la dynamique ARN VIH au niveau rectal et liquide séminal

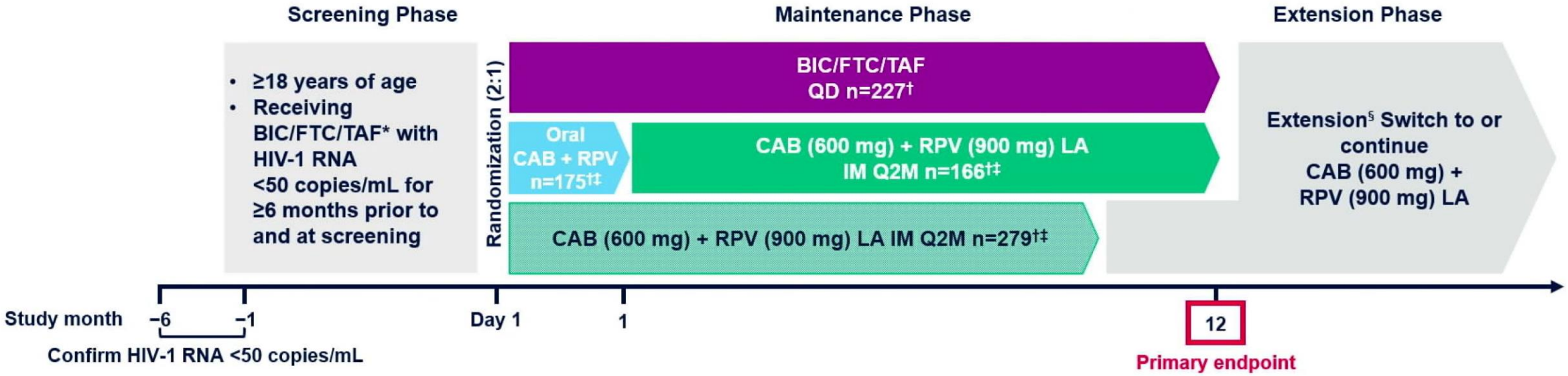
Résultats

- Maintien de la suppression virale dans les compartiments rectaux et seminal comparable,
- blips aussi frequent avec les 2 régimes de traitement

Masia M, Clin Infect Dis 2023 Feb 8;76(3):e748-e751

SOLAR Study Design

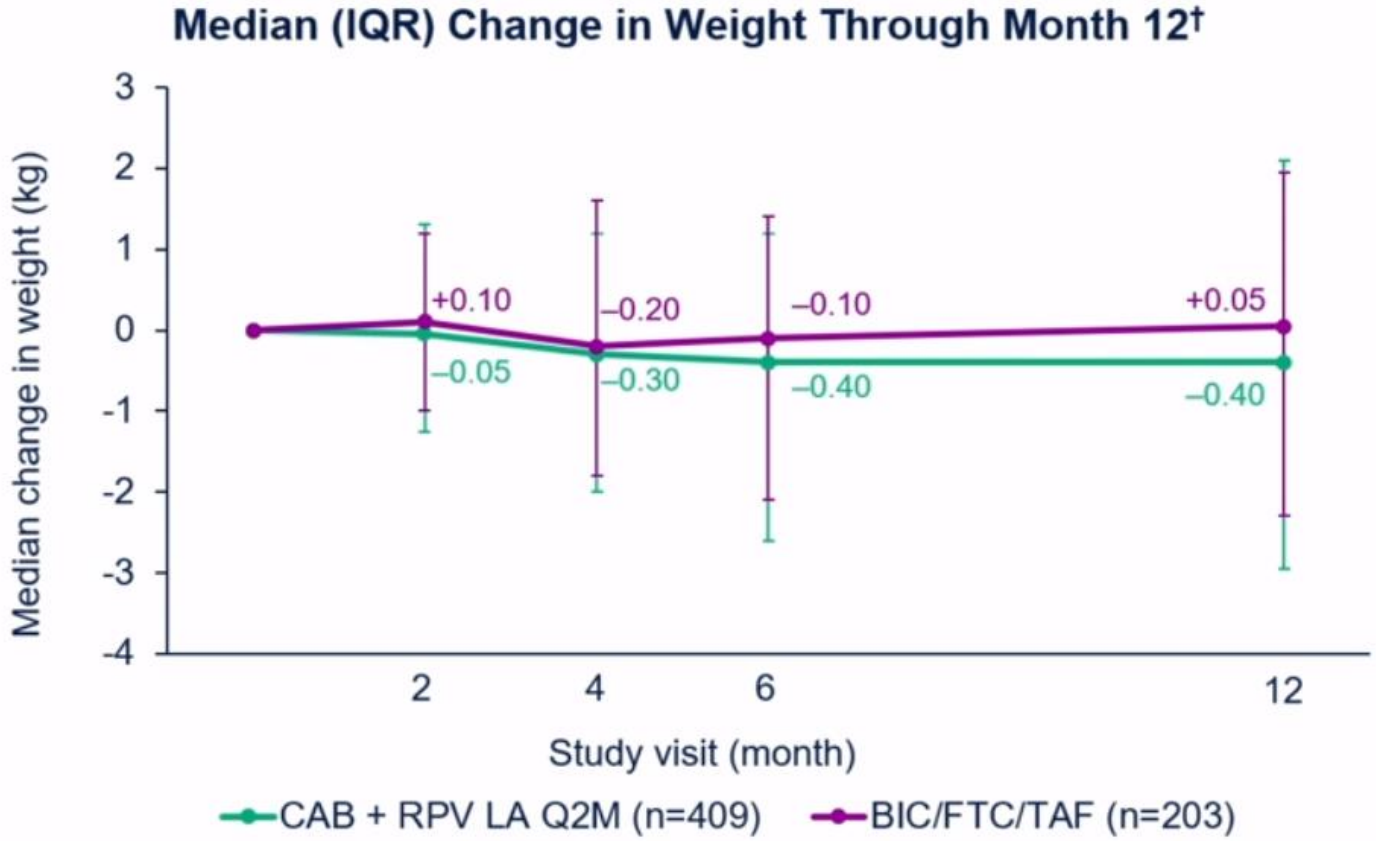
Phase 3b, Randomized (2:1), Open-Label, Active-Controlled, Multicenter, Parallel-Group, Noninferiority Study



*A single prior INI regimen is allowed if BIC/FTC/TAF is a second-line regimen 6 months prior to screening. Any prior change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must not have been done for treatment failure (HIV-1 RNA ≥400 copies/mL).
†n values are based on the safety population.
‡Participants randomized to the LA arm were offered an optional OLI; the decision was determined by the participants following informed consent discussions with the investigator.
§The extension phase will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur Q2M.
IM, intramuscular; LA, long-acting; OD, once daily; OLI, oral lead-in; Q2M, every 2 months.

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

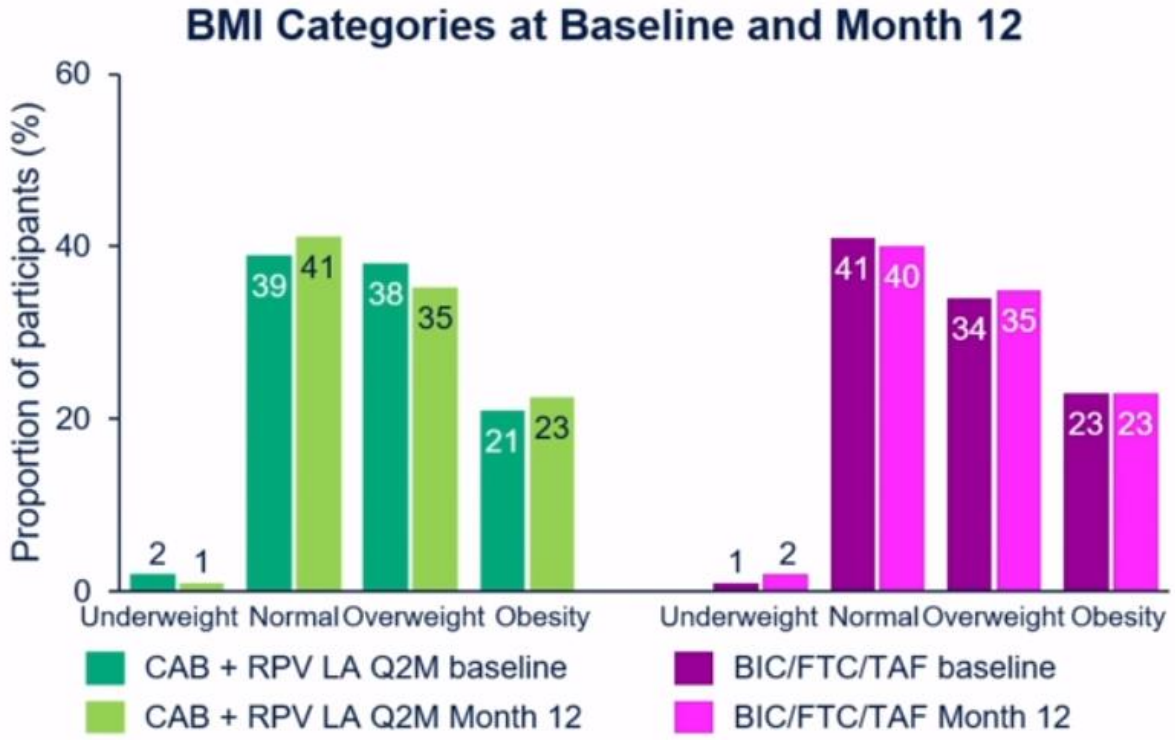
Change in Weight Through Month 12 by Treatment Regimen*

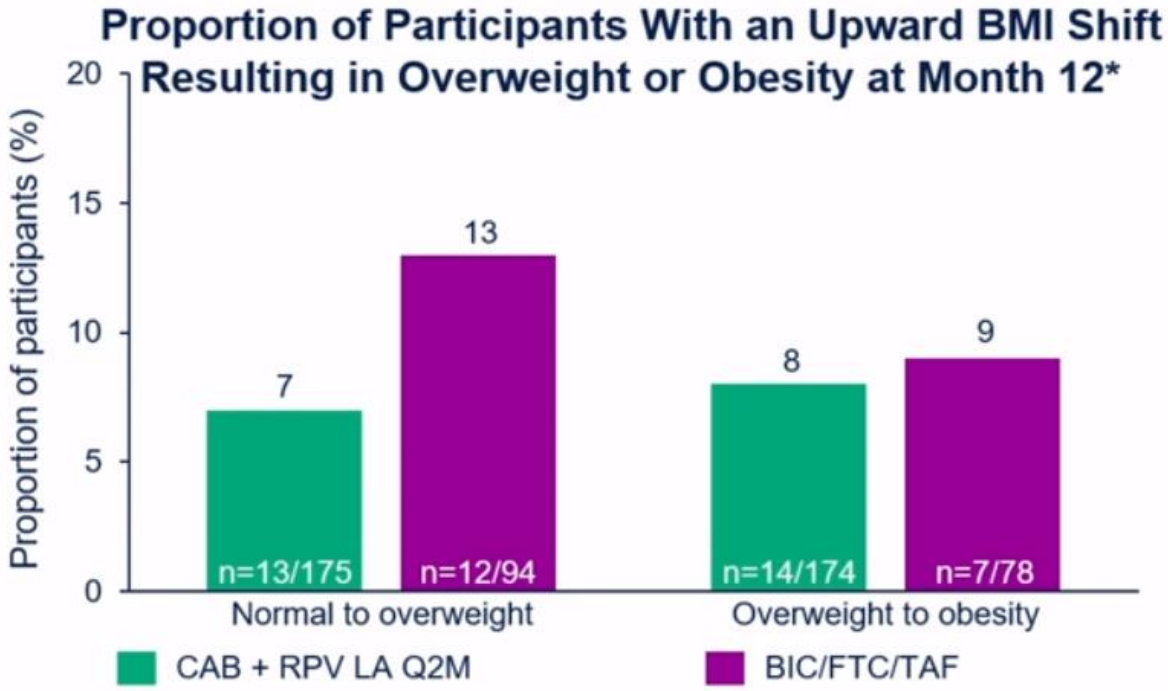


- At Month 12, median (IQR) change in weight in the BIC/FTC/TAF group was +0.05 (-2.30, +1.95) kg and in the CAB + RPV LA group was -0.40 (-2.95, +2.10) kg

*Any participant that started lipid-modifying agents during the study was non-evaluable in anthropometric assessments. †Median (IQR) weight (kg) at baseline: CAB + RPV LA, 81.3 (70.70, 91.80); BIC/FTC/TAF, 79.0 (69.40, 91.70).

Change in BMI Through Month 12 by Treatment Regimen

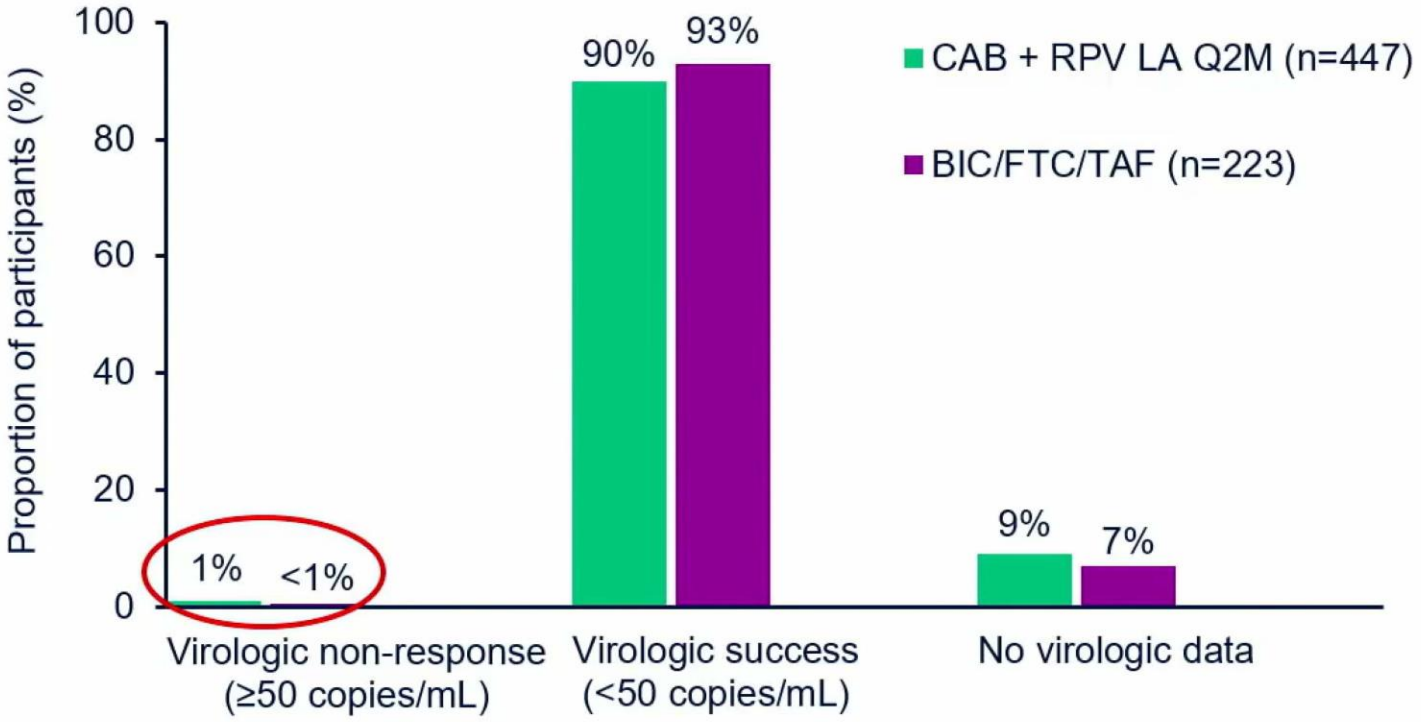


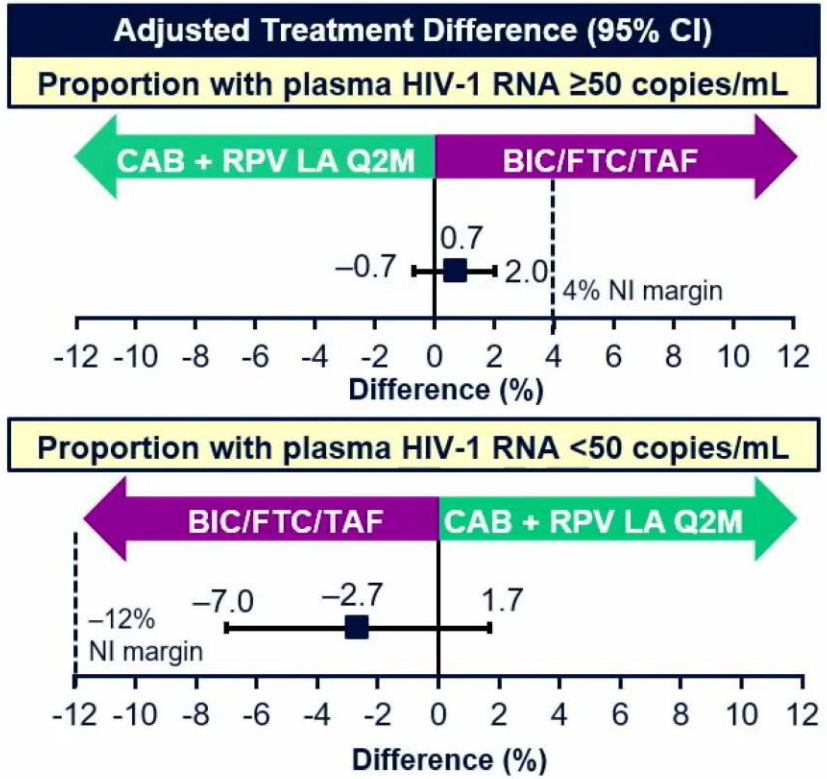


- Overall, the proportion of individuals in BMI categories remained similar at Month 12

*No participant shifted from normal to obesity or underweight to overweight.

Virologic Outcomes at Month 12 (mITT-E Population)





- At Month 12, CAB + RPV LA demonstrated noninferior efficacy compared with BIC/FTC/TAF for the proportion of participants with HIV-1 RNA ≥50 copies/mL and <50 copies/mL in the mITT-E, ITT-E, and per-protocol populations*

*In the ITT-E population, 89% (n=406/454) and 93% (n=211/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL; adjusted treatment difference [95% CI], –3.5% [–7.9, 0.9]), 1% (n=6/454) and <1% (n=1/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV-1 RNA ≥50 copies/mL; adjusted treatment difference [95% CI], 0.9% [–0.5, 2.2]), and 9% (n=42/454) and 7% (n=15/227) of participants receiving LA and BIC/FTC/TAF had no virologic data, respectively. In the per protocol population, 91% (n=394/433) and 93% (n=203/218) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL; adjusted treatment difference [95% CI], –2.1% [–6.4, 2.2]), <1% (n=4/433) and <1% (n=1/218) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV ≥50 copies/mL; adjusted treatment difference [95% CI], 0.5 [–0.8, 1.7]). ITT-E, intention-to-treat exposed; mITT-E, modified intention-to-treat exposed; NI, noninferiority.

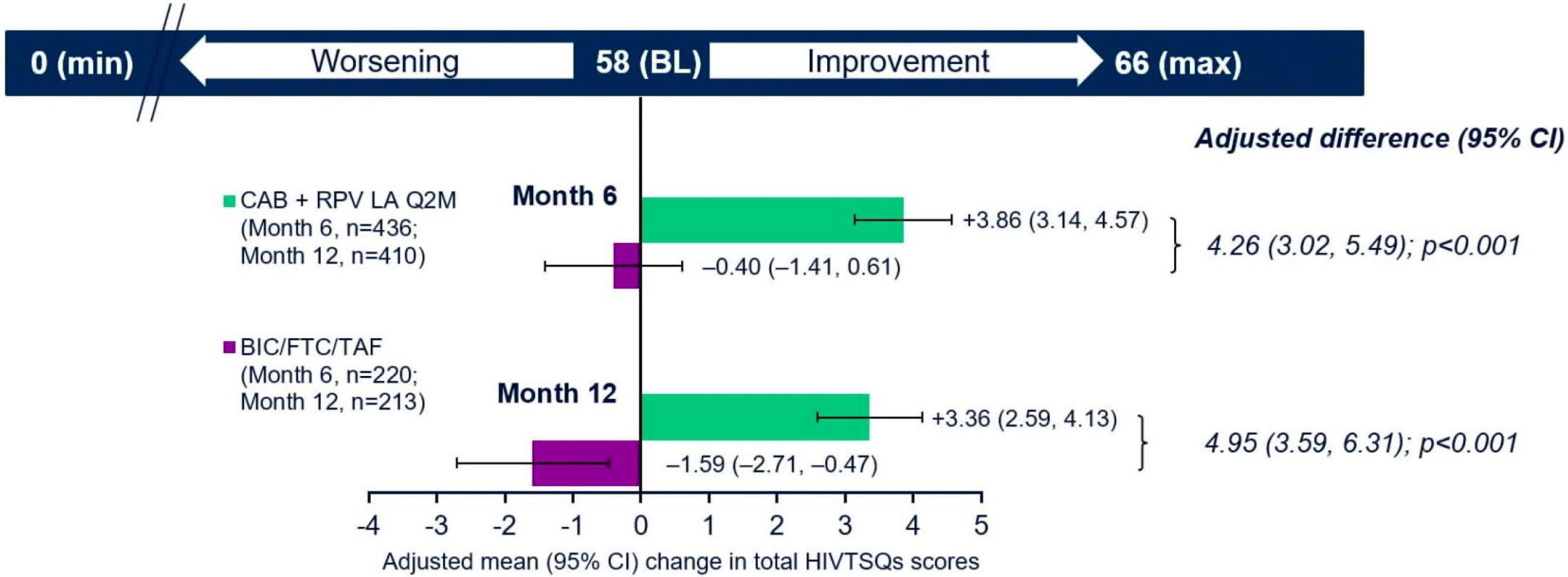
Participants With Confirmed Virologic Failure (CVF)

Participants With CVF in the mITT-E Population									
Sex at birth, country	**Baseline BMI (kg/m^2)**	**HIV-1 subtype at baseline**	**Viral load at SVF/CVF (copies/mL)**	**RPV RAMs observed at baseline (proviral DNA)**	**INI RAMs observed at baseline (proviral DNA)**	**RPV RAMs observed at failure (viral RNA)**	**INI RAMs observed at failure (viral RNA)**	**Phenotypic resistance (fold-change) to RPV/CAB**	**SVF timepoint (month)**
Male, Italy*	21.5	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, Spain†	22.9	AE	6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡									
Male, United States	30.5	C§	3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

- Two (0.4%) participants receiving CAB + RPV LA in the mITT-E population, and one additional participant receiving CAB + RPV LA in the ITT-E population, met the CVF criterion through Month 12
  - Two of the participants had on-treatment RPV and/or INI RAMs (genotyping for third participant failed at baseline)
- No participants in the BIC/FTC/TAF arm met the CVF criterion through Month 12

*Prior to enrolling in the study, the participant received BIC/FTC/TAF, and after discontinuation re-suppressed on darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. †Prior to enrolling in the study, the participant had received abacavir/dolutegravir/lamivudine and BIC/FTC/TAF; they re-suppressed on BIC/FTC/TAF and darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. The participant did not continue in the long-term follow-up phase. ‡Prior to enrolling in the study, the participant had received prohibited prior ART with at least three prior INI regimens; they re-suppressed on BIC/FTC/TAF during long-term follow-up. This participant was excluded from the mITT-E population due to significant and persistent non-compliance to protocol entry requirements at the study site. §Participant had HIV-1 subtype C at Month 3. Baseline analysis failed.
ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NA, not available; RAM, resistance-associated mutation; SVF, suspected virologic failure.

Treatment Satisfaction



- Mean adjusted HIVTSQs scores improved significantly for CAB + RPV LA vs. BIC/FTC/TAF participants from baseline (LA, 57.88; BIC/FTC/TAF, 58.38) to Month 6 (LA, +3.86; BIC/FTC/TAF, –0.40) and Month 12 (LA, +3.36; BIC/FTC/TAF, –1.59) demonstrating greater improvement from baseline in HIV treatment satisfaction for participants receiving CAB + RPV LA compared with BIC/FTC/TAF

HIVTSQs, HIV Treatment Satisfaction Questionnaire status version.

CAB + RPV LA : prédiction des échecs virologiques à S152 (3)

Echec virologique confirmé
Analyse multivariée incluant seulement les facteurs à l'inclusion

	Risque relatif incidence ajusté (IC 95 %) [p], (n = 1 363)
Mutations de résistance à RPV : Oui/Non	21,7 (5,80-80,8) [< 0,0001]
Sous-type VIH-1 A6/A1 : Oui/Non	12,9 (4,42–37,5) [< 0,0001]
IMC à l'inclusion (kg/m^2) : par une unité supplémentaire *	1,09 (1,00-1,19) [0,0447]

* Pour IMC ≥ 30 kg/m² : RRI = 3,97 (p = 0,001)

- Le schéma d'administration (Q4S ou Q8S) et la mutation L74I ne sortent pas dans le modèle

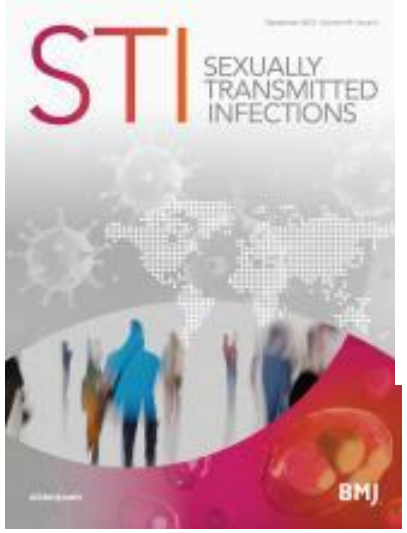
Nombre de facteurs de risque et échec / CV < 50 c/ml

	Echec virologique confirmé, n (%)	CV < 50 c/ml, n (%)
Aucun facteur	4/970 (0,4%)	844/970 (87,0%)
1 seul facteur	8/404 (2,0%)	343/404 (84,9%)
≥ 2 facteurs	11/57 (19,3%)	44/57 (77,2%)
Total	23/1431 (1,6%)	1231/1431 (86,0%)

Bonne sensibilité et spécificité de la présence de ≥ 2 facteurs

	VPP	VPN	Sensibilité	Spécificité
≥ 2 facteurs	19,3%	99,1%	47,8%	96,7%
1 facteur, quel qu'il soit	2,0%	98,5%	34,8%	71,9%

Orkin C, HIV Glasgow 2022, Abs. 044



- 120 médecins Allemagne, Italie, Royaume uni, France
- 688 PVVIH
- Intérêt d'un TT coût efficace LA vs TT journalier

CHU Poitiers

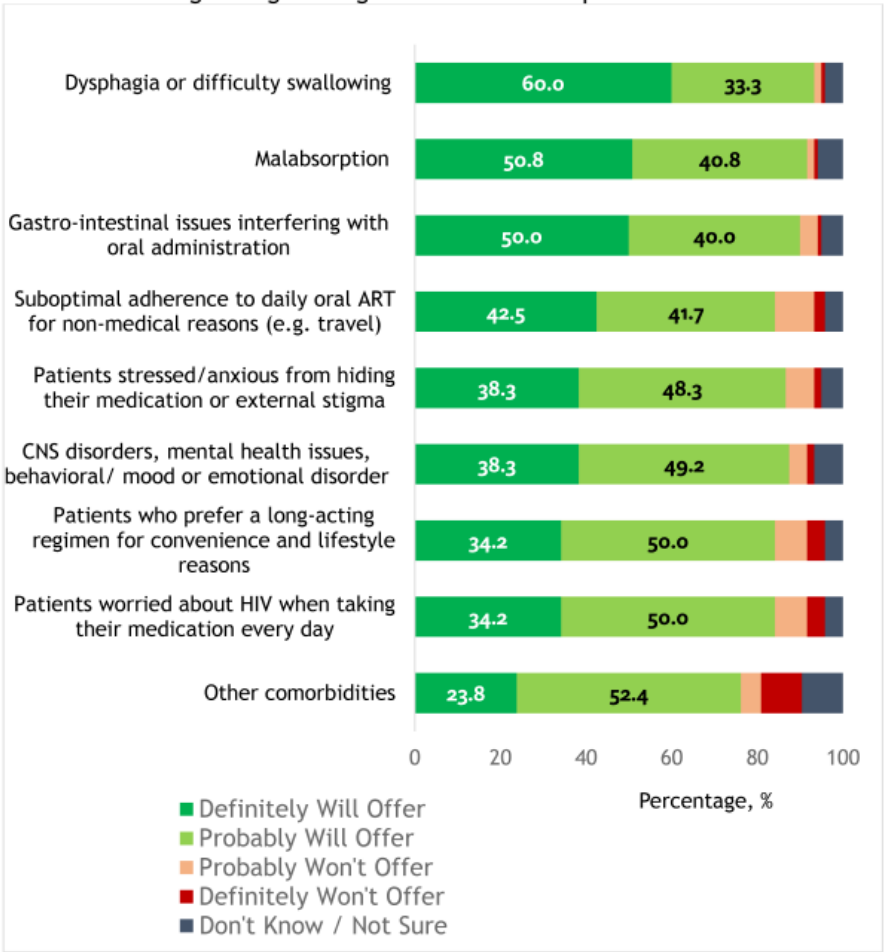
Clinical

Original research

Factors associated with interest in a long-acting HIV regimen: perspectives of people living with HIV and healthcare providers in four European countries

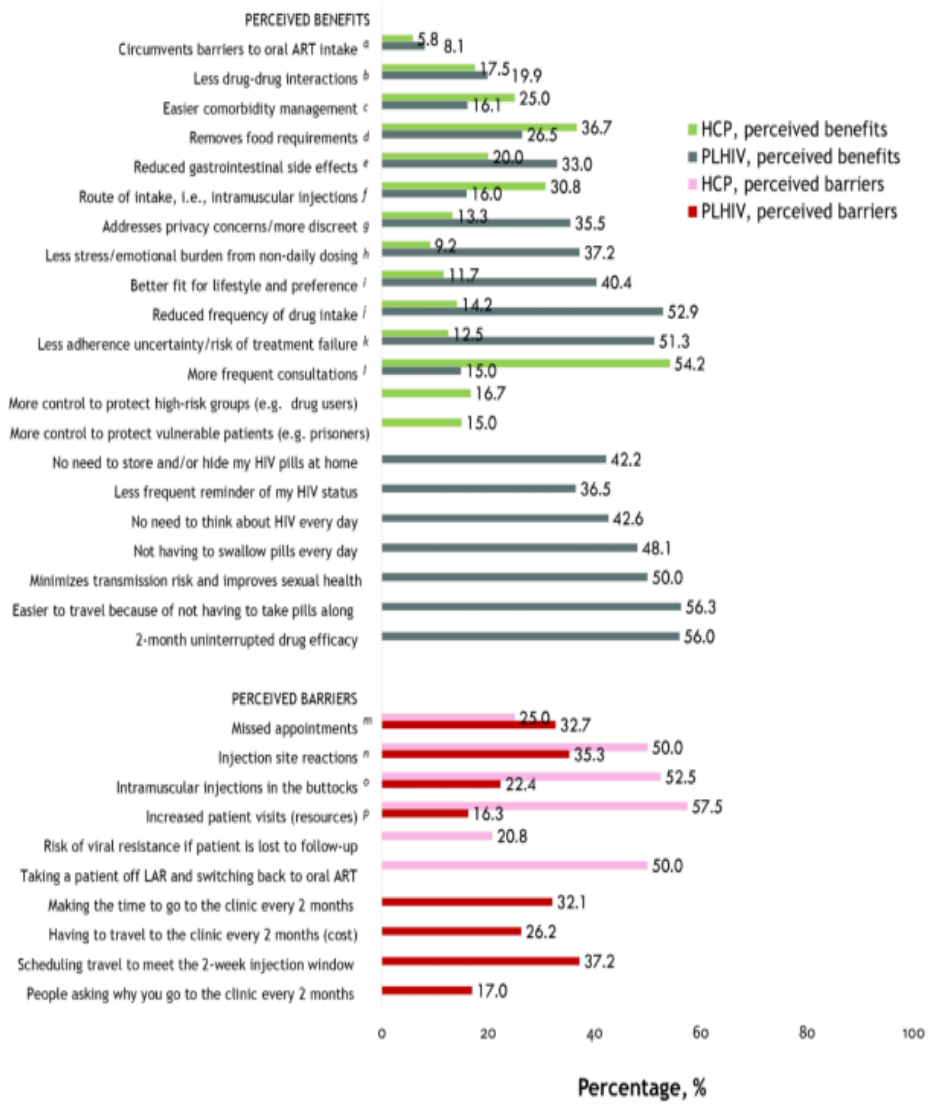
Babatunde Akinwunmi [1], Daniel Buchenberger,[2] Jenny Scherzer,[3] Martina Bode,[3] Paolo Rizzini,[3] Fabio Vecchio,[3] Laetitia Roustand,[4] Gaelle Nachbaur,[4] Laurent Finkielsztejn,[3] Vasiliki Chounta,[3] Nicolas Van de Velde[5]

Supplemental Figure 2. Degree of willingness among HIV physicians to offer a novel long-acting HIV regimen to their HIV+ patients



Note: ART = antiretroviral therapy.

Supplemental Figure 1. Comparison of perceived benefits and concerns regarding the new treatment among HIV physicians and people living with HIV, 2019



Note. Not all perceived benefits or barriers were assessed in both surveys (depending on relevance to the target population). HCP = Healthcare provider; PLHIV = People Living with HIV.

Et en vraie vie?

- Quelques interrogations

AIDS
Articles & Issues For Authors Journal Info

CONCISE COMMUNICATION (CLINICAL)

Single center experience evaluating and initiating people with HIV on long-acting cabotegravir/rilpivirine

Hill, Lucas A.; Abulhosn, Kari K.; Yin, Jeffrey F.; Bamford, Laura P.

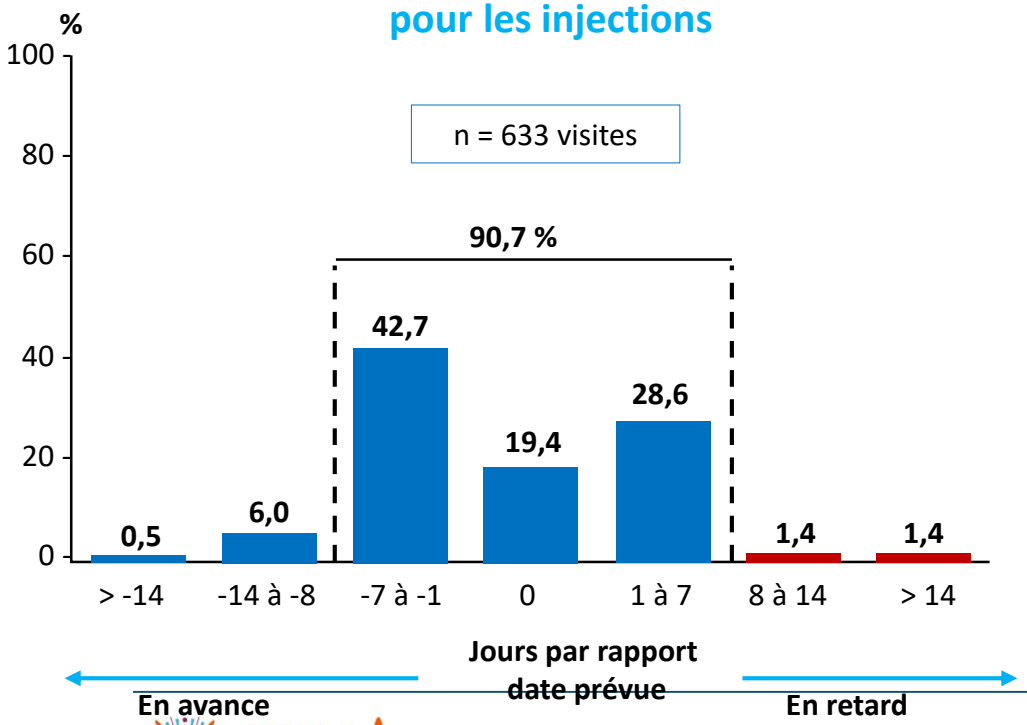
- Objectif : décrire l'expérience d'initiation d'un LA et facteurs associés pour débuter ou non ce type de traitement
- Méthodes :
  - étude rétrospective monocentrique (San Diego)
  - Inclusion de tous les patients intéressés par LA entre 04/21 et 06/22
  - Et qui ont décidés de débuter un traitement par LA
- Résultats :
  - 383 patients inclus et 202 (52,5%) ont vraiment débutés LA
  - Plus jeunes (p=0,02) et plus sous bitherapie ou INI 1ère génération
  - Raisons pour ne pas démarrer
    - Fréquentation irrégulière du service ou difficulté pour être contacté
    - Choix du patient finalement de ne pas débuter
    - 18,5 % des 135 génotypes sur DNA avaient une mutation impactant la réponse au LA

Hill LA et al. AIDS 2022 Nov 29. doi: 10.1097/QAD.0000000000003446

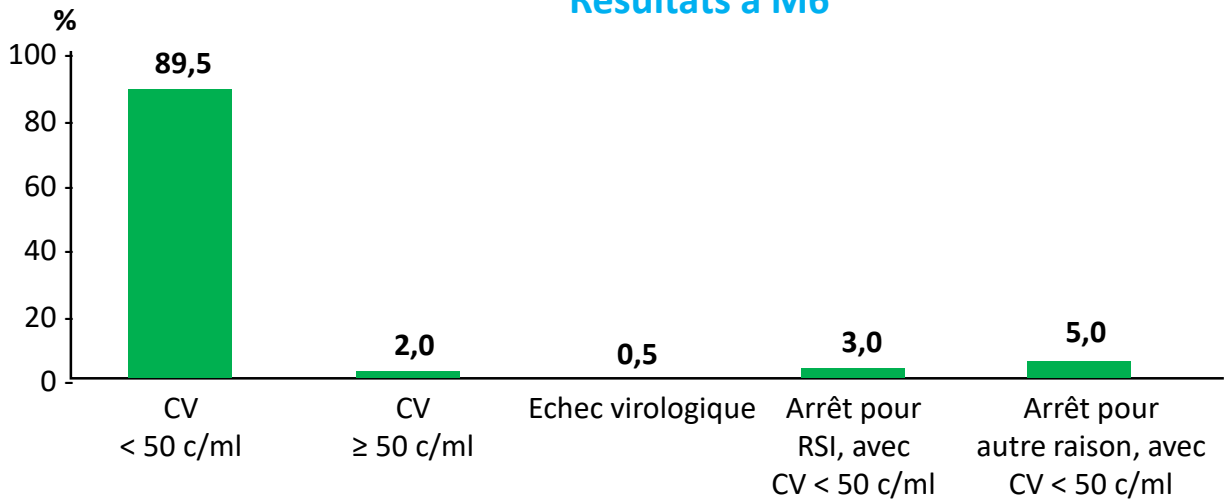
CAB + RPV LA IM : expérience en vie réelle – Allemagne

- Cohorte CARLOS (Allemagne) : étude en vie réelle de CAB + RPV LA IM
- Avril 2021-mai 2022 : 21 centres, 361 patients
- Analyse chez 236 patients (hommes : 95 %)
  - IMC > 30 kg/m^2 : 12 %, sous-type A6/A1 : 2 %, absence de génotype de résistance historique/ récent au switch : 39 %

Observance de la « fenêtre » ± 7 jours pour les injections



Résultats à M6



- 1 échec virologique confirmé : émergence de mutations INI (L74I, T97A, E138K, Q148R, N155H) et INNTI (Y181C) ; sous-type B, IMC = 23 kg/m^2, injections dans la « fenêtre »
- Interruptions : 2 pour EI (céphalées, anxiété), 6 (3 %) pour RSI
- Amélioration significative du score de satisfaction au traitement à M6

Borch J, HIV Glasgow 2022, Abs. O43

Risk factors for low trough levels

- **Cabotegravir:**

Characteristics	M1 cabotegravir trough level			
	< 1120 ng/mL (n=35)	≥ 1120 ng/mL (n=23)	p	p*
Median age, years (IQR)	29 (26 – 34)	31 (28 – 34)	0.7	
Male, n (%)	29 (83)	22 (96)	0.2	
European origin, n (%)	25 (71)	15 (65)	0.8	
Median BMI, kg/m^2 (IQR)	24 (22 – 27)	22 (20 – 25)	**0.01**	**0.009**
No lead-in, n (%)	29 (83)	13 (57)	**0.04**	**0.02**

* Multivariate analysis

Conference on Retroviruses and Opportunistic Infections; February 19-22, 2023; Virtual and Seattle, WA

étude de cohorte prospective, menée sur deux sites hospitaliers de l'APHP

Objectif : identifier des facteurs associés à des concentrations faibles (CAB <1120 ng/mL ou RPV <32 ng/mL)

Résultats :

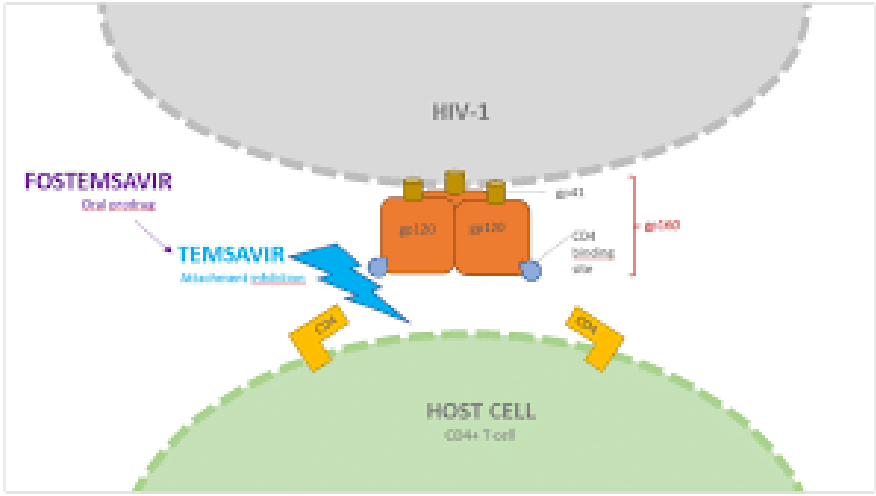
- 58 patients recrutés, HSH, avec en médiane une infection contrôlée depuis 8 ans.
- 1 seul échec chez un homme avec une CV indétectable depuis 2 ans et un IMC à 29, et des concentrations basses
- [CAB] 60% des patients à M1 et 77% à M3 ont des concentrations basses.
- [RPV] les chiffres sont de 28 et 27% respectivement.

Rubenstein E, CROI 2023, Abs. 195

Nouvelles molécules

FOSTEMSAVIR-RUKOBIA®

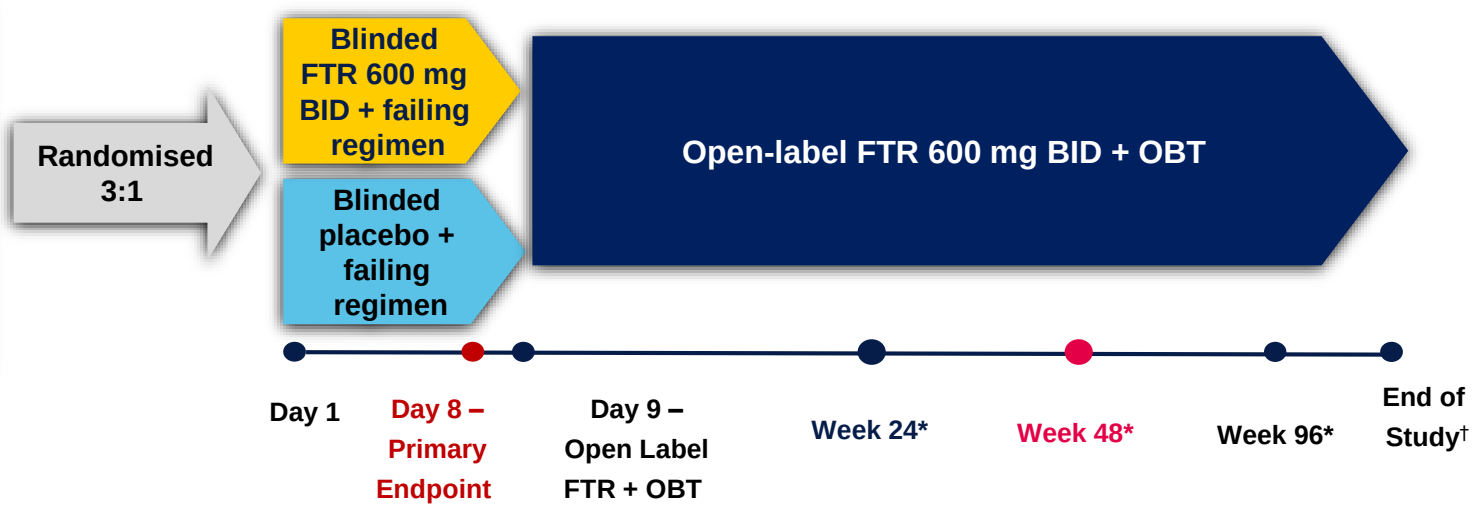
- Prodrogue transformé en TEMSAVIR
  - Fixation sur gp120 (CD4 biding site)
- CRF01AE (Asie SE) et groupe O non sensible
- Actif sur les souches CCR5 et CXCR4
- Pharmaco
  - Pas d'impact de l'alimentation
  - ½ vie 11h ⟶ 2 prises/j
  - Pas d'ajustement de posologie aux IH ou IR (même dialyse)



Phase III Study: Study Design and Endpoints

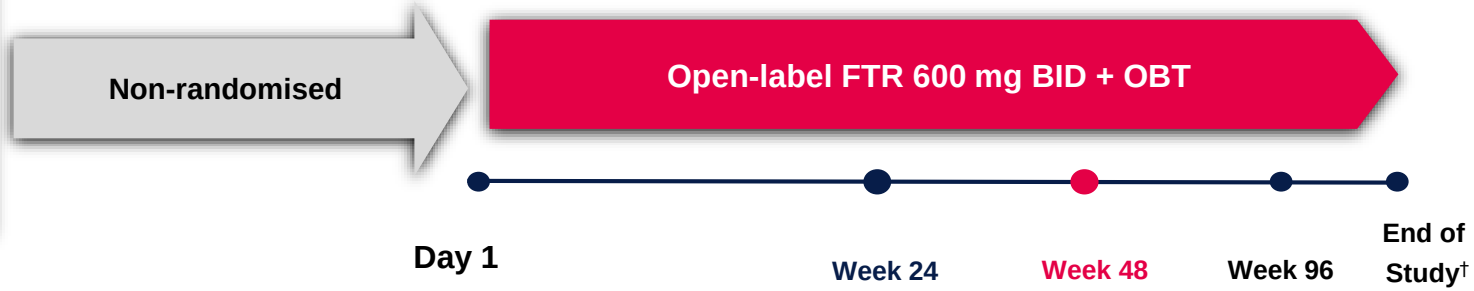
Randomised Cohort [§]**:**
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents



Non-Randomised Cohort [§]**:**
HTE participants, failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 0 ARV classes remaining and no remaining fully active approved agents[‡]



*Measured from the start of open label FTR 600 mg BID + OBT; †The study is expected to be conducted until an additional option, rollover study or marketing approval, is in place; ‡Use of investigational agents as part of OBT was permitted; §There was no screening FTR IC_{50} criteria
BID, twice-daily; OBT, Optimised Background Therapy

Kozal et al. NEJM 2020; 382: 1232-43
Lataillade et al LANCET HIV 2020;7:e740-51
Ackerman et al AIDS 2021; 35:1061-1072 ;

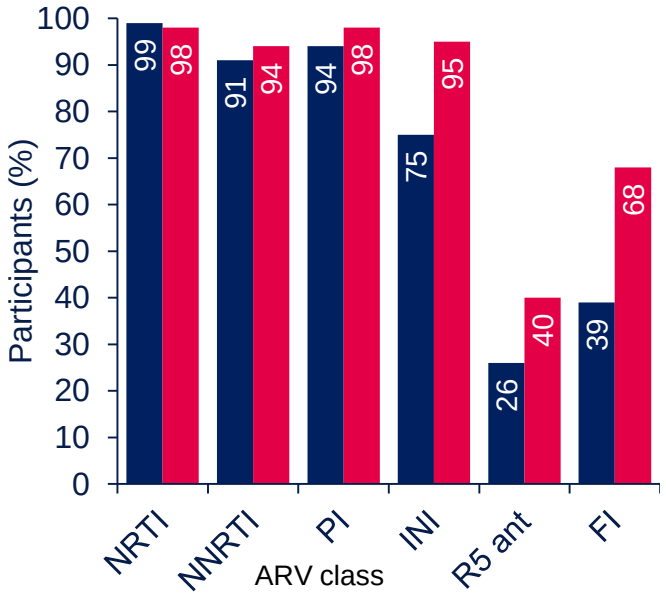
Baseline Characteristics

Parameter	Randomised Cohort		Non-randomised Cohort	
	Placebo BID (N=69)	FTR 600 mg BID (N=203)	FTR 600 mg BID (N=99)	Total Treated Participants (N=371)
Age years, median (range)	45 (19–66)	48 (18–73)	50 (17–72)	49 (17–73)
<50 years, n (%)	46 (67)	116 (57)	44 (44)	206 (56)
Gender, n (%) Male	57 (83)	143 (70)	89 (90)	289 (78)
Race, n (%)				
White	47 (68)	137 (67)	73 (74)	257 (69)
Black/African American	18 (26)	42 (21)	23 (23)	83 (22)
HIV-1 RNA log_{10} c/mL, median (IQR)	4.5 (3.6–5.2)	4.7 (4.0–5.1)	4.3 (3.6–4.8)	4.6 (3.9–5.33
HIV-1 RNA c/mL, n (%)				
<400	7 (10)	14 (7)	5 (5)	26 (7)
400 to <1000	3 (4)	7 (3)	4 (4)	14 (4)
1000 to <100,000	35 (51)	126 (62)	75 (76)	236 (64)
≥100,000	24 (35)	56 (28)	15 (15)	95 (26)
CD4+ T-cells/µL, median (IQR)	100 (23–244)	99 (15–203)	41 (6–161)	80 (11–202)
CD4+ T-cells/µL, n (%)				
<20	17 (25)	55 (27)	40 (40)	112 (30)
20 to <50	6 (9)	19 (9)	14 (14)	39 (11)
50 to <200	26 (38)	76 (37)	25 (25)	127 (34)
200 to <500	16 (23)	42 (21)	18 (18)	76 (20)
≥500	4 (6)	11 (5)	2 (2)	17 (5)

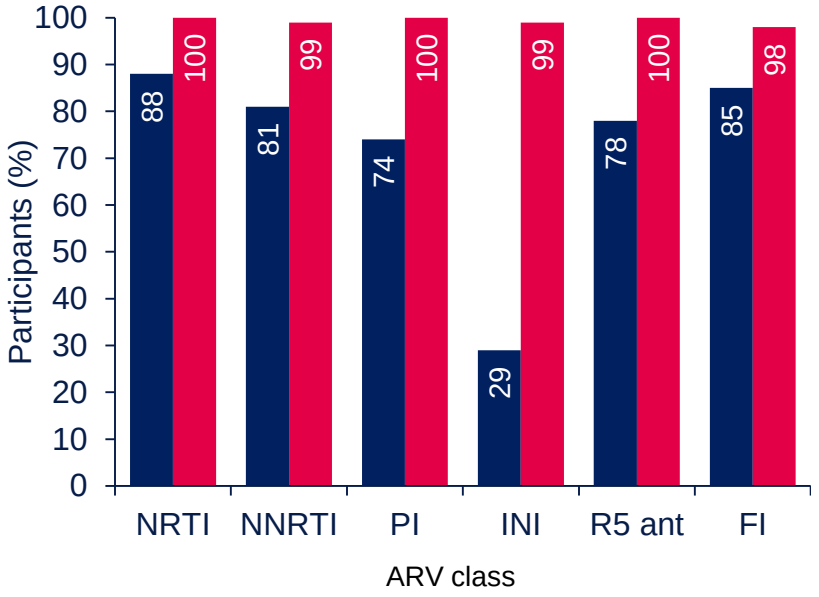
Kozal et al. NEJM 2020; 382: 1232-43
Lataillade et al LANCET HIV 2020;7:e740-51
Ackerman et al AIDS 2021; 35:1061-1072 ;

Baseline Prior ARV Exposure and Resistance

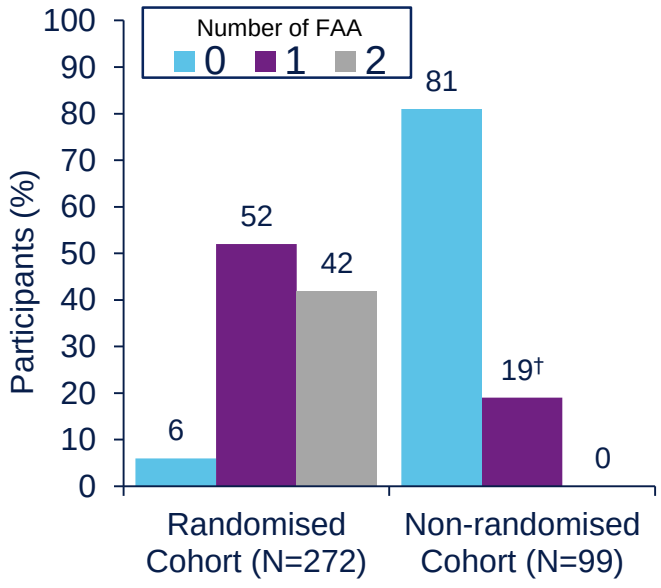
Prior exposure to ARV classes



ARV classes exhausted at baseline*



Fully Active and Available ARV (FAA) in initial OBT



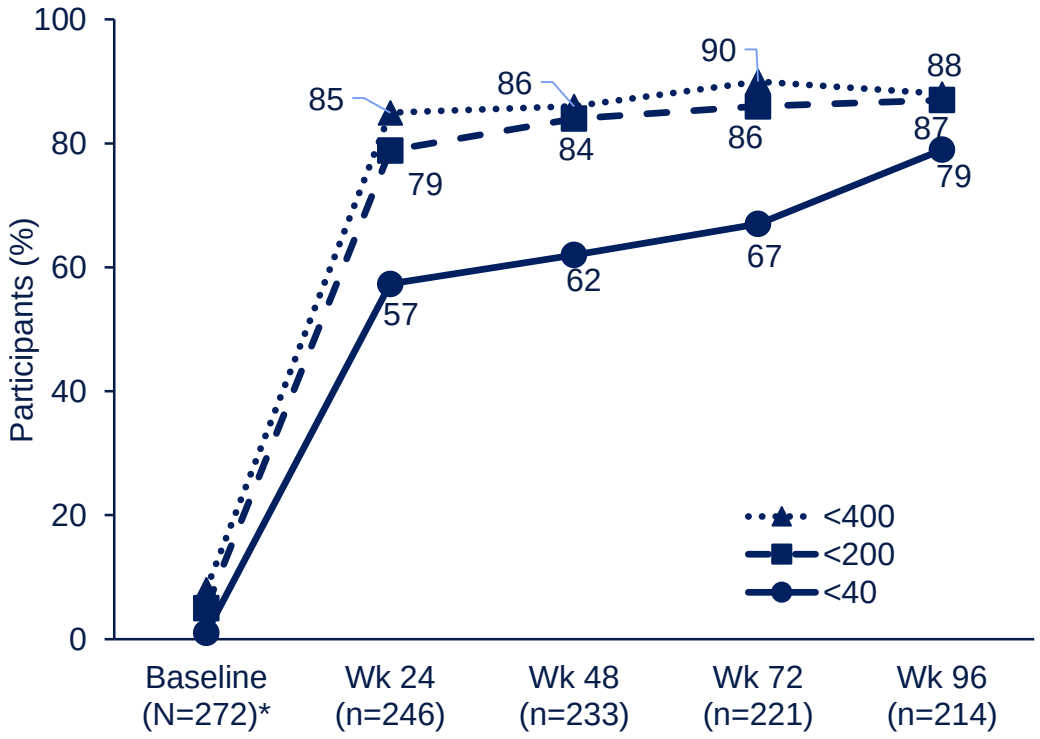
Randomised Cohort (N=272) Non-randomised Cohort (N=99)

*Proportions of participants for whom there are no remaining FAAs within the indicated ARV class, based on Monogram assays (PhenoSense® GT Plus Integrase, Trofile®, and PhenoSense® Entry), historical resistance, eligibility, and tolerability. †15/19 received investigational ARV ibalizumab and 4/19 were incorrectly assigned to the Non-randomised Cohort
FAA, fully active and Available ARV; FI, fusion inhibitor; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; R5 ant, CCR5 antagonist

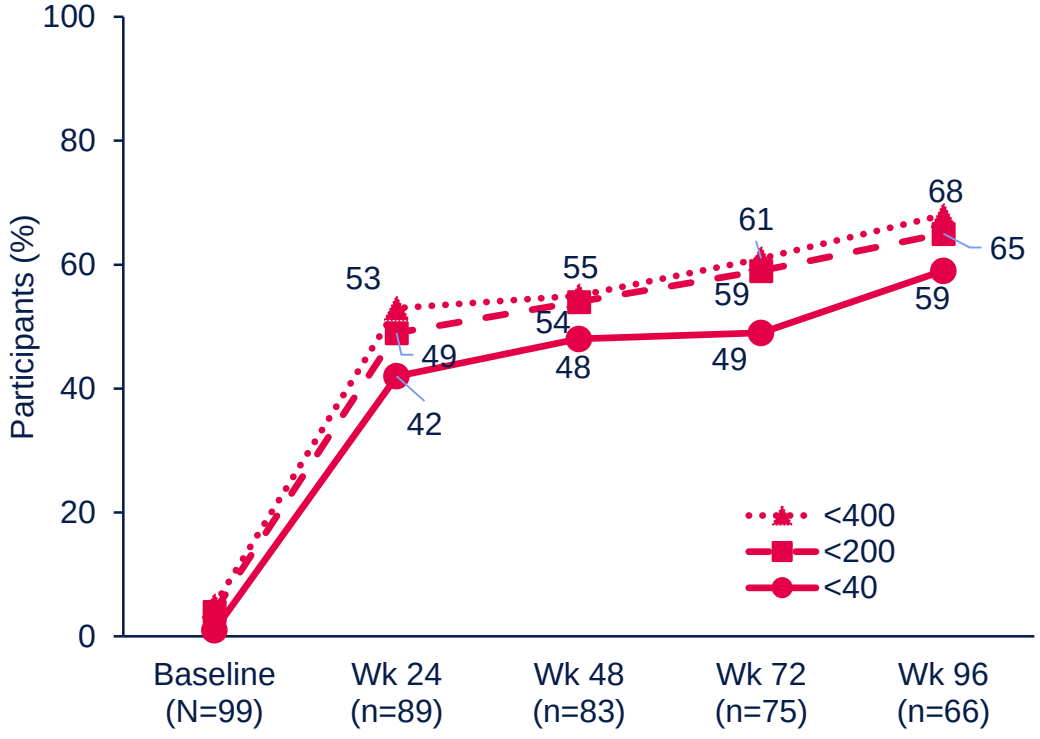
Kozal et al. NEJM 2020; 382: 1232-43
Lataillade et al LANCET HIV 2020;7:e740-51
Ackerman et al AIDS 2021; 35:1061-1072 ;

Virologic Response Over Time- Observed Analysis

Randomized Cohort (N=272)



Non-randomized Cohort (N=99)

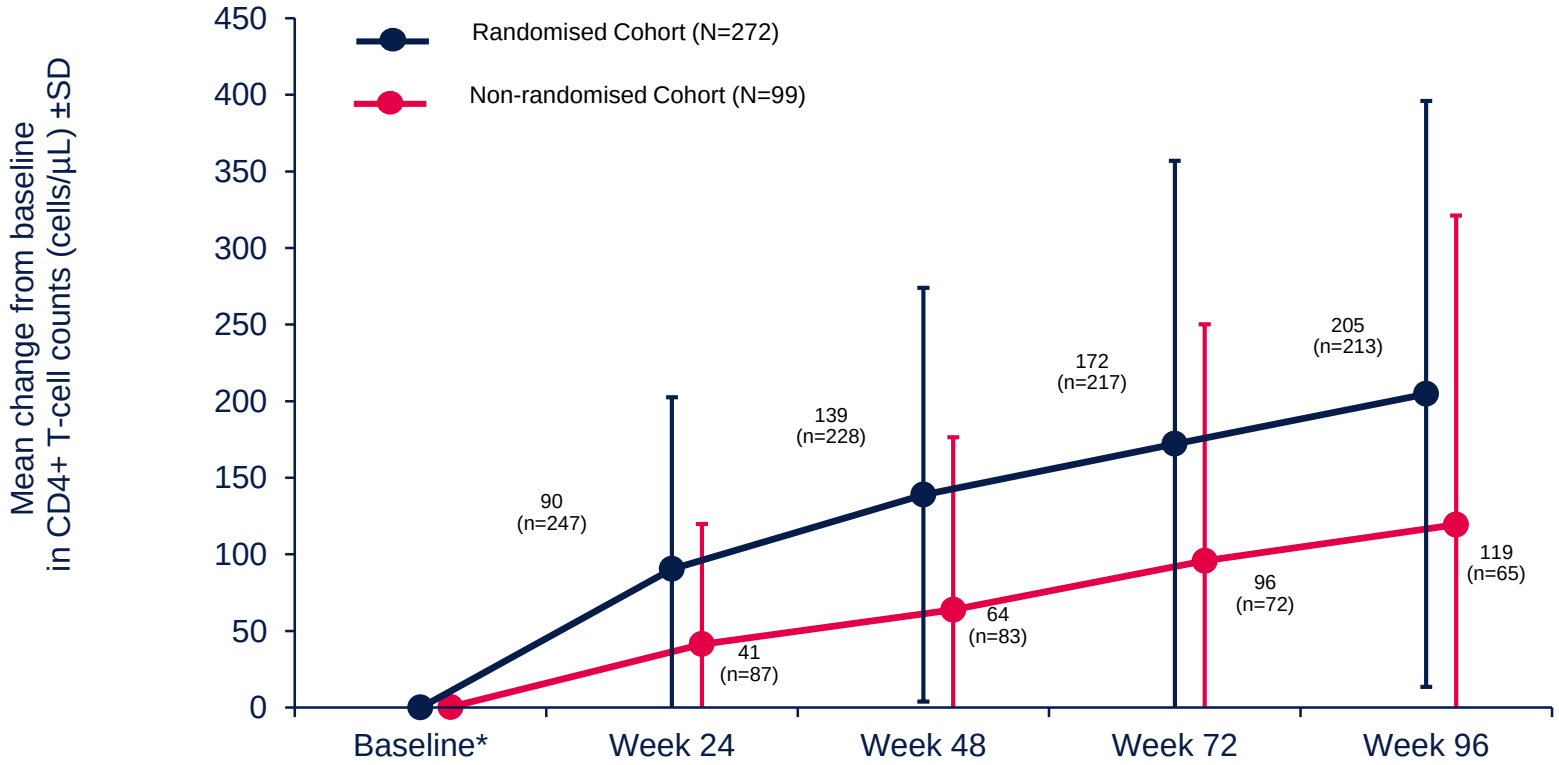


*At baseline 8 participants had HIV-1 RNA <400 copies/mL, 5 had HIV-1 RNA <200 copies/mL, and 1 had HIV-1 RNA <40 copies/mL.
†At baseline 5 participants had HIV-1 RNA <400 copies/mL, 4 had HIV-1 RNA <200 copies/mL, and 1 had HIV-1 RNA <40 copies/mL.

Lataillade et al LANCET HIV 2020;7:e740-51

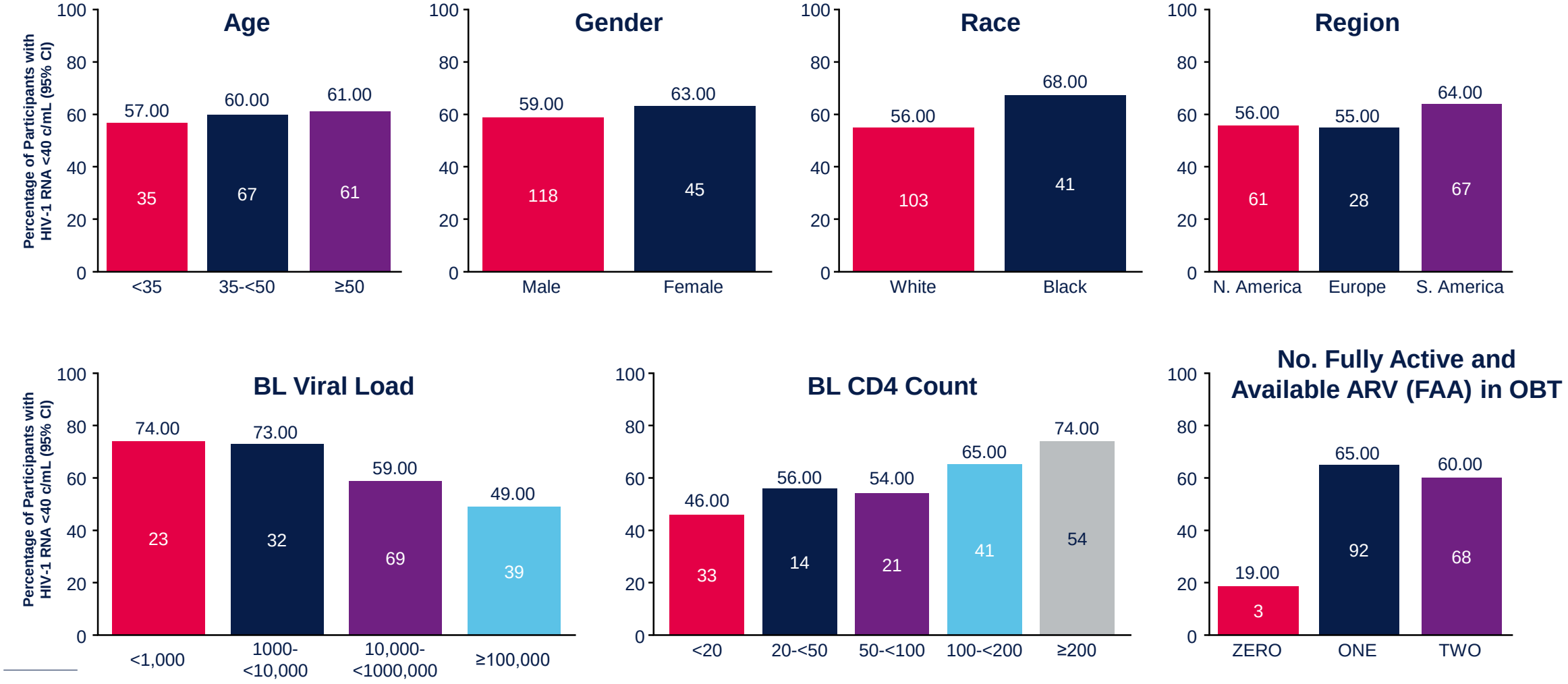
Mean Change in CD4 Count Over Time- Observed Analysis

- Mean Baseline CD4+ T-cell count for Randomized Cohort was 153 cells/µL and 99 cells/µL for Non-Randomized subjects



Lataillade et al LANCET HIV 2020;7:e740-51

Virologic Response* (HIV-1 RNA <40 c/mL) at Week 96 by Subgroup: Randomized Cohort



*Response by FDA Snapshot (ITT) analysis where change in OBT= failure
FAA, Fully Active and Available ARV

Lataillade et al LANCET HIV 2020;7:e740-51

Serious Adverse Events

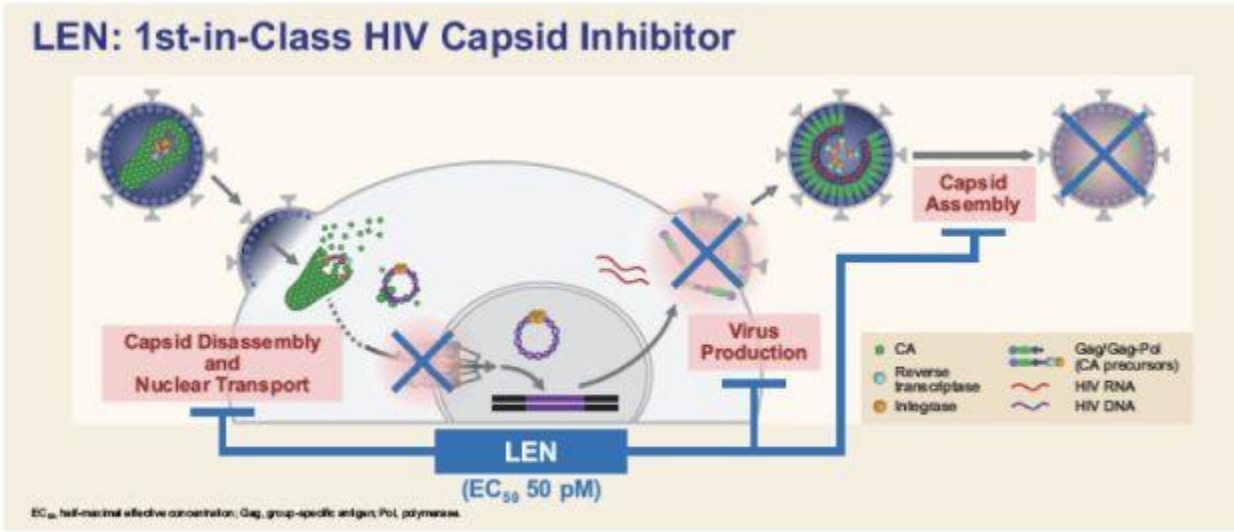
- 38% (n= 140) of subjects experienced at least one SAE through the W96 data lock (34% and 48% in the Randomized and Non-randomized Cohorts, respectively)
- SAEs were most commonly from the Infections/Infestations SOC (n= 61; 16%); most related to respiratory infections (pneumonia/bronchitis)
  - Neoplasms second most common SOC (n= 30; 8%)
- Few SAEs led to d/c of study medication (~1% of all SAEs; n=16)
  - Most SAEs leading to d/c secondary to infections (6), followed by neoplasms (4), and liver failure (2)
  - One each secondary to: transaminase elevation, AKI, respiratory failure (on PBO), rhabdomyolysis
- 12 (3%) subjects had SAEs “related” to study medication
  - 3 IRIS cases (neurotoxoplasmosis, CNS lesion, atypical mycobacterial infection)
  - 3 with Renal events (acute renal failure and nephrolithiasis x2)
  - 1 subject each with: disorientation, hepatocellular injury, hyperkalemia, hyperglycemia, IUGR, loss of consciousness, myocarditis, rash, and rhabdomyolysis

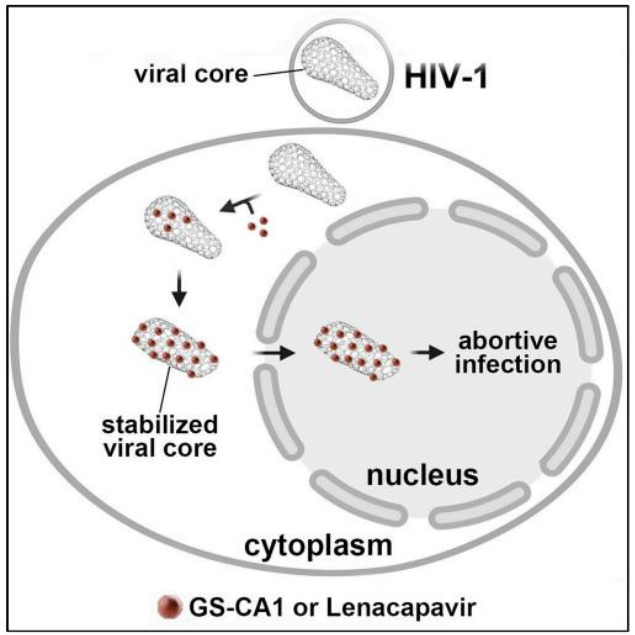
FOSTEMSAVIR bilan

- Molécule de « rescue »
- A associer avec au moins 1 molécule active
- Modalités de prise (2 fois par jour) semblent condamner son développement

LENACAPAVIR Sunlenca®

- Inhibiteur de capside
- Pas de résistance croisée avec les différentes classes d'IE
- Propriétés PK/PD
  - Longue ½ vie
    - 11-13j oral prise hebdomadaire
    - 49-75j sc prise biannuelle
  - Métabolisme hépatique UGT1A1>>CYP3A4
    - Pas d'ajustement de dose en cas d'IH faible/modérée
  - Inhibiteur modéré CYP3A4 et faible de la PgP
  - Grande variabilité inter et intraindividuelle





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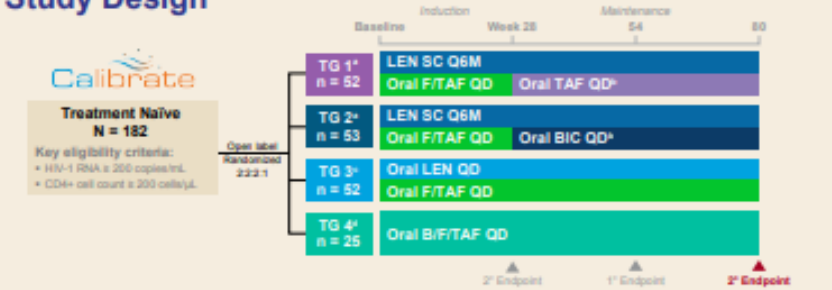
Long-Acting Lenacapavir in a Combination Regimen for Treatment Naïve PWH: Week 80

Debbie Hagins,[1*] Ellen Koenig,[2] Rachel Safran,[3] Lizette Santiago,[4] Michael Wohlfeiler,[5] Chiu-Bin Hsiao,[6] Shan-Yu Liu,[7] Laurie A. VanderVeen,[7] Hadas Dvory-Sobol,[7] Martin S. Rhee,[7] Jared Baeten,[7] Samir Gupta[8]

[1]Chatham County Health Department, Savannah, GA; [2]IDEV: Instituto Dominicano de Estudios Virologicos, Santo Domingo, Dominican Republic; [3]MultiCare Rockwood Internal Medicine & HIV Clinic, Spokane, WA; [4]Hope Clinical Research, Inc., San Juan, PR; [5]AIDS Healthcare Foundation-South Beach, Miami Beach, FL; [6]Allegheny Health Network, Pittsburgh, PA; [7]Gilead Sciences, Inc., Foster City, CA; [8]Indiana University-Purdue University, Indianapolis, IN

*Presenting author

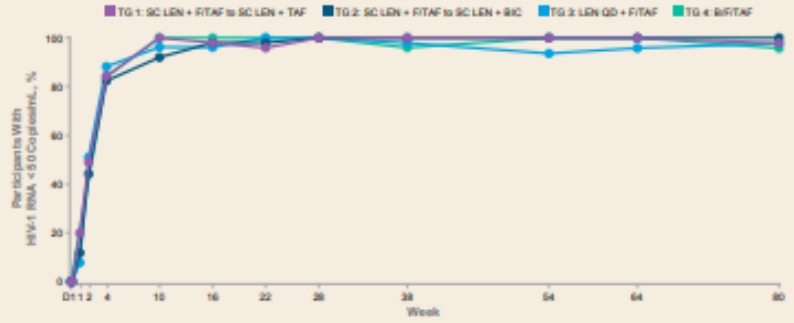
Study Design



[a]LEN PO load-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN 927 mg SC on Day 15; F/TAF 200/25 mg; [b]Participants in treatment groups (TGs) 1 and 2 needed to have HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate TAF 25 mg or BIC 75 mg at Week 28; participants with HIV-1 RNA ≥ 50 copies/mL discontinued study at Week 28; 3 participants (2 in TG 1 and 1 in TG 2) discontinued due to having HIV-1 RNA ≥ 50 copies/mL prior to Week 28; [c]LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; [d]B/F/TAF 50/200/25 mg.

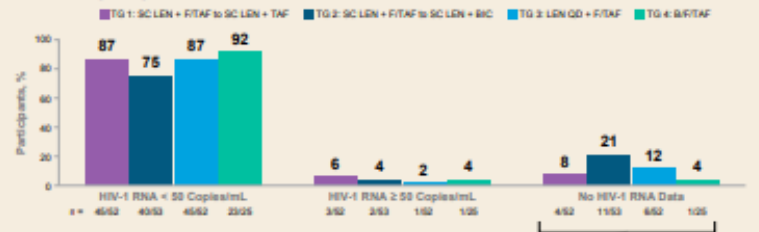
Participants With HIV-1 RNA < 50 Copies/mL by Visit

Missing = Excluded (on Treatment)



	TG 1 n = 46	TG 2 n = 40	TG 3 n = 46	TG 4 n = 25
Participants with HIV-1 RNA < 50 copies/mL, % (n)	98 (45)	100 (40)	98 (45)	96 (23)

Efficacy by FDA Snapshot at Week 80



	TG 1	TG 2	TG 3	TG 4
Discontinued study drug due to AE/death	1 (2)	3 (8)	0	0
Discontinued study drug due to other reason (last available HIV-1 RNA < 50 copies/mL)	2 (4) • 1 investigator's discretion • 1 lost to follow-up	8 (15) • 4 participant decision • 2 investigator's discretion • 2 lost to follow-up	6 (12) • 5 participant decision • 1 lost to follow-up	1 (4) • 1 participant decision
Missing data during window, but on study drug	1 (2)	0	0	0

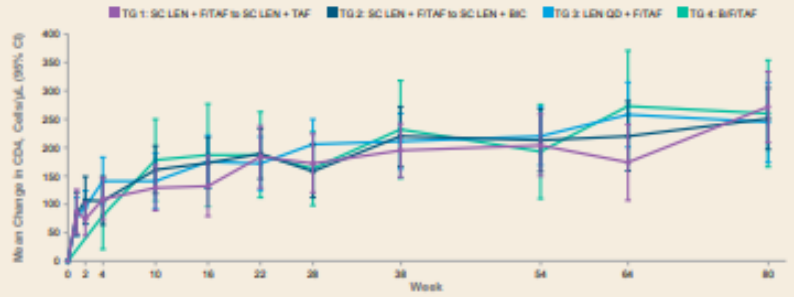
AE = adverse event.

Baseline Characteristics

	LEN Total			B/F/TAF	
	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25	Overall N = 182
Age, median (range), years	31 (19-61)	28 (19-56)	28 (19-72)	29 (21-61)	29 (19-72)
Sex, % female at birth	10	2	12	0	7
Race, % Black	46	45	60	64	52
Ethnicity, % Hispanic/Latinx	48	40	46	48	45
HIV-1 RNA, median log$_{10}$ copies/mL	4.27	4.32	4.53	4.37	4.37
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.86, 4.74
> 100,000 copies/mL, %	10	17	17	16	15
CD4 count, median cells/µL	404	450	409	462	437
Q1, Q3	320, 599	332, 599	301, 600	393, 527	332, 599
< 200 cells/µL, %	0	2	6	0	2

CD4 = cluster of differentiation-4; Q = quartile.

Changes in CD4



	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25
Change in CD4 at Week 80, cells/µL	272	251	245	260

CI = confidence interval.

Resistance Analysis

Participants, n	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25
Met resistance testing criteria	2	1	3	1
Emergent LEN resistance	1	1	1	0
Q67H	1	1	1	0
K70R	1	1	1	0

Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥ 50 copies/mL and < 1-log$_{10}$ HIV-1 RNA reduction from Day 1 at Week 10 visit, any visit after achieving HIV-1 RNA < 50 copies/mL and rebound to ≥ 50 copies/mL, and any visit with > 1-log$_{10}$ increase from nadir.

- Bonne tolérance
- Analyse de résistance
  - 5 échecs (2 avec mutation)
  - Profil unique : Q67H
  - [LEN] OK mais [TFV] < LOQ

Study Design[1,2]

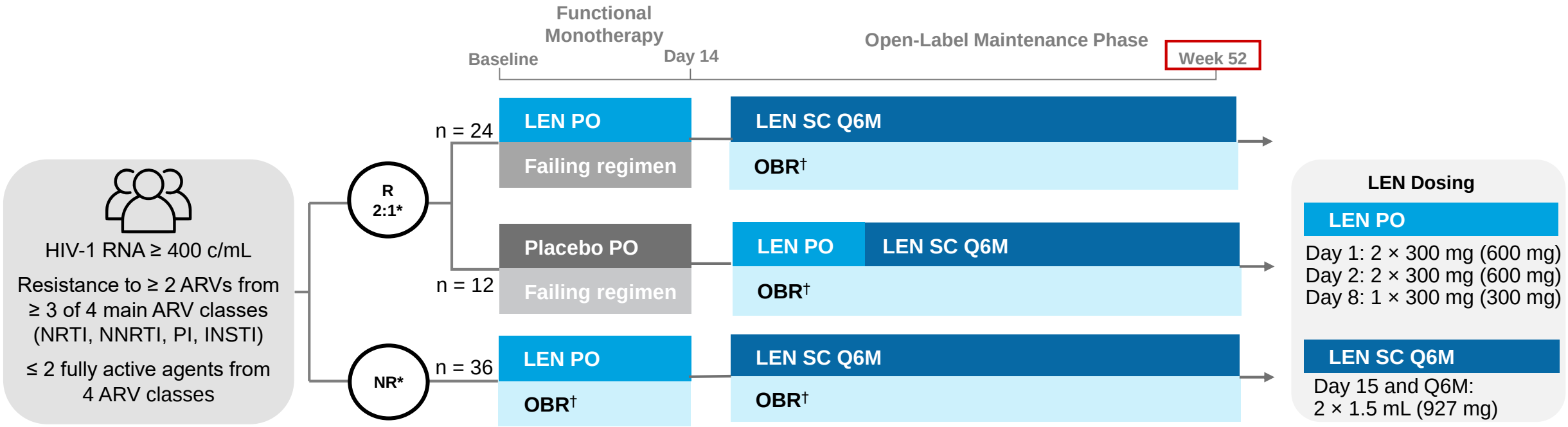
N = 72

HTE PLWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

Primary: ≥ 0.5 $\log_{10}$ c/mL reduction in HIV-1 RNA from baseline at Day 15
Secondary: HIV-1 RNA < 50 c/mL and < 200 c/mL at Week 26 and 52 (FDA Snapshot)

2019–present (ongoing)



LEN Dosing

LEN PO
Day 1: 2 × 300 mg (600 mg)
Day 2: 2 × 300 mg (600 mg)
Day 8: 1 × 300 mg (300 mg)

LEN SC Q6M
Day 15 and Q6M:
2 × 1.5 mL (927 mg)

*Participants with < 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the R cohort; participants with ≥ 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the NR cohort;
†Investigational agents (e.g., fostemsavir) permitted; atazanavir, atazanavir/cobicistat, atazanavir/ritonavir, efavirenz, etravirine, nevirapine, tipranavir not permitted
HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized; OBR, optimized background regimen; PO, orally; Q6M, every 6 months; R, randomized

1. Ogbuagu O, et al. IDWeek 2022, Oral 1585; 2. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-1803

Baseline Characteristics

Characteristic	Randomized (n = 36)	Nonrandomized (n = 36)	Total (N = 72)
Age, years, median (range)	54 (24–71)	49 (23–78)	52 (23–78)
Female sex at birth, %	28	22	25
Black, %	46	31	38
Hispanic/Latinx, %	29	14	21
HIV-1 RNA, $\log_{10}$ c/mL, median (range)	4.5 (2.3–5.4)	4.5 (1.3–5.7)	4.5 (1.3–5.7)
> 100,000 c/mL, %	19	19	19
CD4 count, cells/μL, median (range)	127 (6–827)	195 (3–1,296)	150 (3–1,296)
< 200 cells/μL, %	75	53	64
Number of prior ARV agents, median (range)	9 (2–24)	13 (3–25)	11 (2–25)
Number of fully active agents in OBR, %			
0	17	17	17
1	39	36	36
≥ 2	44	47	47
Known resistance to ≥ 2 drugs in class, %			
NRTI	97	100	99
NNRTI	94	100	97
INSTI	75	64	69
PI	78	83	81

HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. IDWeek 2022, Oral 1585

Composition of Failing Regimen and OBR

	Randomized cohort (n = 36)		Total (N = 72)	
	Failing regimen	OBR	Failing regimen	OBR
Class/agent, %				
NRTI	83	89	82	85
INSTI	69	69	68	65
PI	56	58	63	63
NNRTI	25	28	31	33
Ibalizumab (CD4-directed post-attachment inhibitor)	11	33	18	24
Maraviroc (CCR5 entry inhibitor)	11	17	14	14
Fostemsavir (attachment inhibitor)	6	8	6	11
Enfuvirtide (fusion inhibitor)	6	8	6	7
Number of fully active ARV agents, %				
0	53	17	42	17
1	31	39	36	38
≥ 2	17	44	22	46
OSS, median*	0.8	1.8	1.0	2.0

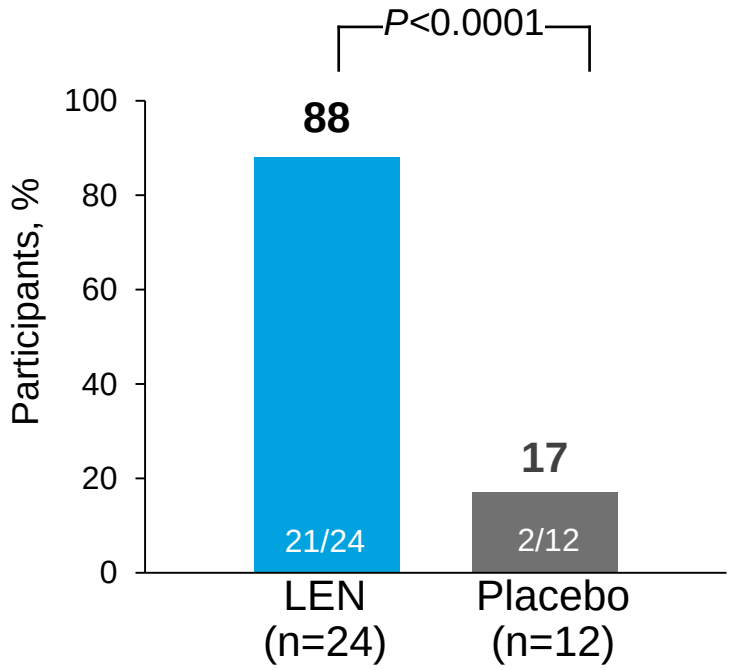
- **16/72 participants (22%) had no changes in their OBR (12/36 [33%] in the randomized cohort)**

*OSS (1, 0.5 or 0 for full, partial or no susceptibility, respectively) determined based on proprietary algorithm (Monogram Biosciences Inc., South San Francisco, CA); for historical resistance reports, scores were derived from data provided by investigators; OSS of OBR was sum of individual scores
CCR5, C-C chemokine receptor type 5; HTE, heavily treatment-experienced; OBR, optimized background regimen; OSS, overall susceptibility score

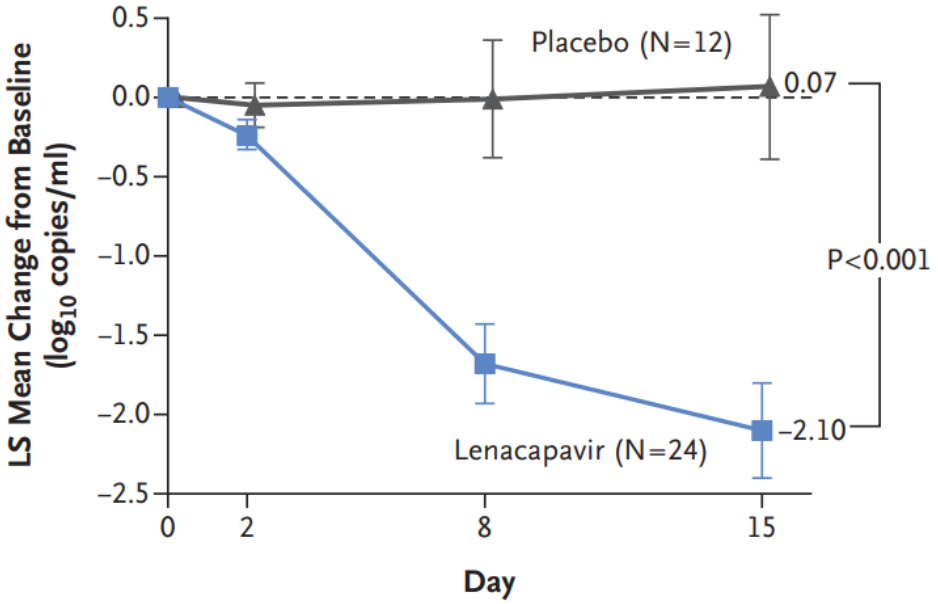
Antiviral Activity During Functional Monotherapy, Randomized Cohort

Primary Endpoint D15

Proportion Achieving HIV-1 RNA Decline ≥ 0.5 log_{10} copies/mL



Mean Change in HIV-1 RNA by Visit (95% CI)



LEN showed potent antiviral activity when added to a failing regimen

HTE, heavily treatment-experienced

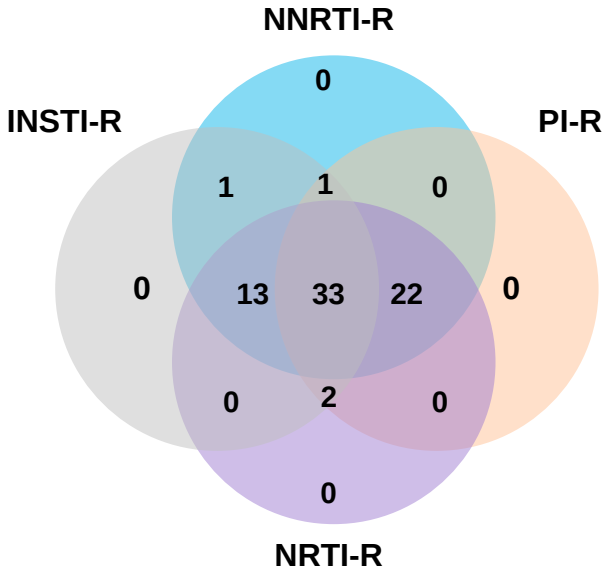
Segal-Maurer S, et al. vCROI 2021. Oral #127

Segal-Maurer et al. NEJM May 2022

Efficacy at Weeks 26 and 52 and Baseline Resistance

Baseline Resistance (N = 72)[1]

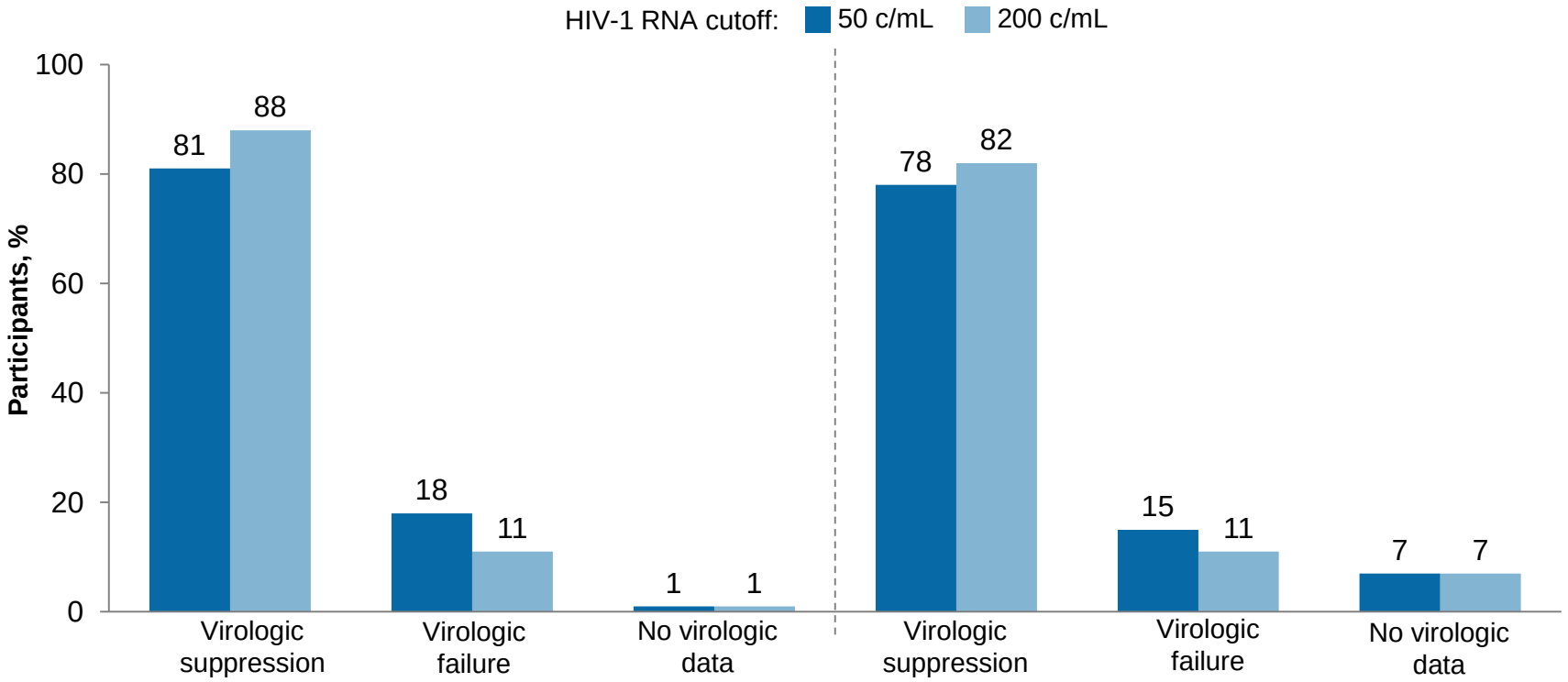
No LEN resistance at baseline



Nearly half (33/72) of all participants had resistance to all 4 classes

Week 26[2]
(Randomized and Nonrandomized Cohorts: N = 72)

Week 52[3]
(Both cohorts N=72*)



LEN in combination with OBR achieved durable high rates of virologic suppression through Week 52 in HTE PLWH

HTE, heavily treatment-experienced; OBR, optimized background regimen; R, resistance * Due to the clinical hold on SC LEN by the FDA during the study, by Week 52, 17 participants took ≥ 1 dose of oral LEN bridging (300 mg QW)

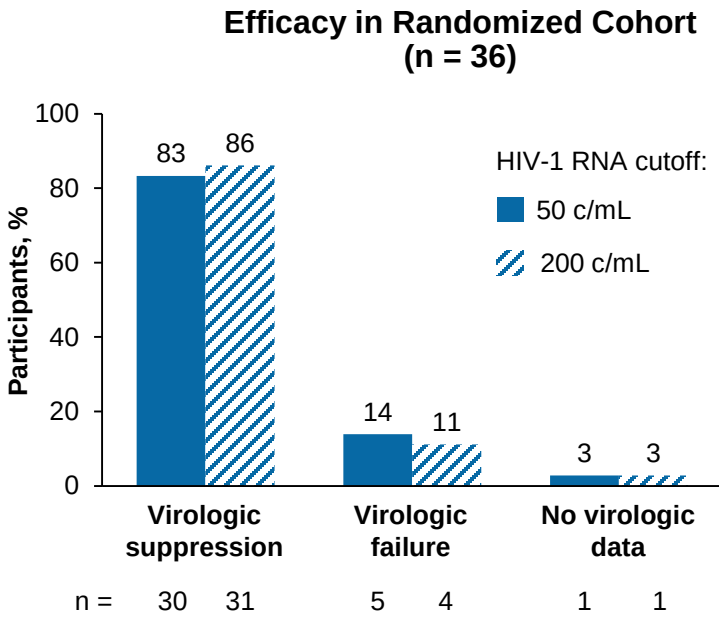
1. Margot N, et al. EACS 2021, oral OS1/1; 2. Ogbuagu O, et al. CROI 2022, Poster 491; 3. Ogbuagu O, et al. IDWeek 2022, Oral 1585

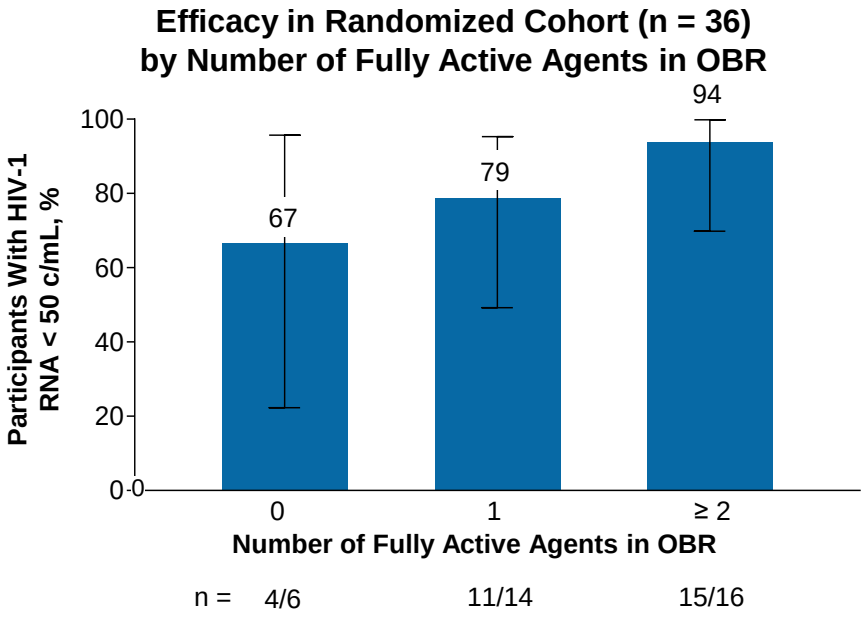
Composition of OBR and Efficacy at Week 52

Composition of OBR (Randomized Cohort)

Number of fully active agents in OBR	LEN (n = 24)	Placebo (n = 12)
0	17%	17%
1	29%	58%
≥ 2	54%	25%

Efficacy at Week 52





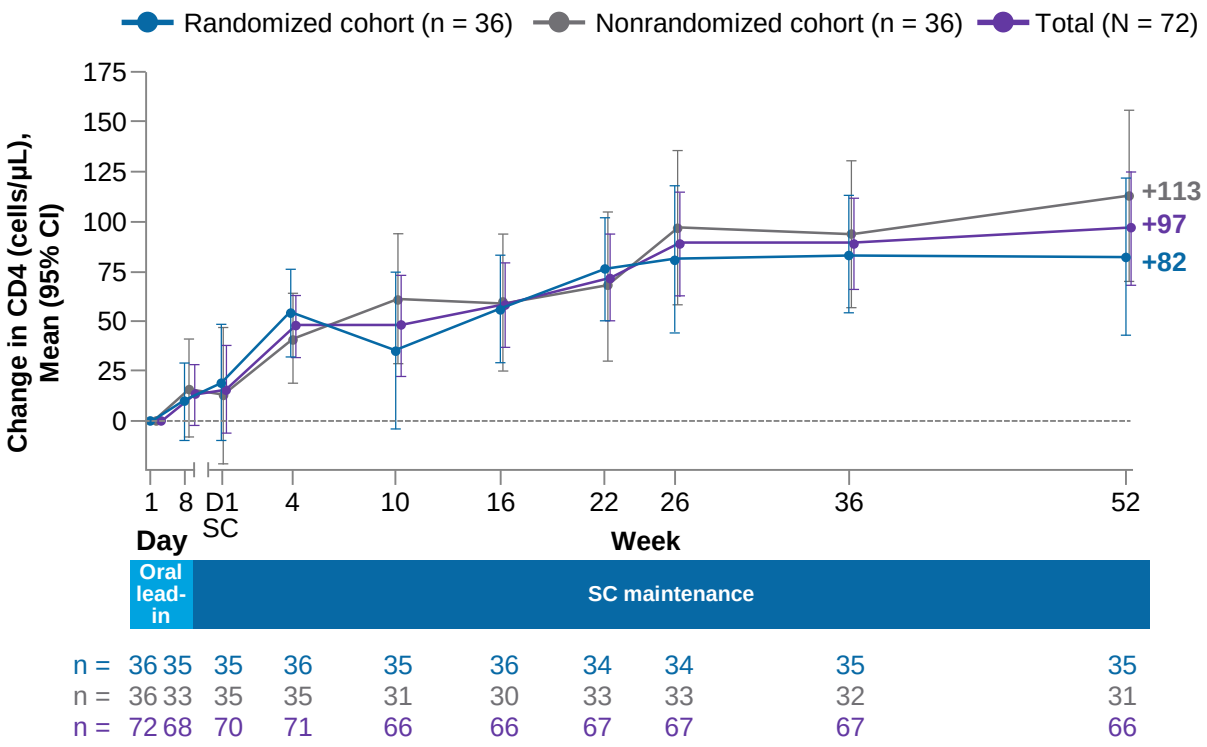
LEN in combination with OBR led to high rates of virologic suppression in HTE PLWH

HTE, heavily treatment-experienced; OBR, optimized background regimen
Ogbuagu O, et al. vCROI, 2022, Poster 491

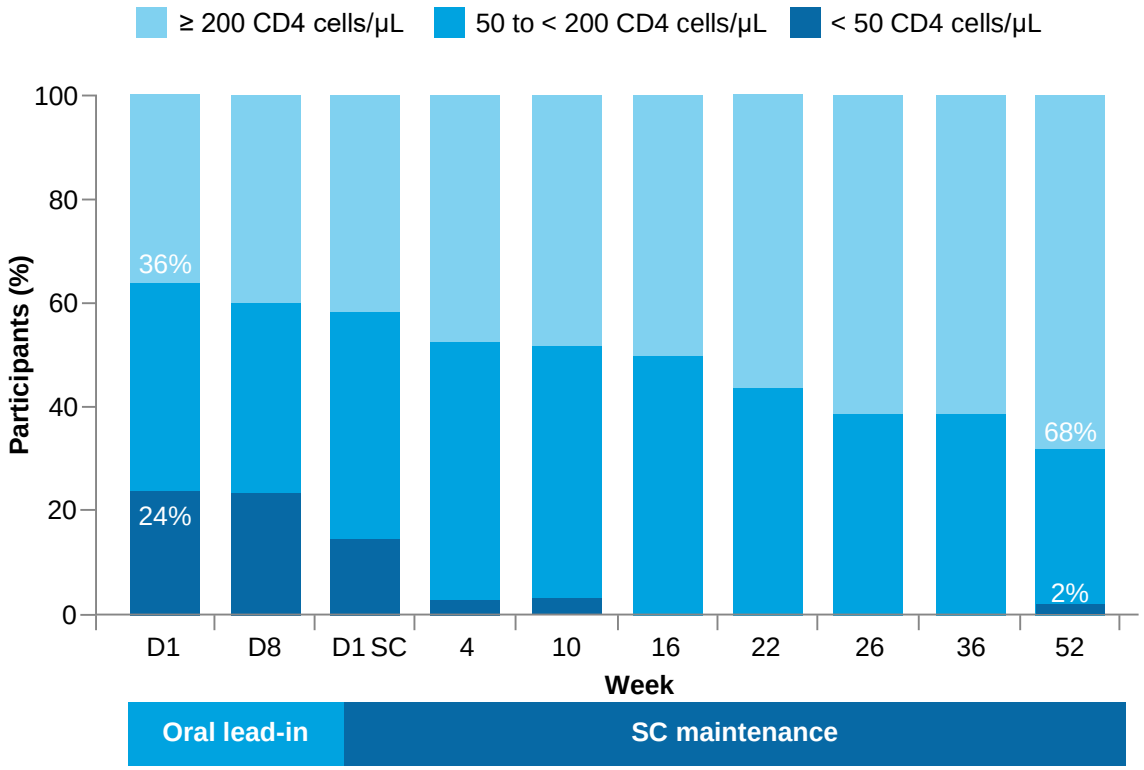
Phase 2/3: LEN in HTE PLWH

Changes in CD4 at Week 52: Randomized and Nonrandomized cohort (N = 72)

Mean Change in CD4 Count



Changes in CD4 by Category



LEN in combination with an OBR led to clinically meaningful improvement in CD4 cell count at Week 52 in HTE PLWH

D, day; D1 SC, 1st day of SC LEN; HTE, heavily treatment-experienced; OBR, optimized background regimen

Emergent LEN Resistance by Week 52

	Randomized cohort n = 36	Nonrandomized cohort n = 36	Total N = 72
Participants meeting criteria for resistance testing, n (%)	11 (31)	11 (31)	22 (31)
With data	11 (31)	10 (28)	21 (29)
Emergent LEN resistance, n (%)	4 (11)	5 (14)	9 (13)
M66I	4	2	6
Q67H/K/N	1	3	4
K70H/N/R/S	1	3	4
N74D	3	0	3
A105S/T	3	1	4
T107A/C/N*	1	3	4

- Since Week 26, 1 additional participant had emergent LEN resistance at Week 52 (Q67H)
- All 9 participants with emergent LEN resistance were at high risk of resistance development
  - 4 had no fully active drugs in OBR
  - 5 had inadequate adherence to OBR†
- All 9 remained on LEN
  - 4 participants virologically resuppressed at a later visit
    - 2 without OBR change and 2 with OBR change
- The most common pattern was M66I ± other mutations (median LEN fold change = 234)

All 9 cases of emergent LEN resistance occurred in the setting of functional monotherapy.
More than half of participants who met criteria for resistance testing did not develop LEN resistance.

*One participant had emergent T107A mutation in capsid protein with no loss in LEN susceptibility before achieving HIV-1 RNA suppression; participant was not categorized as having emergent capsid resistance; †OBR adherence assessed by plasma drug levels. HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. IDWeek 2022, Oral 1585

Algorithme ANRS V33 – octobre 2022

ANRS - AC 43: RESISTANCE GROUP

GENOTYPE INTERPRETATION: CAPSID INHIBITORS

	Mutations associated with resistance	Mutations associated with « possible resistance »
LEN	• L56I [1] • M66I [1] • Q67H/K/N [1,3,4, 5] • K70H/N/R/S [1,2,3,4,5] • N74D/S [1] • T107A/C/N [1,3, 4]	

LEN: lenacapavir

AEs (Excluding ISRs) at Week 52

Any grade AEs ≥ 10%	LEN + OBR Total: N = 72
Diarrhea	14% (n = 10)
Nausea	14% (n = 10)
Constipation	13% (n = 9)
Cough	11% (n = 8)
Pyrexia	11% (n = 8)

- No SAEs were related to study drug
- No study drug-related AEs occurred in more than 5%
- Two deaths:
  - One SAE of malignant neoplasm
  - One AE of acute respiratory failure
  - Neither related to study drug

LEN in combination with an OBR was generally well tolerated

HTE, heavily treatment-experienced; ISR, injection-site reaction; OBR, optimized background regimen

Ogbuagu O, et al. IDWeek 2022, Oral 1585

Incidence of ISRs Related to SC LEN*

Incidence of ISRs Related To SC LEN[1,2]

ISR type, %	After first SC dose at Week 1 (n = 72)	After second SC dose at Week 26 (n = 70)	Median duration, days
Swelling	26	13	12
Erythema	24	11	6
Pain	22	21	3
Nodule	22	11	180
Induration	11	10	118

ISRs

- All nodules were Grade 1, except in 1 participant
  - (n = 1) Grade 2 nodules after the 2nd and 3rd injections (both resolved after 3 days)
- Most ISRs were Grade 1 or 2 in severity (no Grade 4)
  - Grade 3 ISRs in 2 participants:
    - (n = 1) swelling and erythema, resolved in 4 and 8 days, respectively
    - (n = 1) pain, resolved in 1 day
- 1 participant discontinued due to ISR
  - Due to nodule (Grade 1) at Week 52

LEN was generally well tolerated with a single discontinuation (n = 1/72) due to ISR in HTE PLWH

*Only includes AEs related to LEN and excludes AEs unrelated to LEN.
HTE, heavily treatment-experienced; ISR, injection-site reaction

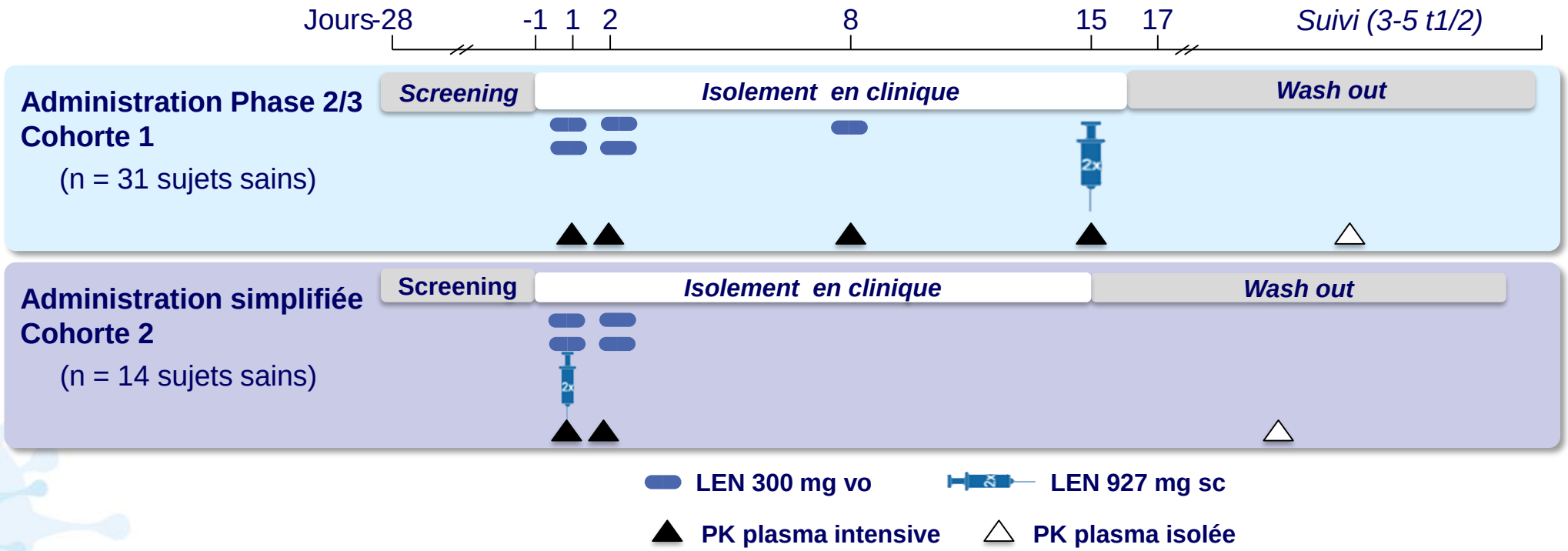
1. Molina JM, et al. vIAS 2021, OALX01LB02; 2. Ogbuagu O, et al. CROI 2022, Poster 491

Schéma de prise

Lénacapavir : nouveau schéma d'administration simplifié en sc + po dès J0 (1)

- **Objectifs :** (essais NCT04925752 et NCT04994509)
  - Comparer les PK plasma de LEN du schéma d'administration initial de phase 2/3 (Cohorte 1) et d'un nouveau schéma simplifié (Cohorte 2) où administrations orales et sc sont concomitantes
  - Evaluer la tolérance des 2 schémas d'administration dans les 2 cohortes

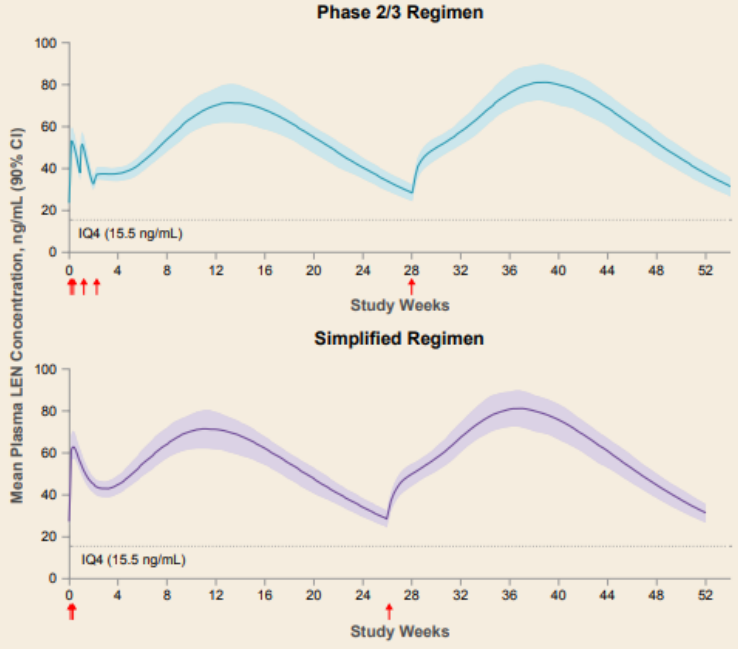
Schéma de l'étude



Jogiraju V, AIDS 2022, Abs. PESUB22

Quid en cas d'oubli de dose?

Figure 1. Simulated LEN Concentration-Time Profiles for Phase 2/3 and Simplified Regimens in Adults With HIV



Red arrows indicate LEN dosing, occurring on Days 1, 2, 8, and 15, and Week 28 for Phase 2/3 regimen, and on Days 1 and 2, and Week 26 for simplified regimen.

- Phase 2/3 and simplified regimens' simulated LEN C_{trough} values at various weeks are shown in Table 1 and Figure 2

Figure 2. Simulated LEN C_{trough} at Weeks 24-32 in Adults With HIV

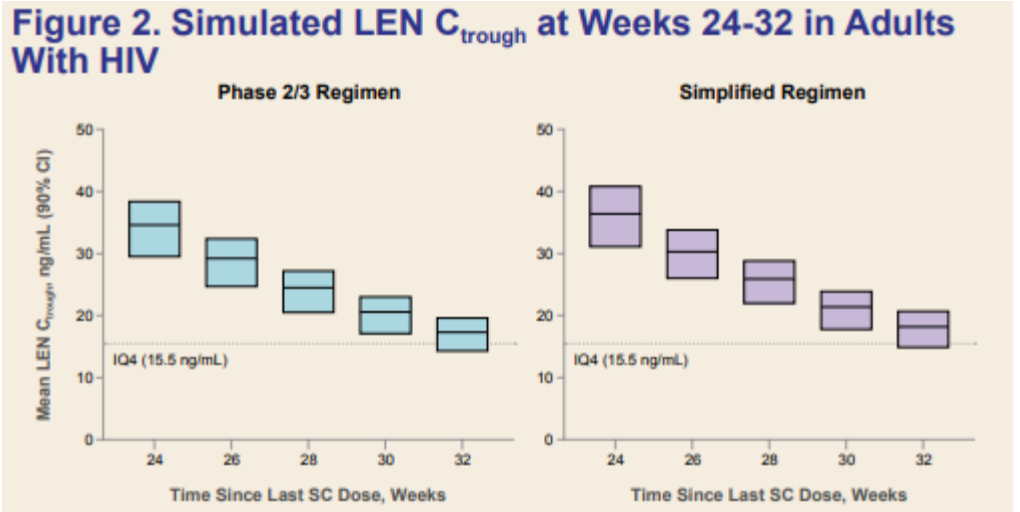


Table 1 reports values for Weeks 24, 26, and 28; Phase 2/3, mean LEN C_{trough} (90% CI) ng/mL at Weeks 30 and 32: 20.6 (17.0, 23.1) and 17.3 (14.2, 19.7), respectively; corresponding simplified, mean LEN C_{trough}: 21.4 (17.7, 24.0) and 18.2 (14.8, 20.8).

Table 1. LEN C_{trough} Following Phase 2/3 or Simplified Regimen Administration

	Phase 2/3 Regimen		Simplified Regimen	
	LEN C_{trough} ng/mL (90% CI)	IQ	LEN C_{trough} ng/mL (90% CI)	IQ
Week 24	34.6 (29.4, 38.5)	8.9 (7.5, 9.9)	36.4 (31.0, 40.9)	9.4 (8.0, 10.5)
Week 26	29.2 (24.6, 32.5)	7.5 (6.3, 8.4)	30.3 (25.9, 33.9)	7.8 (6.7, 8.7)
Week 28	24.5 (20.4, 27.3)	6.3 (5.2, 7.0)	25.9 (21.9, 28.9)	6.7 (5.6, 7.4)

Conclusion

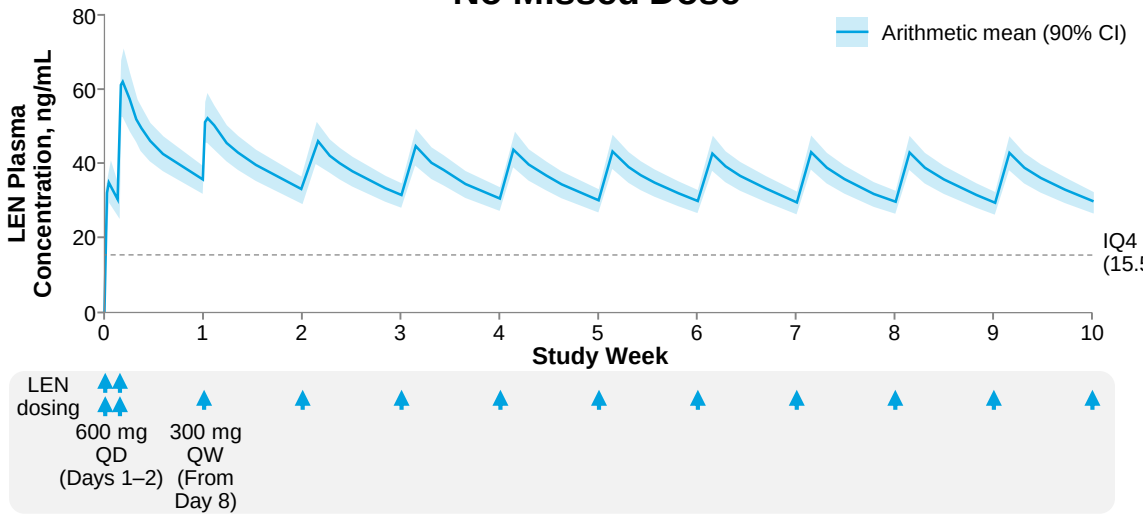
- In administering SC LEN Q6M, a 4-week dosing window (± 2 weeks around the scheduled injection) is adequate to maintain safe and efficacious exposure

LEN: PK (population PK model)

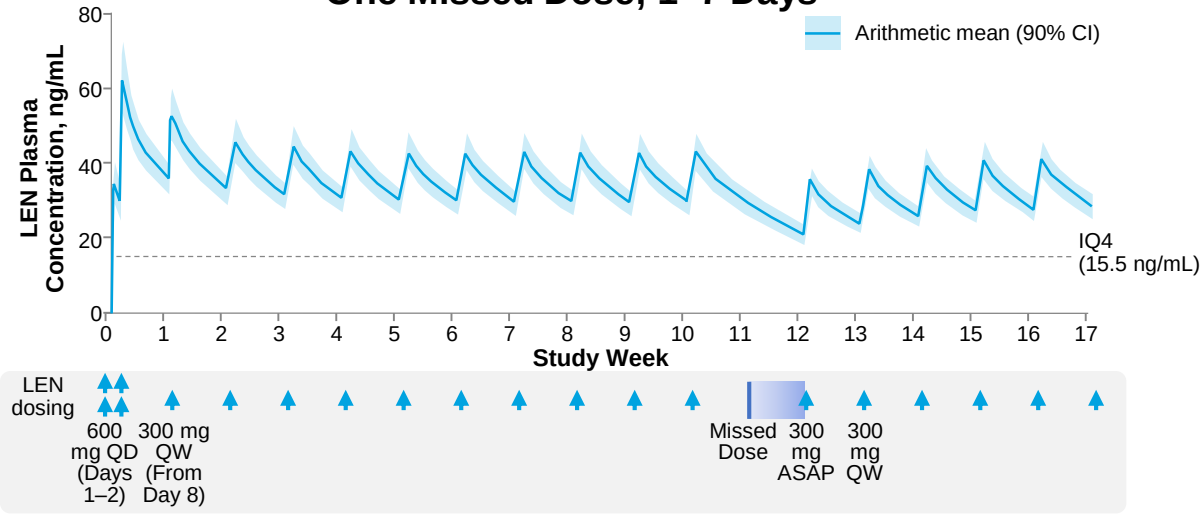
Simulations for Once-Weekly Dosing of Oral LEN

Simulations for LEN QW Dosing Regimen*

No Missed Dose



One Missed Dose; 1–7 Days

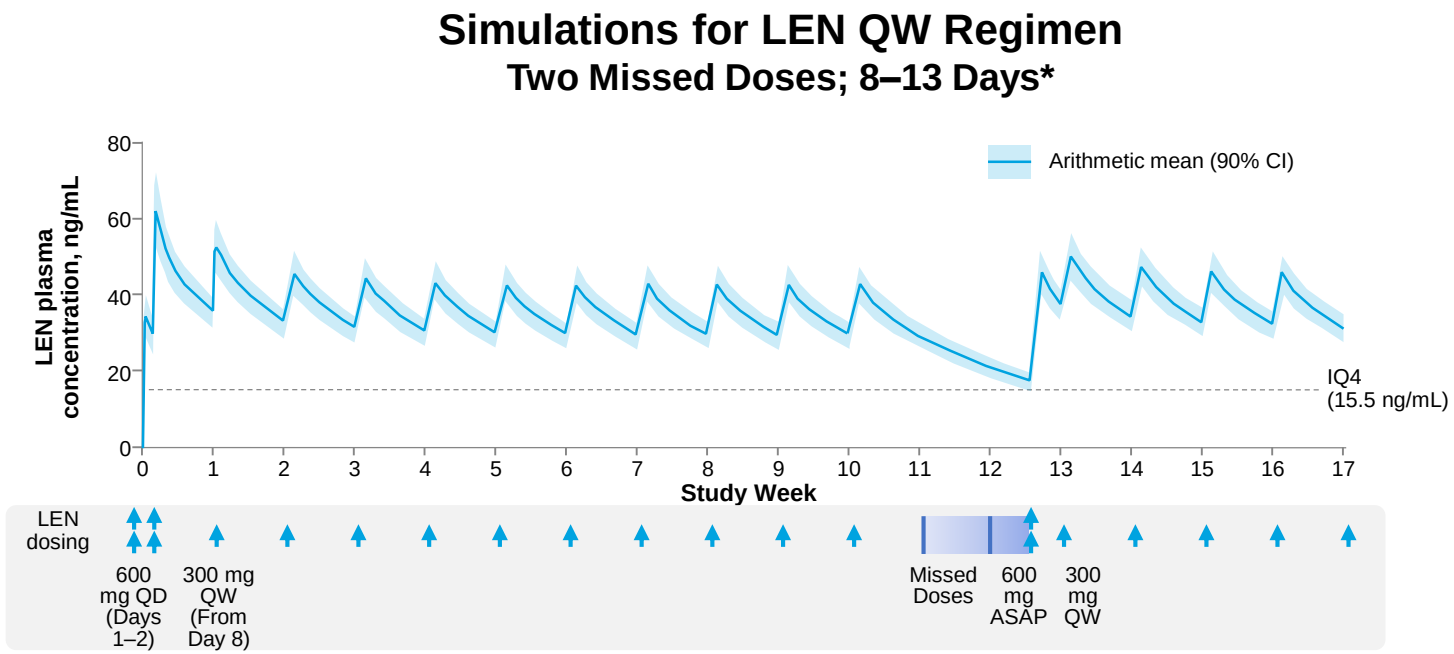


- Oral loading dose of 600 mg on Days 1 and 2 followed by oral 300 mg QW doses maintained the lower bound of the 90% CI of mean C_{trough} above IQ4 through the dosing interval
- If one oral LEN QW dose is missed, it should be taken ASAP and then normal dosing regimen can be resumed (i.e., taking one dose (300 mg) on scheduled day)

LEN is well suited to be studied as part of a QW oral regimen.
Simulations suggested that LEN 300 mg QW allows for a 7-day forgiveness window.

*Oral loading 600 mg QD on Days 1–2, then 300 mg QW from Day 8
ASAP, as soon as possible; C_{trough}, concentration at end of dosing interval; IQ, inhibitory quotient; PK, pharmacokinetic(s)
Shaik N, et al. AIDS 2022, Poster PESUB23

Simulations for Once-Weekly Dosing of Oral LEN



- If two oral LEN QW doses are missed, simulations indicated taking two doses (600 mg) ASAP and then resuming the normal regimen on the scheduled day will result in concentrations above IQ4 and within the safety margin
  - If taking doses on the scheduled dosing day, only two doses should be taken; never take three doses on the same day

Simulations suggested that LEN 300 mg QW allows for a 7-day forgiveness window

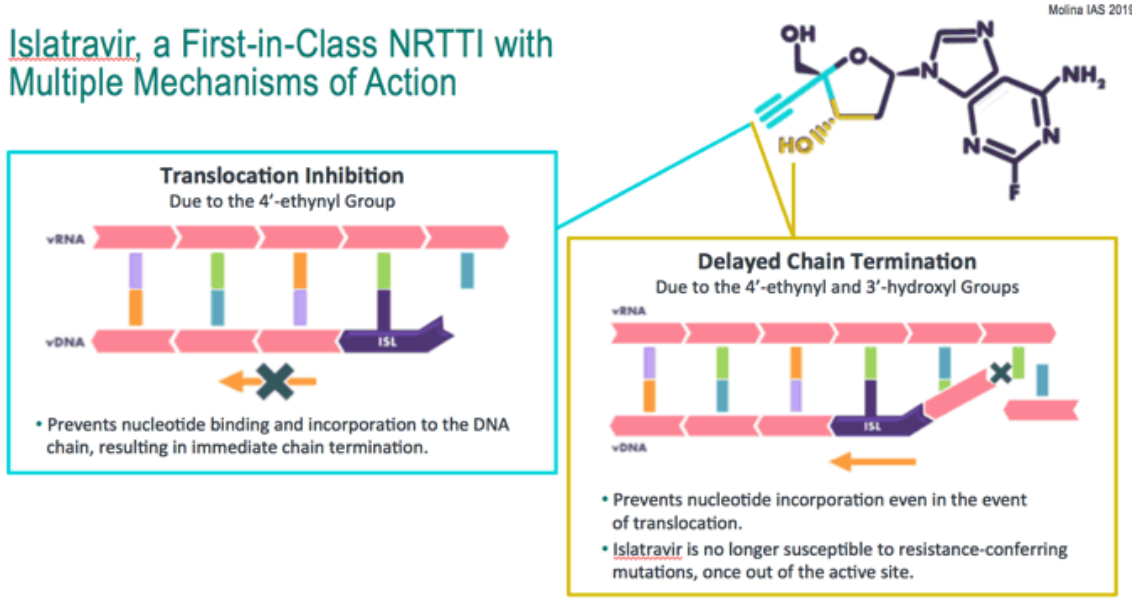
*Scenario represents missing 2nd consecutive dose 8-13 days from last dose.
ASAP, as soon as possible; IQ, inhibitory quotient; PK, pharmacokinetic(s)

Shaik N, et al. AIDS 2022, Poster PESUB23

LENACAPAVIR bilan

- Pas de monothérapie
  - Fonctionnelle attention à l'observance
  - Avec traitement optimisé efficace (>1 ARV)
- Développement
  - switch
    - Islatravir 2mg + LEN 300 mg prise orale hebdomadaire
    - Bictegravir : BIC 75mg + LEN 25mg ou 50mg
  - bNabs : Teropavimab et Zinlirvimab
  - Prep

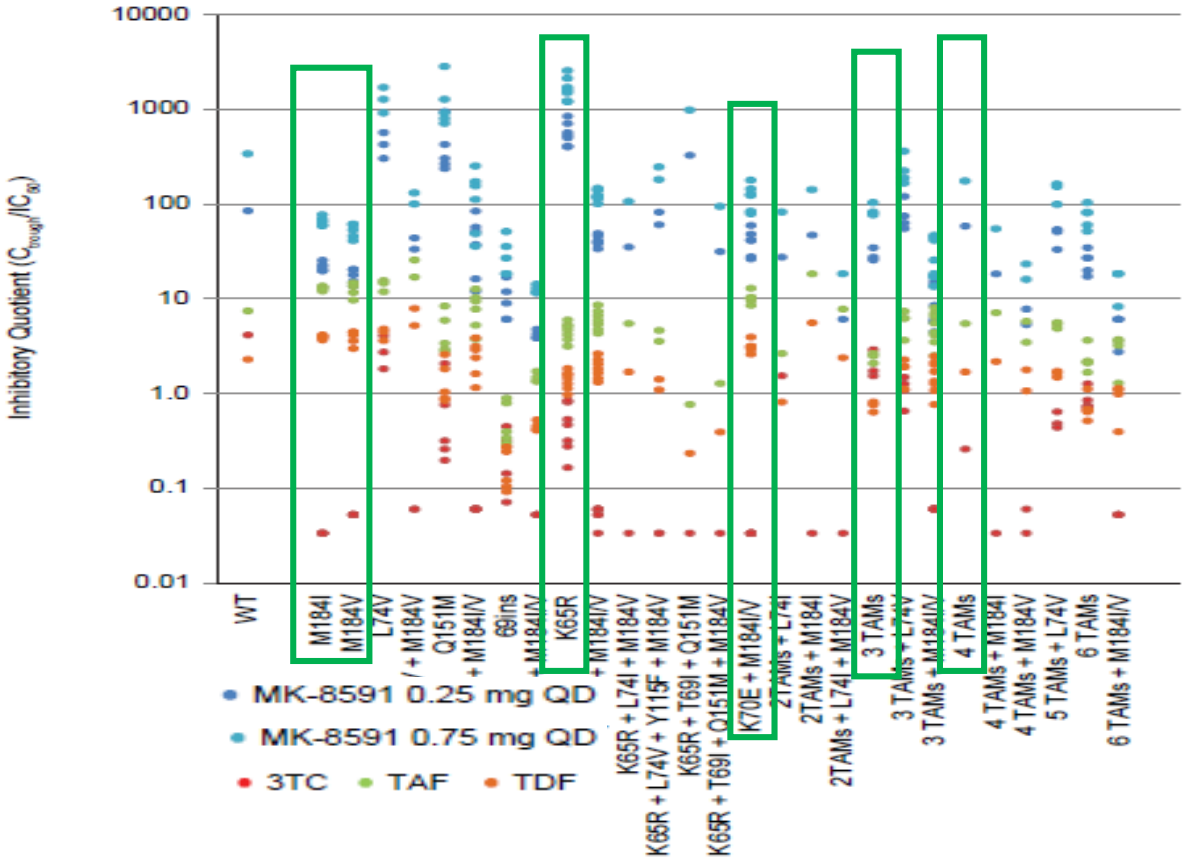
ISLATRAVIR le retour



- Inhibiteur nucléosidique de translocation
  - Terminaison de chaine
- Profil de résistance particulier
  - M184, A114S
- PK/PD
  - Longue ½ vie
  - Pas d'interaction significative
  - Elimination urinaire mais pas d'ajustement de poso chez l'IR sévère
  - Bonne pénétration rectale et vaginale
- Toxicité?
  - **ISL-TP** s'accumule préférentiellement dans les lymphocytes à un tx supra-thérapeutique : **apoptose**
  - **Pas de toxicité mitochondriale**

Quotients inhibiteurs de MK-8591, évalués in vitro, sur différents sous-types du VIH-1 et isolats cliniques avec des mutations aux INTI

Quotient inhibiteur de MK-8591 sur un panel de mutants résistants aux INTI issus d'isolats cliniques



- Le Quotient Inhibiteur est le rapport entre la concentration résiduelle de MK-8591-TP et l'activité antivirale (QI=Ctrough/CI50).
- QI élevé = puissance antivirale

- Sur les souches sauvages : les QIs du MK-8591 sont les plus élevés.

- **Sur les souches mutantes les plus communes (M184I/V, TAMs, K65R et K70E), malgré une augmentation de la CI50 dans certains cas (M184I/V), MK-8591 présente les QIs les plus élevés.**

- Le QI et la demi-vie élevés suggèrent l'utilisation de faibles doses de MK-8591 et une haute barrière génétique à la résistance.

CHU Poitiers

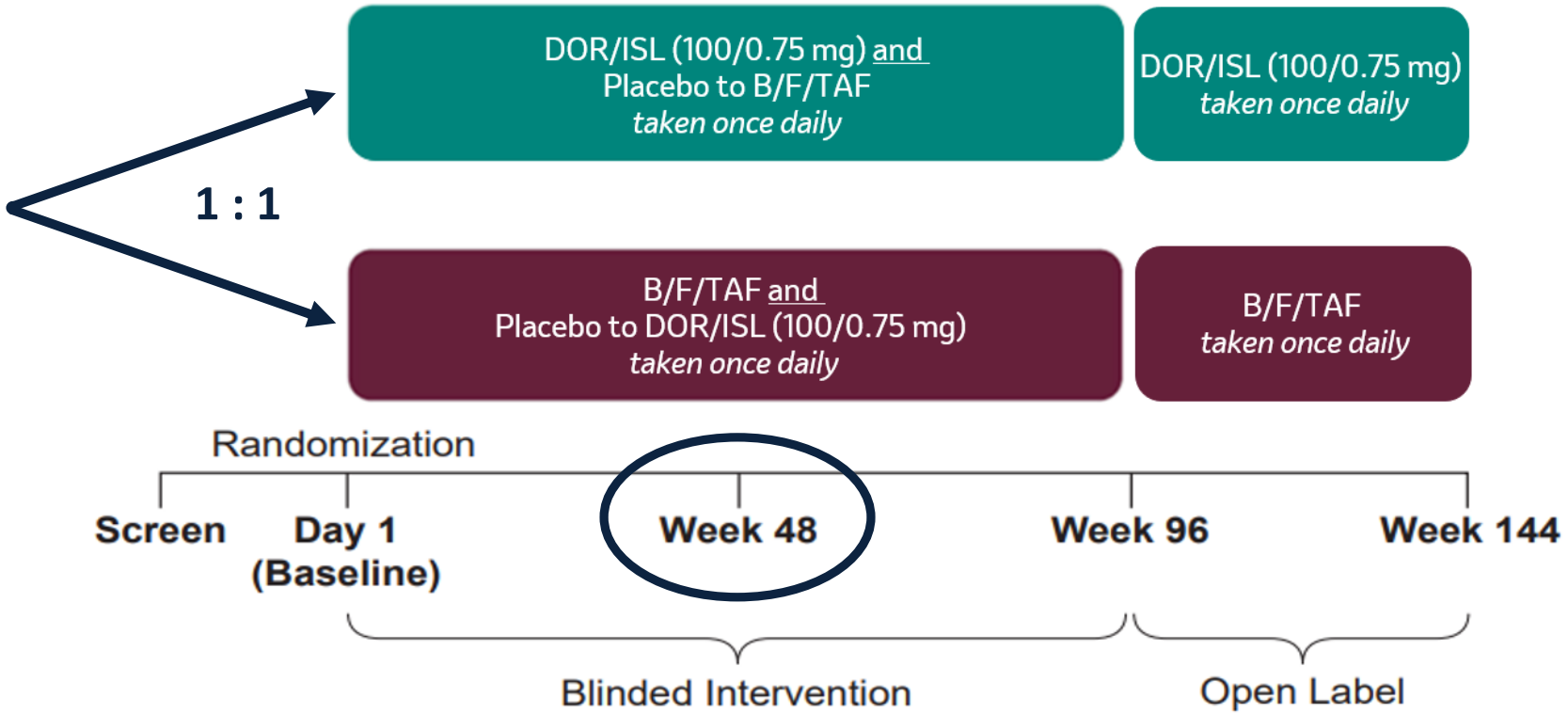
Grobler J, CROI 2019, # 481

Study Design: DOR/ISL (100/0.75 mg) vs. B/F/TAF

Population

- PLWH ≥18 years of age
- Virologically suppressed (plasma RNA <50 copies/mL) for ≥3 months on B/F/TAF
- Documented HIV-1 RNA <50 copies/mL at screening
- No history of treatment failure on any regimen
- No known resistance to DOR*
- No active HBV infection

*V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L or Y318F

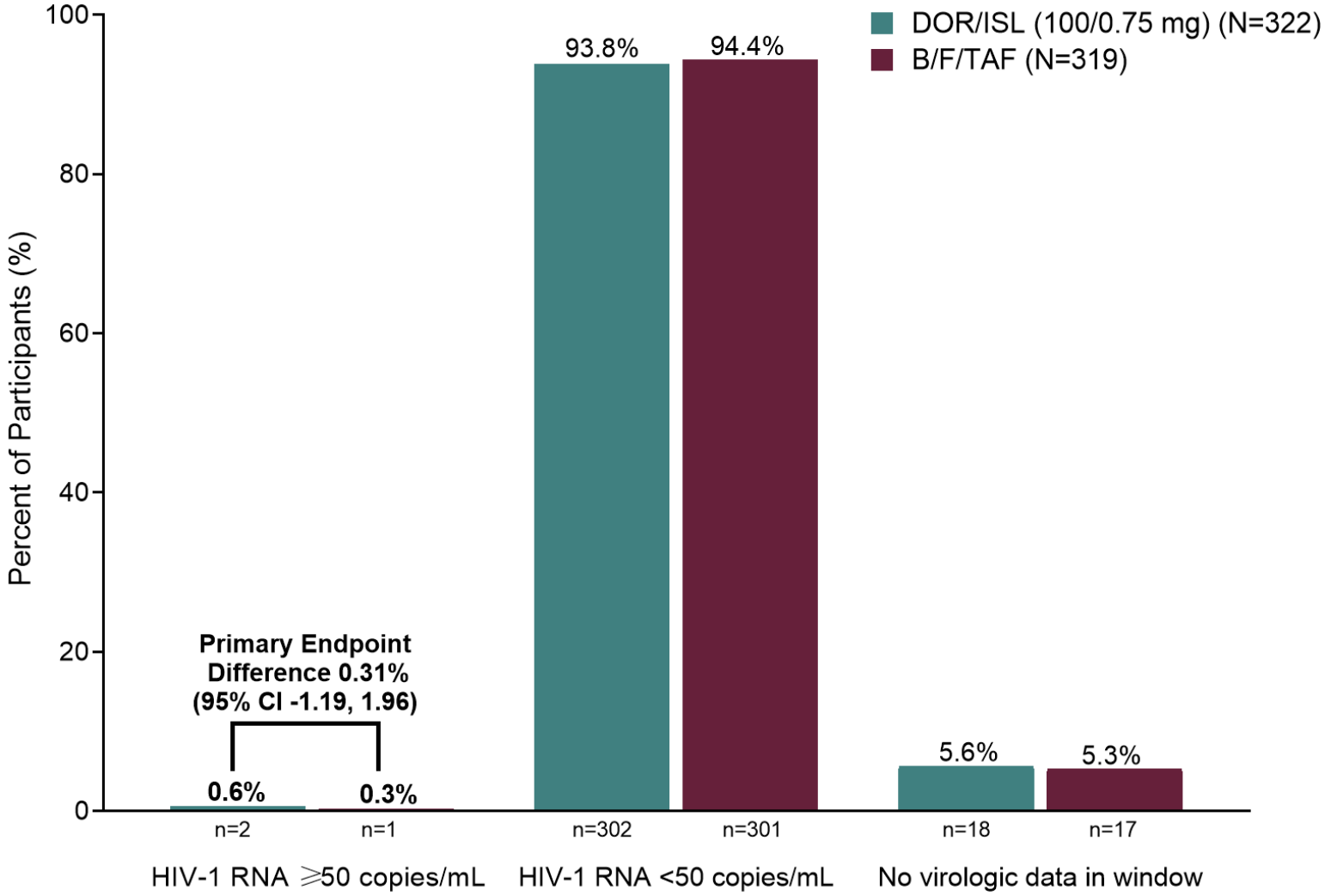


Primary Efficacy Endpoint: HIV-1 RNA ≥50 copies/mL at Week 48 (FDA snapshot approach), non-inferiority margin 4%

B/F/TAF=bictegravir/emtricitabine/tenofovir alafenamide.

Virologic Outcomes Week 48, FDA snapshot Approach

DOR/ISL (100/0.75 mg) vs. B/F/TAF

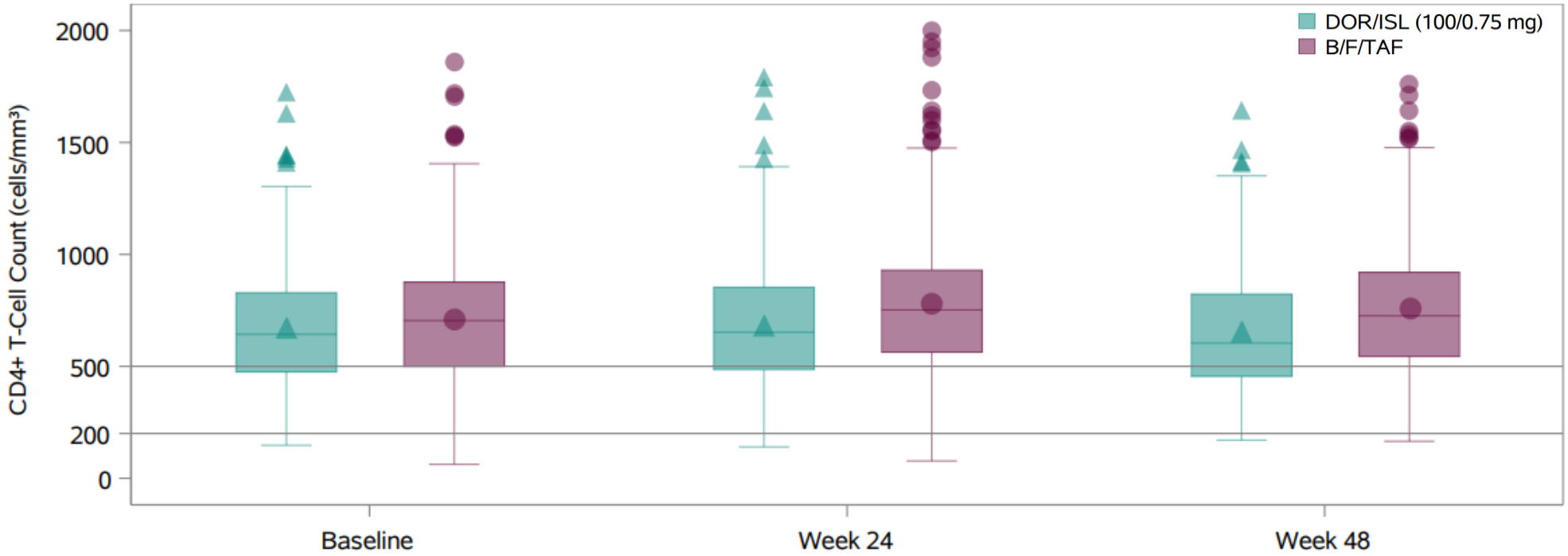


One participant taking DOR/ISL had virologic failure (confirmed plasma HIV-1 RNA ≥200 copies/mL) at Week 12

- No resistance detected to DOR or ISL in plasma samples
- ISL was not detected in plasma samples collected at Week 12

CD4+ T-Cell Count

DOR/ISL (100/0.75 mg) vs. B/F/TAF



	Baseline		Week 24		Week 48	
	DOR/ISL	B/F/TAF	DOR/ISL	B/F/TAF	DOR/ISL	B/F/TAF
N	322	319	304	302	301	298
Mean (cells/mm³)	679	715	687	782	661	761
Mean Change (cells/mm³)	-	-	10.9	67.6	-19.7	40.5
Mean % Change	-	-	5.2%	15.7%	0.9%	12.8%

Difference -68.1, 95% CI -94.7, -41.4

One DOR/ISL participant, with a CD4+ T-cell count >2300 cells/mm³ at all timepoints, is not shown in the figure.

Most Common Adverse Events

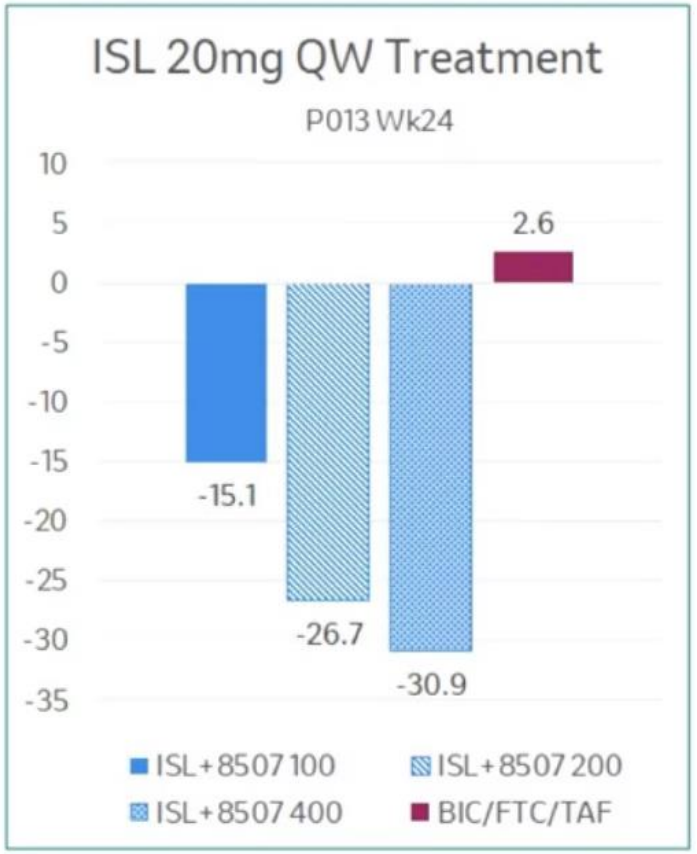
DOR/ISL (100/0.75 mg) vs. B/F/TAF

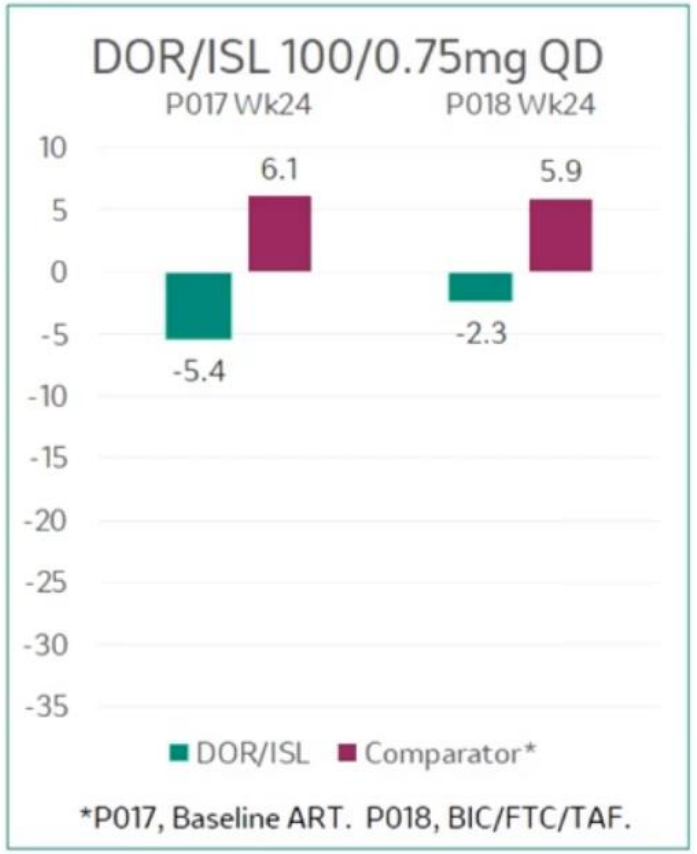
n (%) of participants	DOR/ISL (100/0.75 mg) (N=322)	B/F/TAF (N=319)	Difference (95% CI)
All causality events (≥5% incidence in either group)			
Headache	25 (8)	23 (7)	0.6 (-3.6, 4.8)
COVID-19	19 (6)	18 (6)	0.3 (-3.5, 4.0)
Arthralgia	17 (5)	19 (6)	-0.7 (-4.4, 3.0)
Back pain	13 (4)	17 (5)	-1.3 (-4.8, 2.1)
Diarrhea	8 (3)	20 (6)	-3.8 (-7.3, -0.7)
Drug-related events (≥5 participants in either group)			
Nausea	8 (3)	2 (1)	1.9 (-0.1, 4.3)
Dizziness	1 (0)	5 (2)	-1.3 (-3.3, 0.3)
Myalgia	0 (0)	5 (2)	-1.6 (-3.6, -0.4)

Infection Related AEs

- Infection rates were comparable between treatment groups (DOR/ISL 31.4% vs B/F/TAF 30.7%)
- 1 CDC AIDS-Defining Category C event in each group
  - DOR/ISL: esophageal candidiasis
  - B/F/TAF: recurrent Kaposi sarcoma

Initial Observations:
Total Lymphocyte Count, Mean % Change from Baseline

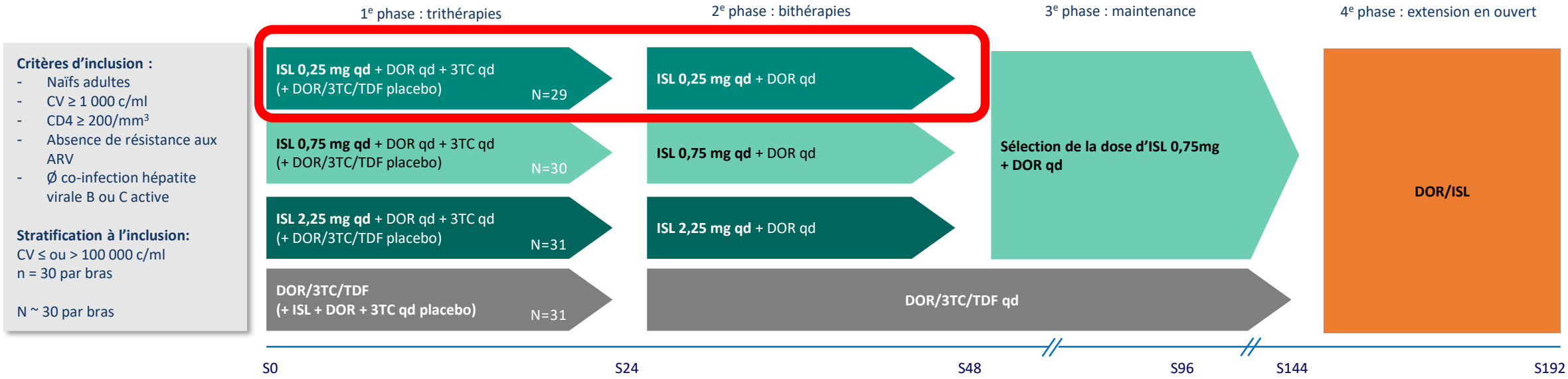




PN011 - Drive 2 Simplify DOR+ISL

Phase 2b chez patients naïfs VIH-1 (S48 et S96)

Etude *dose-ranging* phase 2b, randomisée, en double-aveugle, contrôlée vs comparateur, 24 centres dans 4 pays (Chili, France, UK, USA)



Les patients avec CV<50 cp/ml à la visite S20 et sans échec virologique sont éligibles à la phase 2. Les patients avec une CV≥50 cp/ml à S20 restent dans la phase 1 et switchent en phase 2 aux visites suivantes qu'à l'obtention d'une CV<50 cp/ml et sans échec virologique.

- Protocole d'étude de recherche de doses ISL (0,25 mg, 0,75 mg, 2,25 mg en 1 prise par jour) associé à DOR comportant **4 phases**:
  - **1e phase** : double aveugle, trithérapies, comparaison d'ISL (3 doses différentes) et TDF associés à DOR et 3TC
  - **2e phase** : ouverte, bithérapies ISL (3 doses en aveugle) + DOR comparée à DOR/3TC/TDF
  - **3e phase** : ouverte, maintenance avec sélection de la dose d'ISL
  - **4e phase**: extension en ouvert

88% des patients (groupes ISL) rentrent en phase 2 à S24.

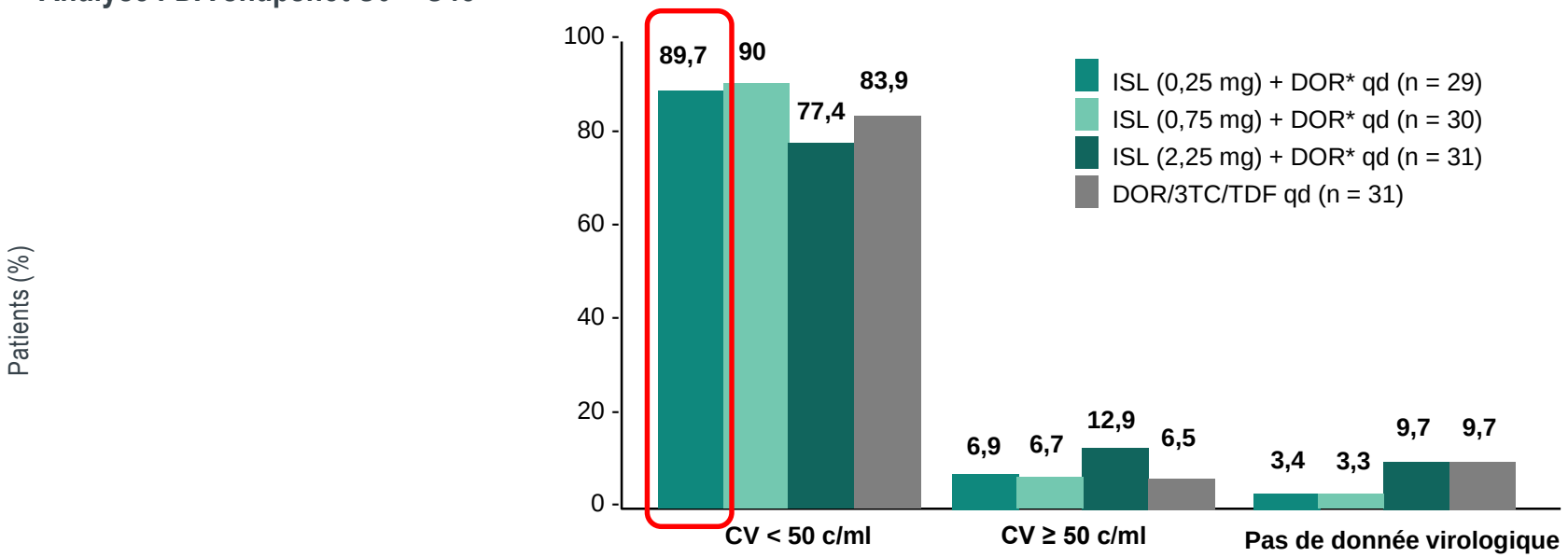
Molina J.-M. et al. Lancet HIV 2021 May 14. Molina et al. Islatravir in Combination With Doravirine Maintains HIV-1 Viral Suppression Through 96 Weeks Glasgow 2020.

PN011 - Drive 2 Simplify DOR+ISL

Efficacité virologique S48

Critère principal: proportion de patients CV<50 c/ml à S24 et S48 (analyse US FDA snapshot)

Analyse FDA snapshot S0 – S48



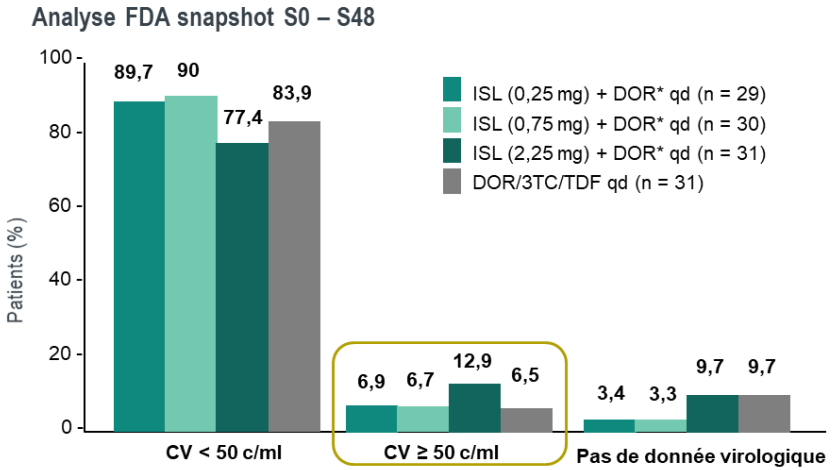
* Participants initially received ISL+DOR+3TC and switched to ISL+DOR during the week 24-48 period of the study

Efficacité virologique confirmée à S24, et S48 cette efficacité du switch vers ISL/DOR des patients initiant ISL/DOR/3TC est comparable à celle de DOR/3TC/TDF.

Molina J.-M. et al. Lancet HIV 2021 May 14. Molina J.-M. Tolerability, Safety, and Efficacy of Islatravir (MK-8591) at Doses of 0.25 to 2.25 mg QD, in Combination With Doravirine and Lamivudine Through 24 Weeks in Treatment-Naïve Adults With HIV-1 Infection – **IAS 2019**. Molina et al. Islatravir in Combination With Doravirine Maintains HIV-1 Viral Suppression Through 96 Weeks - **Glasgow 2020**.

PN011 - Drive 2 Simplify DOR+ISL

Analyse des échecs virologiques (PDVF) S48



	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, 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)
Details on participants with HIV-1 RNA ≥ 50 copies/mL not classified as PDVF				
Early Discontinuation, n (%)	0 (0)	0 (0)	3 (9.7)	1 (3.2)
Reasons for Early Discontinuation			2 lost to follow-up, 1 participant withdrawal	1 protocol violation for exclusionary criteria

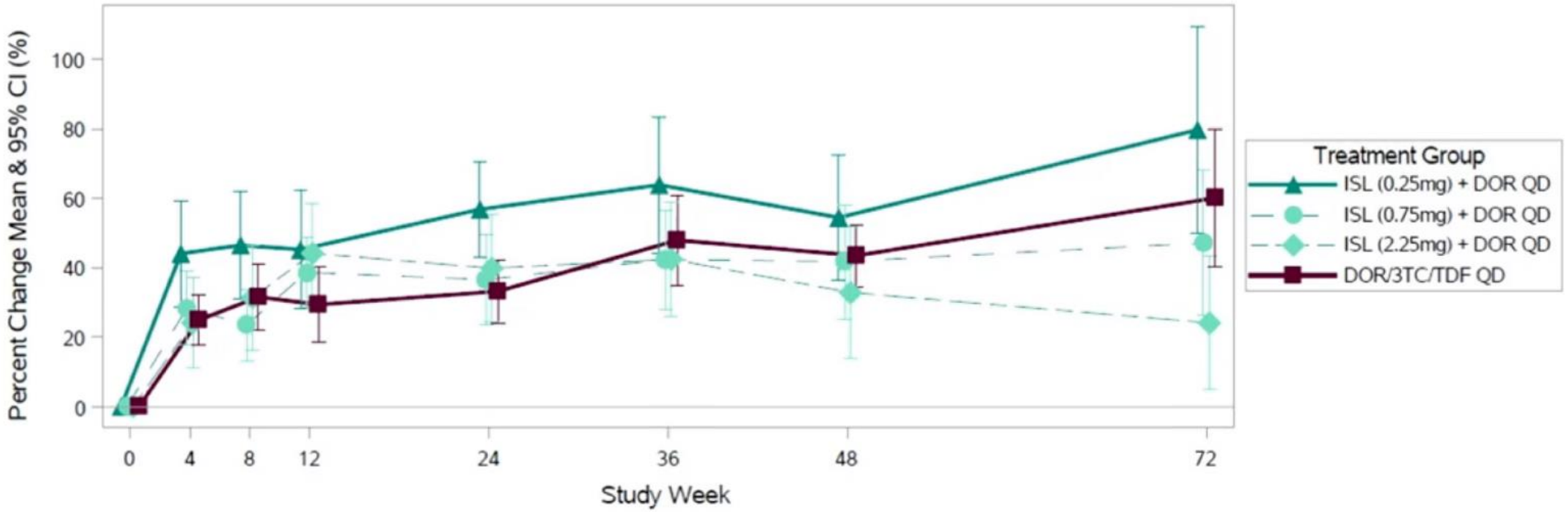
Protocol-defined virologic failure (PDVF) for this study is defined as one of the following: **1. Rebounder**: Confirmed HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study or confirmed HIV-1 RNA >1 log increase from the HIV-1 RNA nadir after a >1 log decrease in HIV-1 RNA from baseline at any time during the study; or **2. Nonresponder**: Confirmed HIV-1 RNA ≥200 copies/mL at any time from week 24 through week 48 or confirmed HIV-1 RNA ≥50 copies/mL at week 48. Initial PDVF HIV-1 must be confirmed by an additional measurement within two weeks.

- Taux faible de PDVF (0 PDVF S0-S24, 6 PDVF S24-S48):
- CV < 80 c/ml pour tous les PDVF à la visite de confirmation (< concentration cliniquement significative de 200 c/ml)
- Aucun participant n'a rempli le critère pour réaliser un test à la résistance (CV > 400 c/ml)

CHU Poitiers

Molina J.-M. et al. Lancet HIV 2021, May 14. Molina J.-M. Islatravir in Combination With Doravirine Maintains HIV-1 **Viral Suppression Through 96 Weeks** - **Glasgow 2020**. Orkin C. **Analysis of Protocol Defined Virologic Failure Through Week 48** from a Phase 2 Trial (P011) of Islatravir and Doravirine in Treatment-Naïve Adults With HIV-1 Infection - **IAC 2020**. C. Orkin. Analysis of **Protocol-Defined Virologic Failure** Through Week 96 From a Phase 2 Trial (P011) of Islatravir and Doravirine in Treatment-Naïve Adults WithHIV-1 Infection. **HIV Glasgow 2020.**

Phase 2b ISL Dose-Ranging Study (MK8591-011)
CD4+ T-Cell Count, through Week 72



- Mean increases from baseline in CD4+ T-cell count were similar for the ISL 0.25-mg and DOR/3TC/TDF groups through Week 72, with smaller mean increases observed for the ISL 0.75- and 2.25-mg groups

PN011 – Drive 2 Simplify DOR+ISL

Profil de tolérance S48 et S96

Cumulative AE Summary, Week 0-48

	ISL 0.25 mg + DOR* QD	ISL 0.75 mg + DOR* QD	ISL 2.25 mg + DOR* QD	Combined ISL Groups	DOR/3TC/TDF QD
Number (%) of Participants	N=29	N=30	N=31	N=90	N=31
with ≥1 AE	21 (72.4)	26 (86.7)	19 (61.3)	66 (73.3)	24 (77.4)
with drug-related AE	0 (0.0)	3 (10.0)	4 (12.9)	7 (7.8)	6 (19.4)
with serious AE	1 (3.4)	2 (6.7)	0 (0.0)	3 (3.3)	2 (6.5)
discontinued due to AE	0 (0.0)	0 (0.0)	2 (6.4)	2 (2.2)	1 (3.2)
with moderate or severe AE	7 (24.1)	13 (43.3)	12 (38.7)	32 (35.6)	15 (48.4)

*Participants initially received islatravir plus doravirine plus lamivudine and switched to islatravir plus doravirine during weeks 24–48.

Most Common AEs, Week 0-48 (Incidence >10% in Any Group)

	ISL (0.25 mg) + DOR* QD	ISL (0.75 mg) + DOR* QD	ISL (2.25 mg) + DOR* QD	Combined ISL Groups	DOR/3TC/TDF QD
Number (%) of participants with	N=29	N=30	N=31	N=90	N=31
Headache	4 (13.8)	2 (6.7)	4 (12.9)	10 (11.1)	2 (6.5)
Diarrhea	0 (0.0)	4 (13.3)	2 (6.5)	6 (6.7)	5 (16.1)
Nausea	1 (3.4)	4 (13.3)	3 (9.7)	8 (8.9)	3 (9.7)
Syphilis	2 (6.9)	3 (10.0)	2 (6.5)	7 (7.8)	4 (12.9)
Arthralgia	1 (3.4)	2 (6.7)	4 (12.9)	7 (7.8)	1 (3.2)
Bronchitis	2 (6.9)	4 (13.3)	0 (0.0)	6 (6.7)	4 (12.9)
Nasopharyngitis	1 (3.4)	4 (13.3)	1 (3.2)	6 (6.7)	3 (9.7)
Vitamin D deficiency	0 (0.0)	4 (13.3)	2 (6.5)	6 (6.7)	1 (3.2)
Sinusitis	3 (10.3)	0 (0.0)	0 (0.0)	3 (3.3)	1 (3.2)
Pain in extremity	3 (10.3)	0 (0.0)	0 (0.0)	3 (3.3)	0 (0.0)

*Participants initially received islatravir plus doravirine plus lamivudine and switched to islatravir plus doravirine during weeks 24–48.

- **Effets indésirables** : Pas de différence du taux d'incidence observé dans les groupes ISL, moins d'effets indésirables reliés aux traitements ISL *vs* DOR/3TC/TDF
- **2 arrêts pour EI** (bras ISL 2,25 mg): 1 pour diarrhées/nausées/vomissement débutés à J200 pendant environ 2 semaines; 1 pour réactivation VHB à J201
- **0 décès jusqu'à S96**, pas d'EI additionnel relié à ISL et pas d'arrêt sup. lié au traitement S48-296

- Effets indésirables les plus fréquents dans tous les bras de traitement: **céphalées (ISL), diarrhée (DOR/3TC/TDF) et nausée**

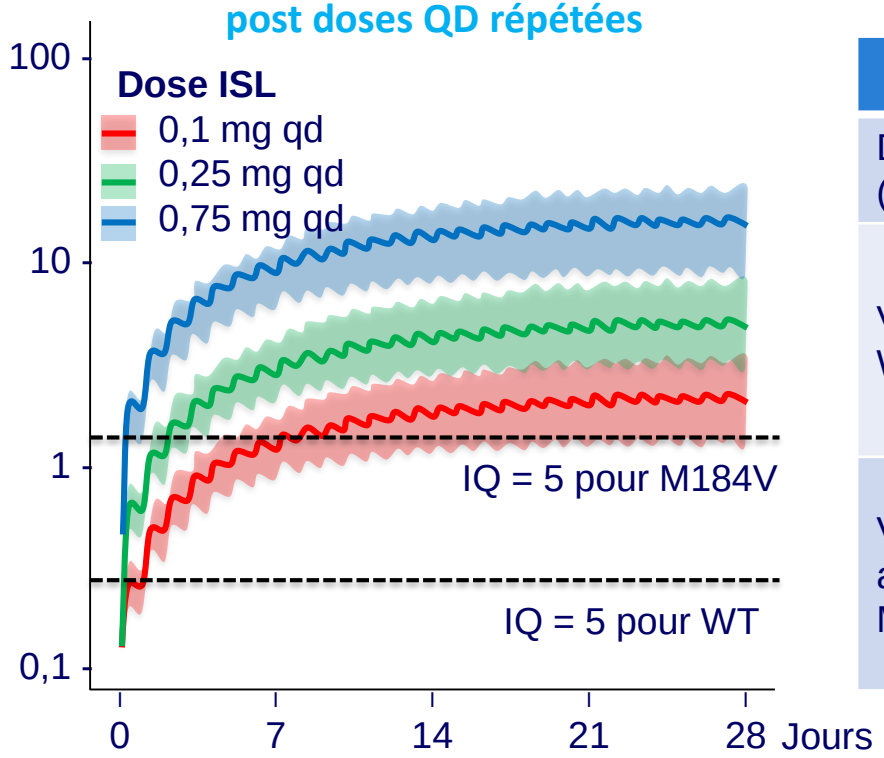
- Bonne tolérance des différentes doses ISL pendant 48S
- Majorité des effets indésirables d'intensité modérée, transitoires et n'ont pas conduit à l'arrêt du traitement
- ISL+DOR = faible impact sur les paramètres métaboliques (changements moyens modestes et non significatifs du cholestérol total, du LDL-C, du HDL-C et des triglycérides entre les bras de traitement) et sur le poids

Molina J.-M. et al. Lancet HIV 2021 May 14. E. DeJesus. Islatravir (ISL, MK-8591) Safety Analysis Through Week 48 From A Phase 2 Trial in Treatment Naïve Adults With HIV-1 Infection – **IAC 2020**.
Molina J.-M. Islatravir in Combination With Doravirine Maintains HIV-1 **Viral Suppression Through 96 Weeks** - **Glasgow 2020**.

Recherche de dose optimale d'ISL chez les patients VIH+ naïfs virologiquement contrôlés

- **Objectif :** recherche de la plus petite dose d'ISL efficace et dénuée d'effet délétère sur les lymphocytes et CD4+
- **Critères de sélection**
  - Efficacité antivirale : dose d'ISL à l'origine d'une exposition PK > seuil d'activité sur VIH WT et avec mutation M184I/V dans les 3 jours post dose
  - Tolérance : à l'origine de modifications identiques sur les lymphocytes comparées au traitement témoin

Simulations des expositions intracellulaires d'ISL-TP (uM) post doses QD répétées



Couverture des doses d'ISL qd sur VIH WT et avec M184V (%)

	Couverture (%)			
Dose ISL (mg qd)		0,1	0,25	0,75
VIH WT	J1	28 %	100 %	100 %
	J3	100 %	100 %	100 %
	EE	100 %	100 %	100 %
VIH avec M84I/V	J1	0 %	0 %	93 %
	J3	26 %	76 %	100 %
	EE	92 %	100 %	100 %

- **Conclusion** : la dose d'ISL 0,25 mg qd permet des expositions intracellulaires d'ISL-TP efficaces en 3 jours sur VIH-1 naïf et porteur de la M184IV
  La dose d'ISL 0,25 mg prédit une réponse CD4 et un profil de tolérance lymphocytaire similaire au traitement ARV standard

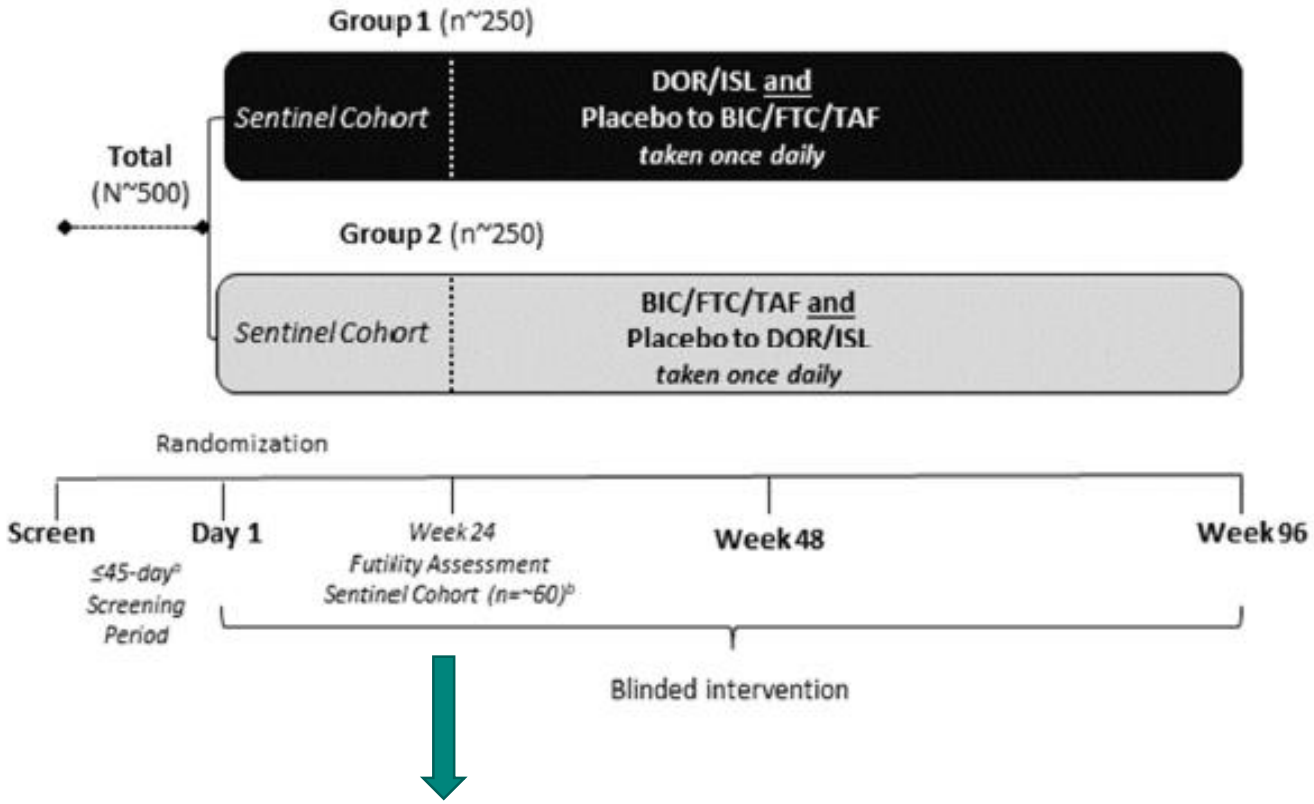
Vargo R, HIV Glasgow 2022, Abs. O45

ISLATRAVIR bilan

- Dose retenue
  - 0,25mg en QD
    - QI > 5 pour WT et M184
    - Pas d'effet sur les Lympocytes et CD4
  - 2mg en QW
- Bonne tolérance
  - Céphalées
  - Pas d'infections
- Plan de développement

Study Design **MK-8591A-053:**

Phase 3 randomized, double-blind
DOR/ISL (100mg/0.25mg) vs BIC/FTC/TAF



Sentinel Cohort enrollment limited to those with Screening HIV-1 RNA level ≤ 100,000 copies/mL

Population

- Treatment naïve adults living with HIV-1

Stratification

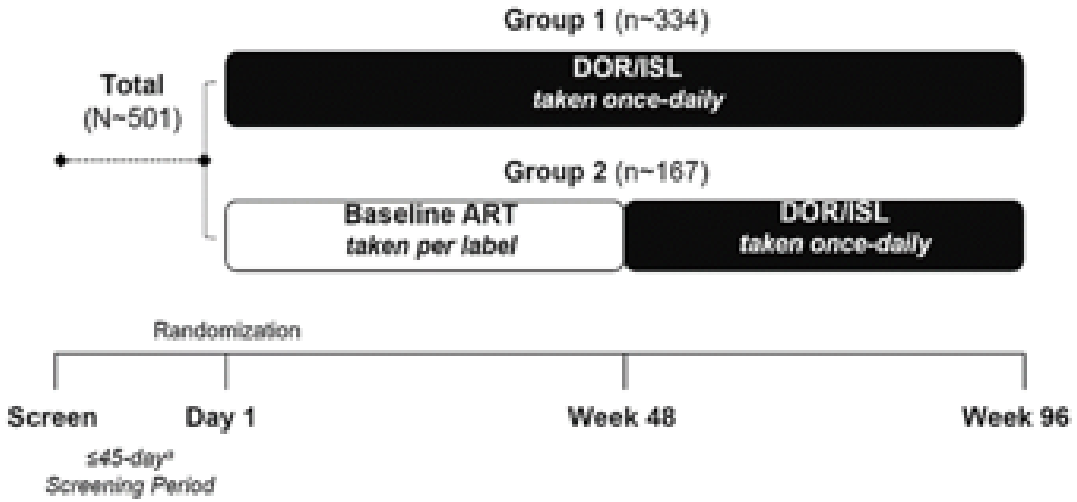
- Screening CD4+ T-cell count:
  - <200 cells/mm^3
  - ≥200 cells/mm^3
- *Screening HIV-1 RNA level:
  - ≤100,000 copies/mL
  - >100,000 copies/mL

*post-Sentinel Cohort

Randomization

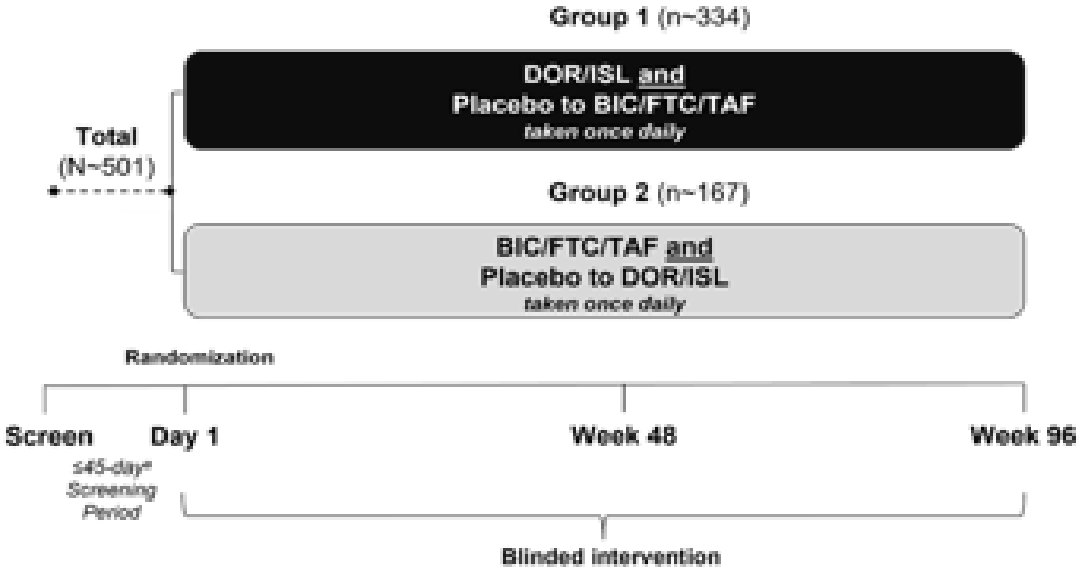
- 1:1 ratio into 1 of 2 treatment groups

DOR/ISL 100 mg/ 0.25 mg Switch Studies (P051/ P052)



P051

- Switch from stable ART
- 2:1 randomization
- Open-label
- Immediate vs. delayed switch (Week 48) from baseline ART
- Stratified by baseline ART
  - InSTI based ART
  - PI based
  - Non-InSTI/Non-PI based

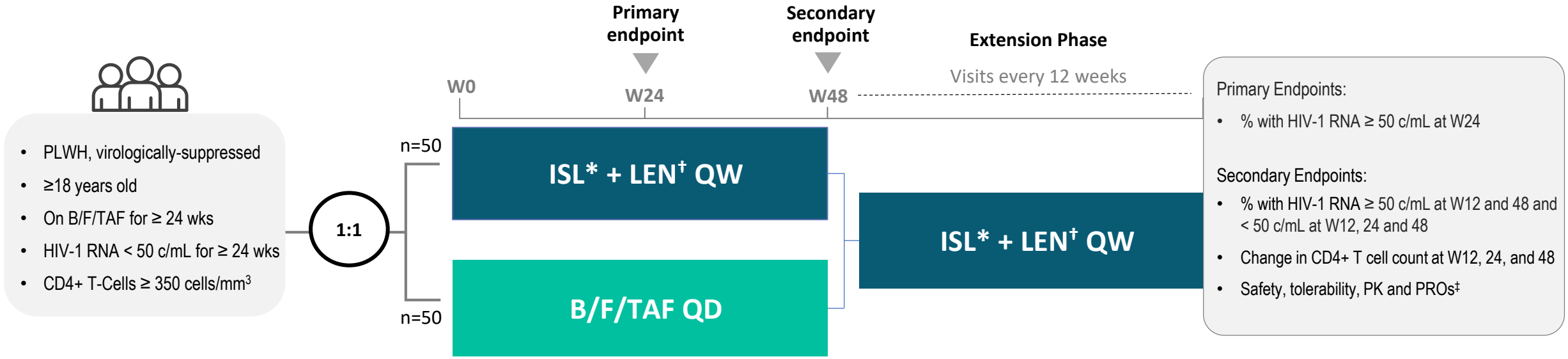


P052

- Switch from BIC/FTC/TAF
- 2:1 randomization
- Double Blind
  - Sponsor unblinded at Week 48
- 96 weeks of follow-up after immediate switch vs. continued BIC/FTC/TAF

ISL + LEN Long-Acting Oral Weekly in PLWH who are Virologically-Suppressed

Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate safety, efficacy, and PK of ISL + LEN in PLWH who are virologically suppressed (N=100)#



*ISL dosing: Day 1: 2 mg [2 × 1 mg capsule]; Day 8 and every week thereafter: 2mg [2 x 1 mg capsule]
†LEN dosing: Day 1: 600 mg [2 × 300 mg tablets]; Day 2: 600 mg [2 × 300 mg tablets]; Day 8 and every week thereafter: 300 mg [1 x 300 mg tablet]
Study design, inclusion criteria, and endpoints depicted for Cohort 2
‡ PROs are exploratory endpoints

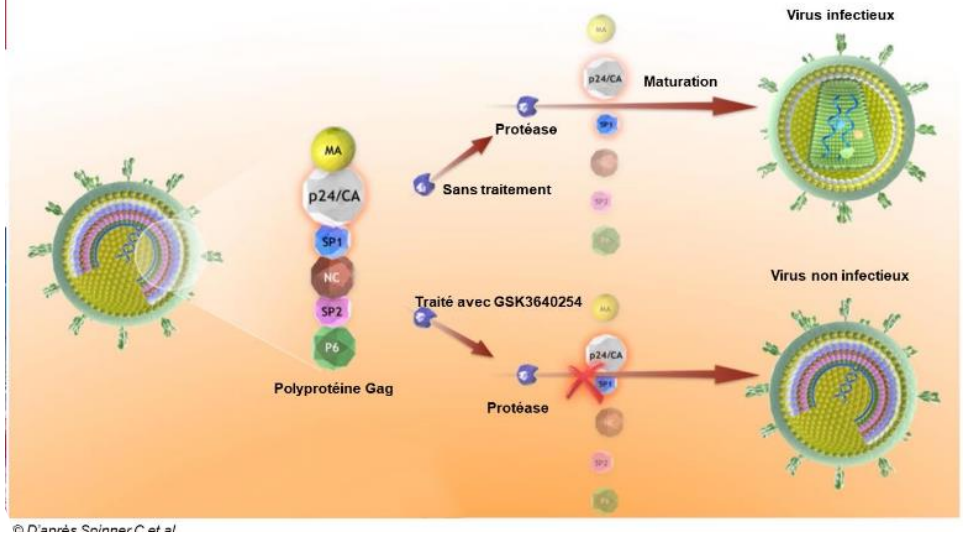
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; ISL, islatravir; LAO, long-acting oral; LEN, lenacapavir; Ph2, Phase 2; PK, pharmacokinetics; PLWH, people living with HIV; PROs, patient reported outcomes; QD, daily; QW, every week; VS, virologically suppressed; W, week; wks, weeks

CHU Poitiers

Clinicaltrials.gov URL: https://clinicaltrials.gov/ct2/show/NCT05052996?term=lenacapavir&draw=1&rank=5. Accessed January 03, 2023

Data on file

Inhibiteur de maturation GSK3640254



- Inhibition de dernier clivage entre la p24 et SP1, entraînant la formation de virus immatures, non infectieux
- PK/PD
  - Absorption lente avec [illegible] graisses
  - T1/2 vie 24h [illegible]
  - Métab[illegible]
- Essa[illegible]
  - A R[illegible]omized, Double-blind, Parallel-group Study to Assess the Effi[illegible]acy, Tolerability, and Resistance Profile of GSK3640254 in Com[illegible]nation With Dolutegravir Compared to Dolutegravir Plus Lamivudine in HIV-1 Infected, Treatment-naïve Adults
  - GSK3640254 100mg + DTG vs GSK3640254 150mg/DTG vs GSK3640254 200mg + DTG vs 3TC 300mg + DTG

ABANDONNE

Les bNab

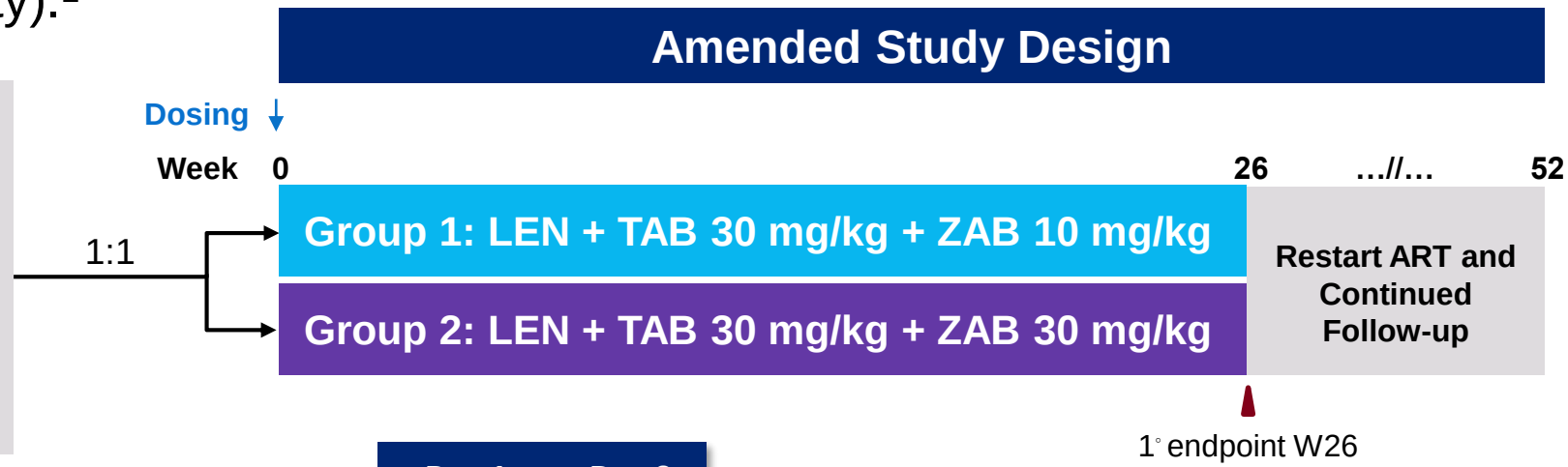
- En association
- En maintenance ou allègement d'ARV?
- Quelle fréquence?

Study Design

- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)
- Study design was modified when LEN was unavailable due to temporary clinical hold (for storage vial compatibility).[1]

Key Inclusion Criteria

- **Adults living with HIV-1**
- **Virologically suppressed ≥ 18 months**
- **Viral susceptibility to both TAB and ZAB**
- **CD4 nadir ≥ 350**
- **CD4 at entry ≥ 500**



	Day 1	Day 2
LEN oral 600 mg		
LEN SC 927 mg		-
TAB IV 30 mg/kg		-
ZAB IV 10 mg/kg or 30 mg/kg		-

HIV RNA measured at least every 4 weeks until Week 26.

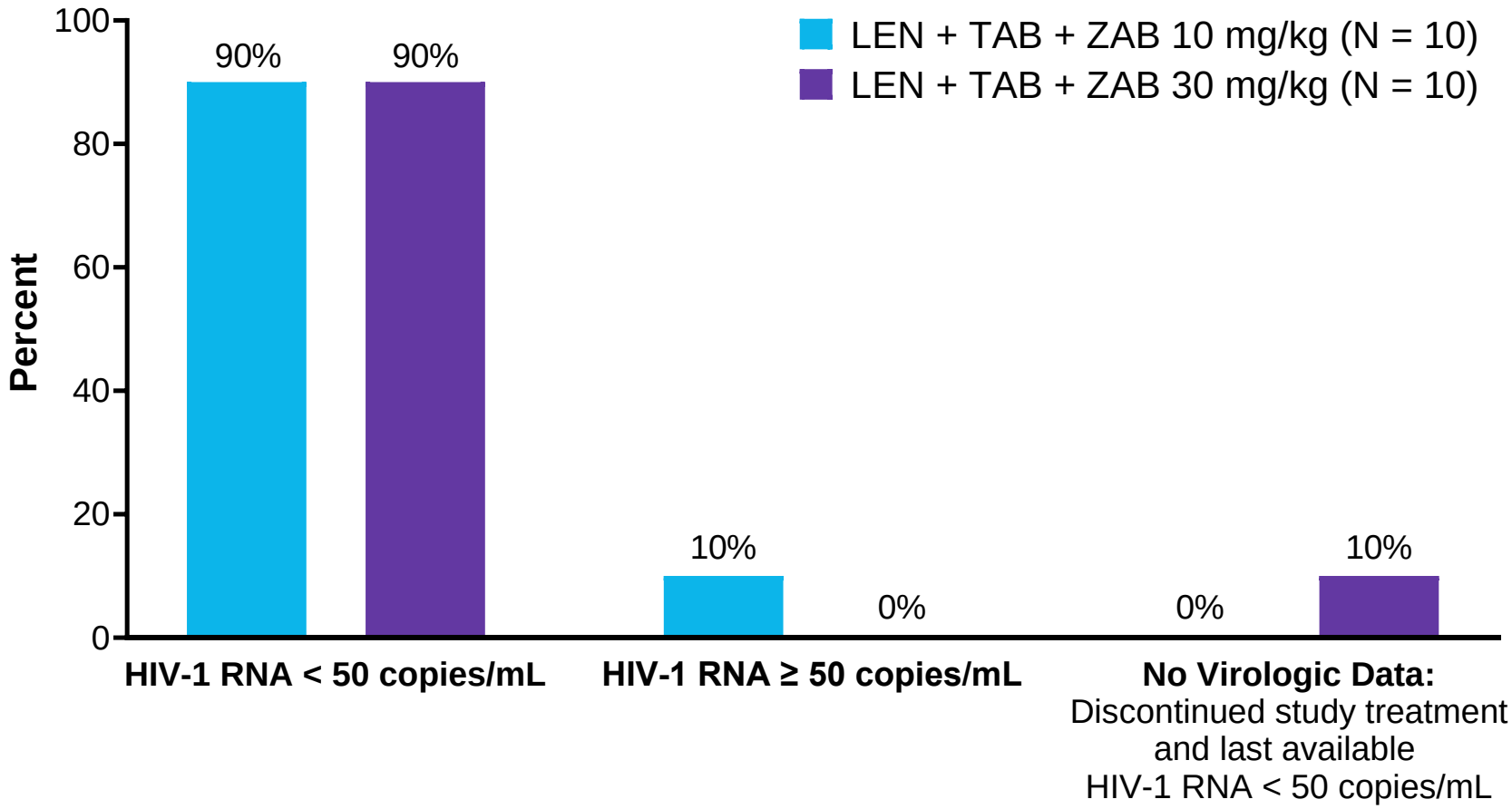
TAB : Teropavimab
ZAB : Zinlirvimab

[1] FDA lifts clinical hold on investigational lenacapavir for the treatment and prevention of HIV. Press release. May 16, 2022.

Enrolled Participant Demographics and Baseline Characteristics

		LEN + TAB + ZAB 10 mg/kg (N = 11)	LEN + TAB + ZAB 30 mg/kg (N = 10)	Total (N = 21)
Age, median (range)		46 (31 to 61)	37 (25 to 59)	44 (25 to 61)
Sex at birth, n	Male	11	7	18
	Female	0	3	3
Race, n	Asian	2	1	3
	Black	1	2	3
	White	7	5	12
	Other	1	2	3
Hispanic or Latino ethnicity, n		4	3	7
Weight (kg), median (range)		90.2 (58.9 to 150.0)	92.9 (60.2 to 143.0)	90.2 (58.9 to 150.0)
Body mass index (kg/m^2), median (range)		30.2 (21.6 to 42.9)	30.2 (21.6 to 54.1)	30.2 (21.6 to 54.1)
CD4 cell count (per mL), median (range)		778 (547 to 1391)	1024 (667 to 1644)	909 (547 to 1644)
Duration of baseline ART (years), median (range)		3.6 (2.4 to 4.8)	2.6 (2.0 to 5.5)	2.6 (2.0 to 5.5)
Time since HIV diagnosis (years), median (range)		12.4 (6.4 to 26.3)	5.3 (2.6 to 22.4)	8.2 (2.6 to 26.3)

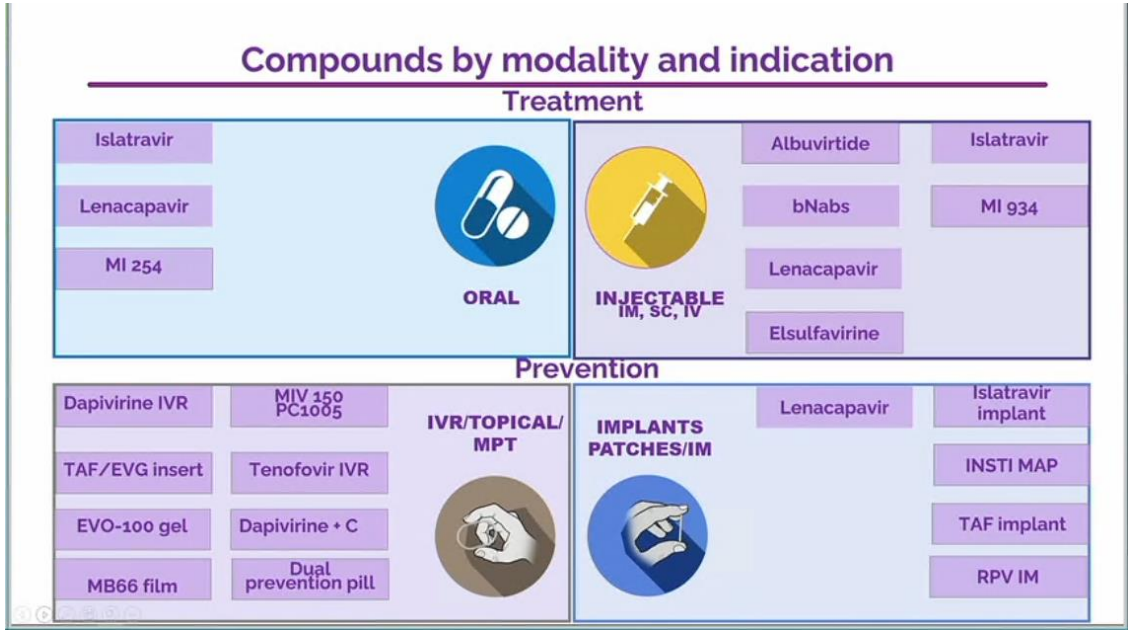
Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

[1] Participant withdrew due to personal decision.

Conclusion



- Développement de molécules
  - Différentes galéniques LA+++
  - « curatif » et préventif
  - Prétraités et naïfs
- Mais avec qui en association
  - Attention au risque de monothérapie fonctionnelle
- Développer des outils pour aider les patients et les soignants