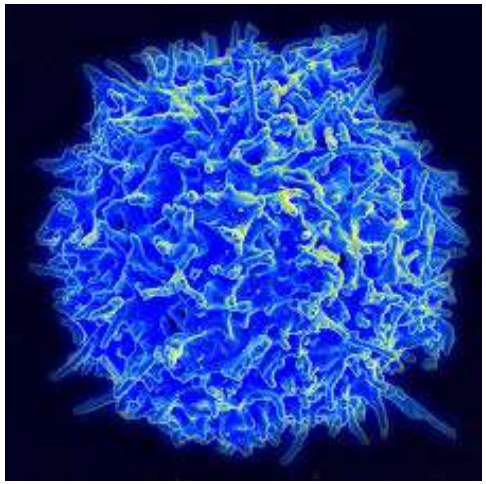
XVI CURSO EN AVANCES EN INFECCIÓN VIH Y HEPATITIS VIRALES

Estrategias de simplificación en TAR: pasado presente y futuro.

El papel de los fármacos long acting

Vigo, 28 y 29 de enero de 2022



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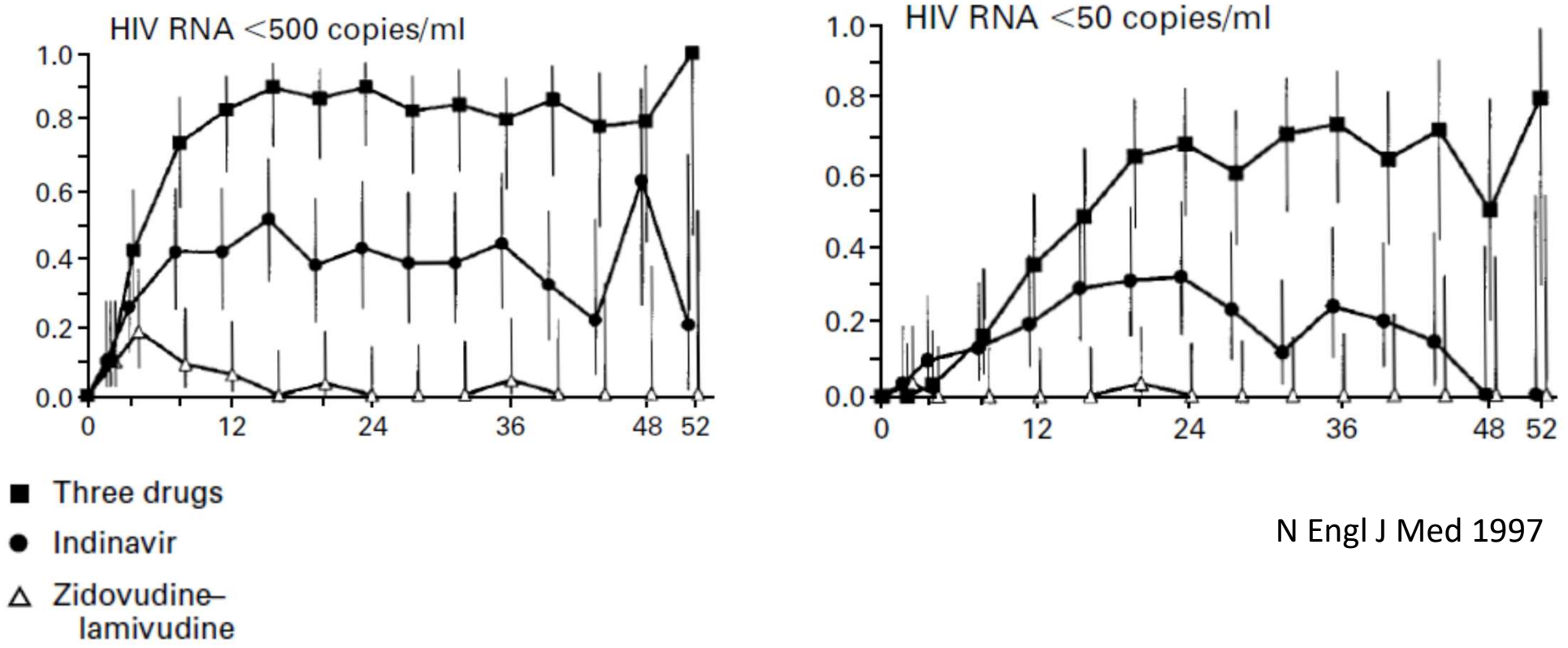
Conflictos de interés

- Research grants and/or honoraria for advisories and/or conferences from Viiv, Gilead, Janssen and MSD.

The New England Journal of Medicine

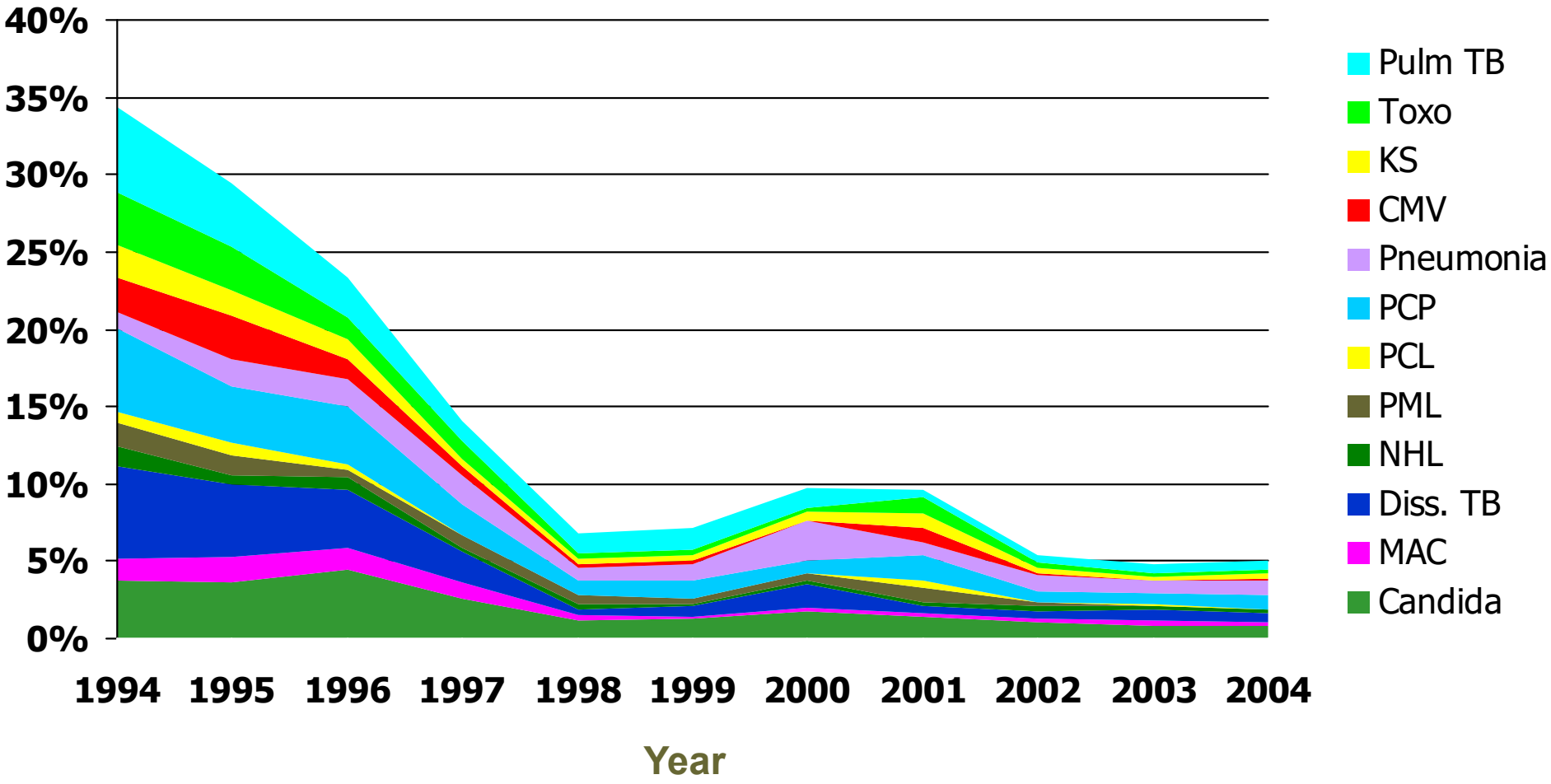
TREATMENT WITH INDINAVIR, ZIDOVUDINE, AND LAMIVUDINE IN ADULTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND PRIOR ANTIRETROVIRAL THERAPY

ROY M. GULICK, M.D., M.P.H., JOHN W. MELLORS, M.D., DIANE HAVLIR, M.D., JOSEPH J. ERON, M.D., CHARLES GONZALEZ, M.D., DEBORAH MCMAHON, M.D., DOUGLAS D. RICHMAN, M.D., FRED T. VALENTINE, M.D., LESLIE JONAS, B.S., ANNE MEIBOHM, PH.D., EMILIO A. EMINI, PH.D., AND JEFFREY A. CHODAKEWITZ, M.D.



N Engl J Med 1997

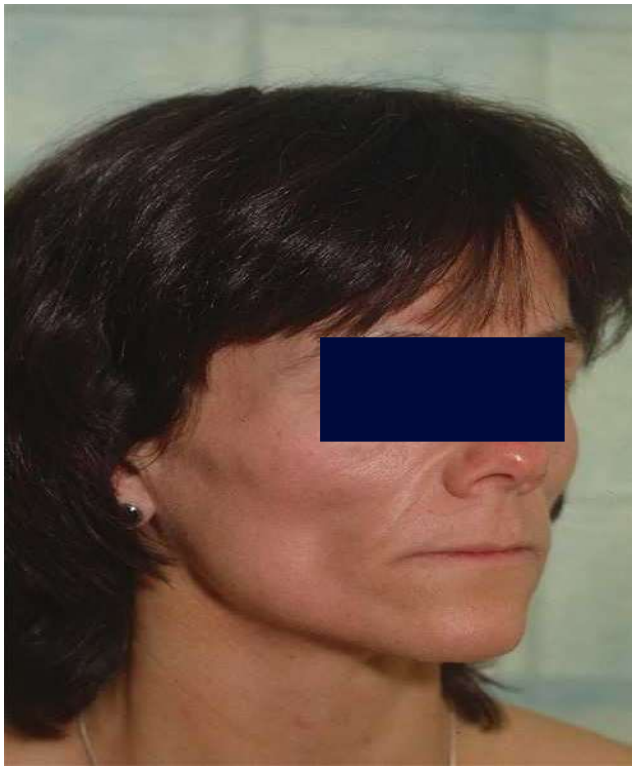
Enfermedades diagnósticas de SIDA Hospital Universitari de Bellvitge Barcelona (1994-2004)

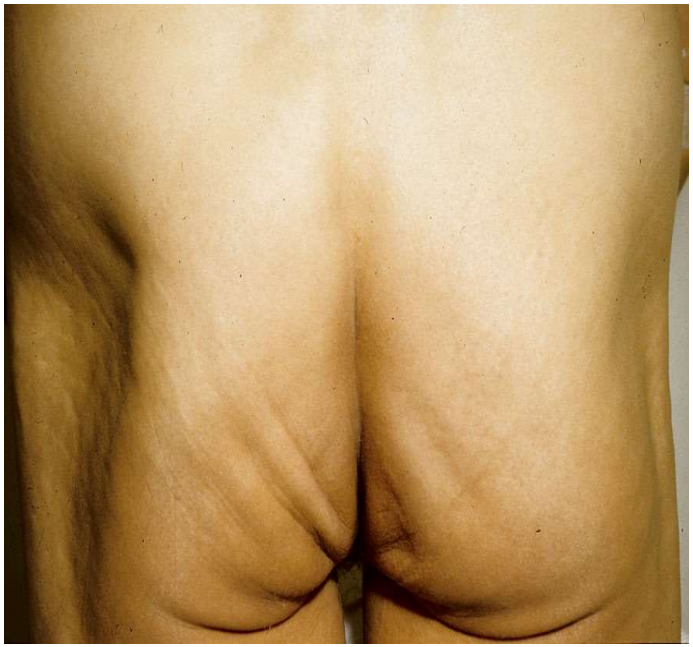


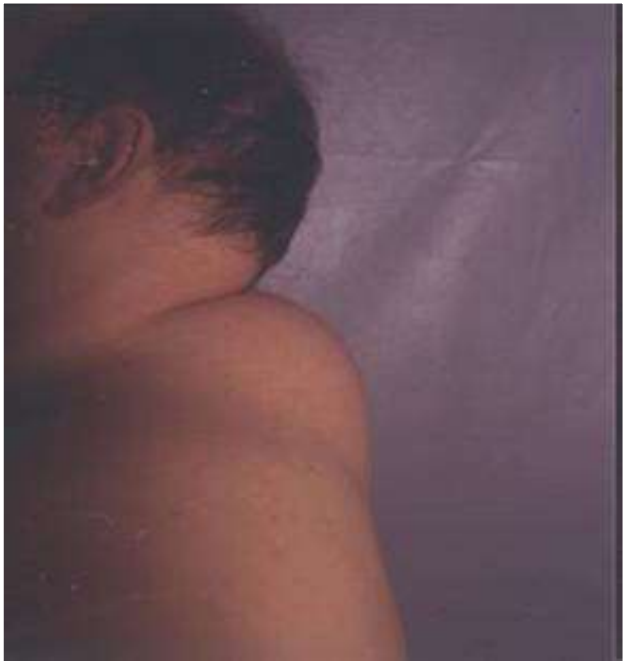
Pero muchas limitaciones del TAR

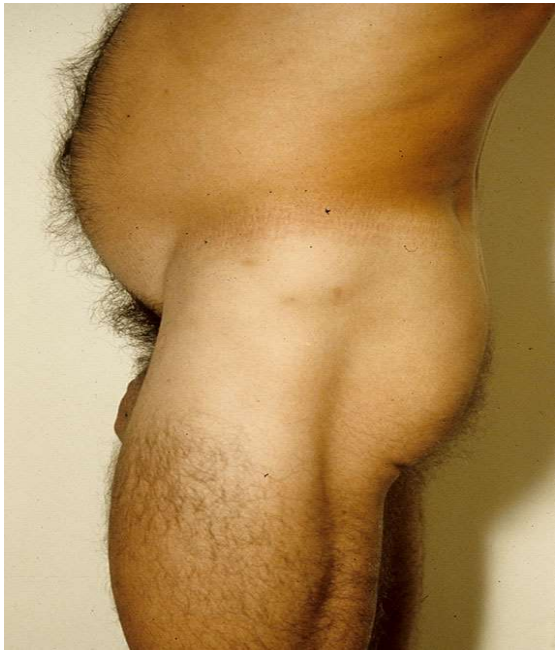
- ✓ **Toxicidades** ***(renal, ósea, metabolica, ….)***
- ✓ **Dificultades en adherencia a largo plazo**

  - *número de pastillas y/o dosis, restricciones alimentarias…*
- ✓ **Interacciones** *(con otros ARV u otros fármacos)*
- ✓ **Coste**









Estrategias de cambio en TAR

- **Objectivo:**

  Mantener la supresión virológica al optimizar el TAR en términos de tolerabilidad a corto y largo, y/o comodidad de administración

Esto puede ayudar a :

- *Reducir toxicidades (metabólica, renal…)*
- *Mejorar la adherencia (pautas más simples)*
- *Mejorar la calidad de vida*
- *Éxito a largo plazo del TAR*

Estrategias de cambio para reducir costes del TAR

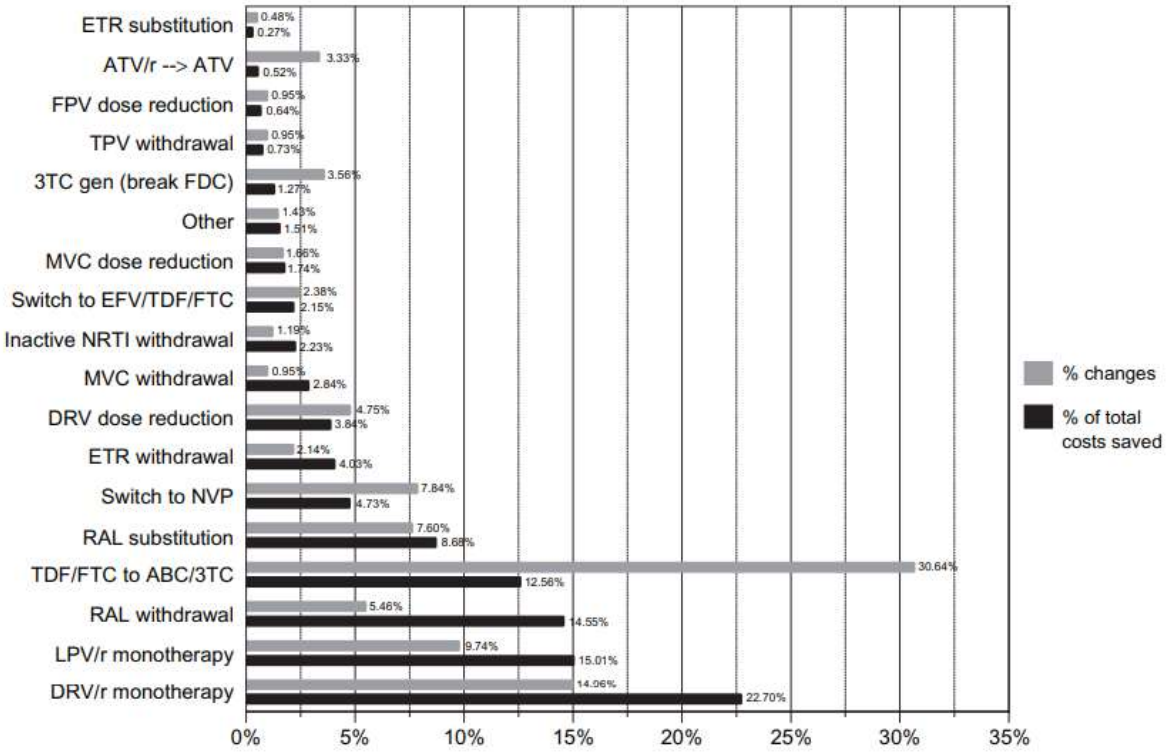


Figure 1 Correlation between the number of switches identified as cost-saving measures and the costs saved with them (shown as percentages).
Abbreviations: ABC/3TC, abacavir/lamivudine; ATV, atazanavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; ETR, etravirine; FDC, fixed-dose combinations; FPV, fosamprenavir; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RAL, raltegravir; TDF/FTC, tenofovir/emtricitabine; TPV, tipranavir; 3TC gen, generic lamivudine.

Cohort, n=2401
16% of treated pts
Savings of €87,410/month

At 48 wks:
84.1% same ARV regimen
2.1% virologic failure
6.9% changes due to AE

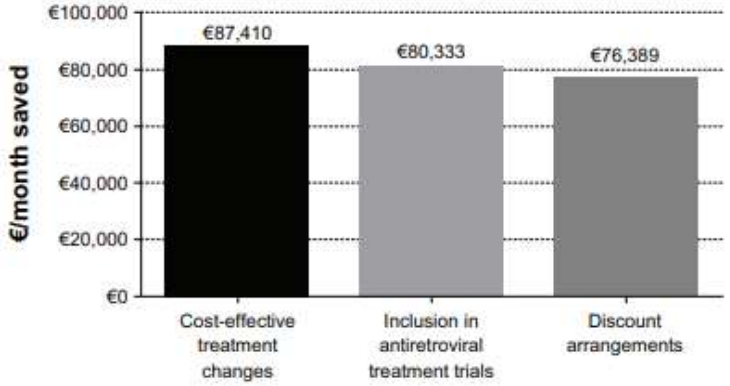


Figure 2 Final savings achieved during the study period with the three main cost-saving strategies: cost-effective treatment changes, inclusion in antiretroviral treatment trials (with antiretroviral medication totally or partially paid for by the sponsor of the clinical trial), and discount arrangements (shown as € per month saved).

Llibre JM, et al. Clin Econ Outcomes Res 2013; 5: 215-21

Estrategias de cambio/simplificación en TAR

Riesgos potenciales:

- Rebote de la carga viral
  - Menor barrera genética, historia de FV y resistencias, restricciones alimentarias
- Interacciones entre fármacos desconocidas o no esperadas
  - con ARV u otros fármacos
- Nuevas toxicidades y/o no mejoría de previas (lipodistrofia, aumento de peso?)

ORIGINAL ARTICLE

Substitution of Nevirapine, Efavirenz, or Abacavir for Protease Inhibitors in Patients with Human Immunodeficiency Virus Infection

Esteban Martínez, M.D., Juan A. Arnaiz, M.D., Daniel Podzamczer, M.D., David Dalmau, M.D., Esteban Ribera, M.D., Pere Domingo, M.D., Hernando Knobel, M.D., Melcior Riera, M.D., Enric Pedrol, M.D., Lluis Force, M.D., Josep M. Llibre, M.D., Ferran Segura, M.D., Cristóbal Richart, M.D., Cristina Cortés, M.D., Manuel Javaloyas, M.D., Miquel Aranda, M.D., Ana Cruceta, M.D., Elisa de Lazzari, B.Sc., and José M. Gatell, M.D., for the Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team*

Table 2. Outcome of Therapy.

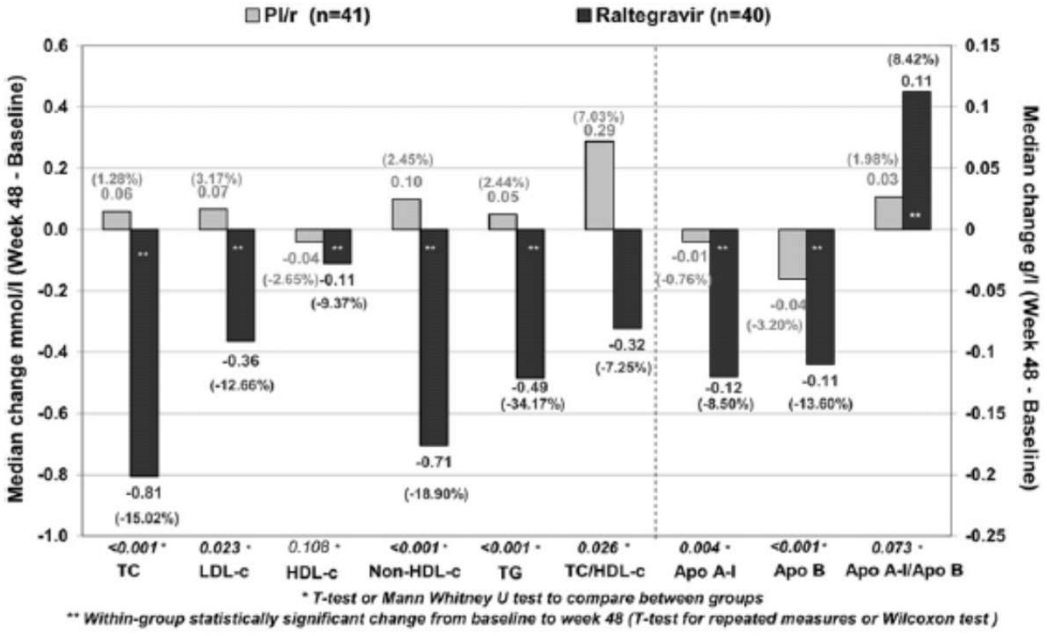
Outcome	Nevirapine (N=155)	Efavirenz (N=156)	Abacavir (N=149)
	no. of patients		
Death	1	2	1
Progression to AIDS*	0	0	2
Virologic failure	14	7	16
While taking study medication	8	5	16
After switching study medication	6	2	0
Lost to follow-up	3	6	8
Switched study medication without virologic failure	20	29	9
Response; still taking study medication at 12 mo†	117	112	113

* AIDS denotes acquired immunodeficiency syndrome.
† Six additional patients in the nevirapine group, four in the efavirenz group, and nine in the abacavir group continued to take study medication at 12 months despite the development of virologic failure.

LDL subclasses and lipoprotein-phospholipase A2 activity in suppressed HIV-infected patients switching to raltegravir: Spiral substudy

Maria Saumoy[a], José Luis Sánchez-Quesada[b], Esteban Martínez[c], Josep Maria Llibre[d], Esteban Ribera[e], Hernando Knobel[f], Josep Maria Gatell[c], Bonaventura Clotet[d], Adrian Curran[e], Jordi Curto[a], Margarita Masó[a], Jordi Ordoñez-Llanos[b], Daniel Podzamczer[a,*]

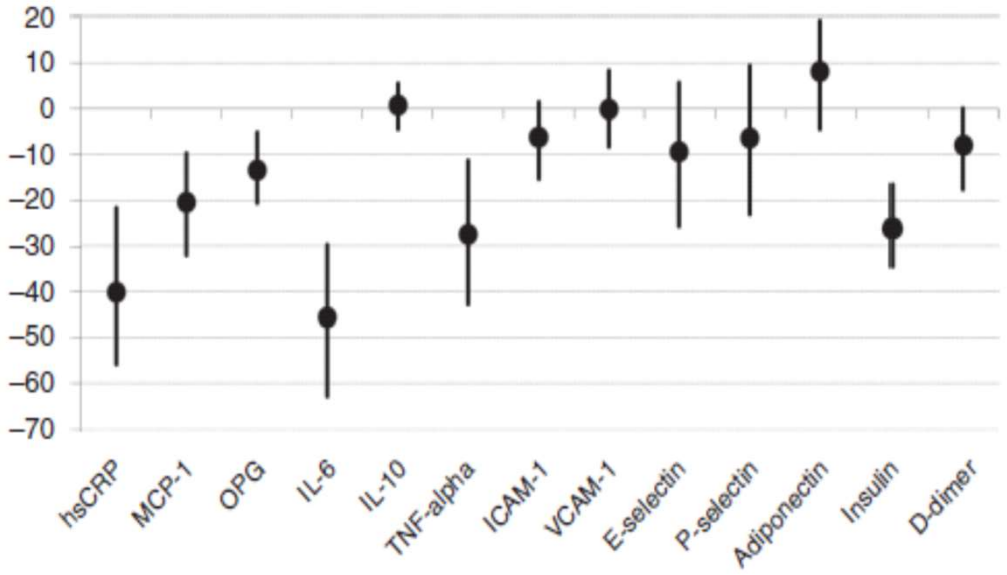
Atherosclerosis 225 (2012) 200–207



Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir

Esteban Martínez[a], Polyana M. D'Albuquerque[a], Josep M. Llibre[b], Felix Gutierrez[c], Daniel Podzamczer[d], Antonio Antela[e], Juan Berenguer[f], Pere Domingo[g], Xabier Moreno[a], Ignacio Perez[a], Judit Pich[a], José M. Gatell[a], for the SPIRAL Trial Group

AIDS 2012, 26:2315–2326



Improvement in lipid parameters and in proinflammatory markers after swtching to RAL

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

(Last updated June 3, 2021; last reviewed June 3, 2021)

Key Considerations and Panel's Recommendations

- Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance have made it possible to consider switching a person with HIV from an effective regimen to an alternative regimen in some situations.
- The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options.
- Adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt a regimen switch.
- It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results before selecting a new ARV regimen **(AI)**.
- A long-acting ARV regimen, such as the combination of injectable cabotegravir and rilpivirine, is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs **(AI)**.

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

(Last updated June 3, 2021; last reviewed June 3, 2021)

Key Considerations and Panel's Recommendations

- Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy **is not recommended (AI)**.
- When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued **(AII)**. Using lamivudine or emtricitabine as the only drug in a regimen with HBV activity **is not recommended (AII)**, because HBV resistance to these drugs can emerge. Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.
- Consultation with an HIV specialist is recommended when planning a regimen switch for a patient with a history of resistance to one or more drug classes **(AIII)**.
- Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Options for 2-drug therapy in VS patients

- Boosted PI +3TC
- DTG/RPV
- DTG/3TC
- DTG + DRVr
- LAI CAB + RPV

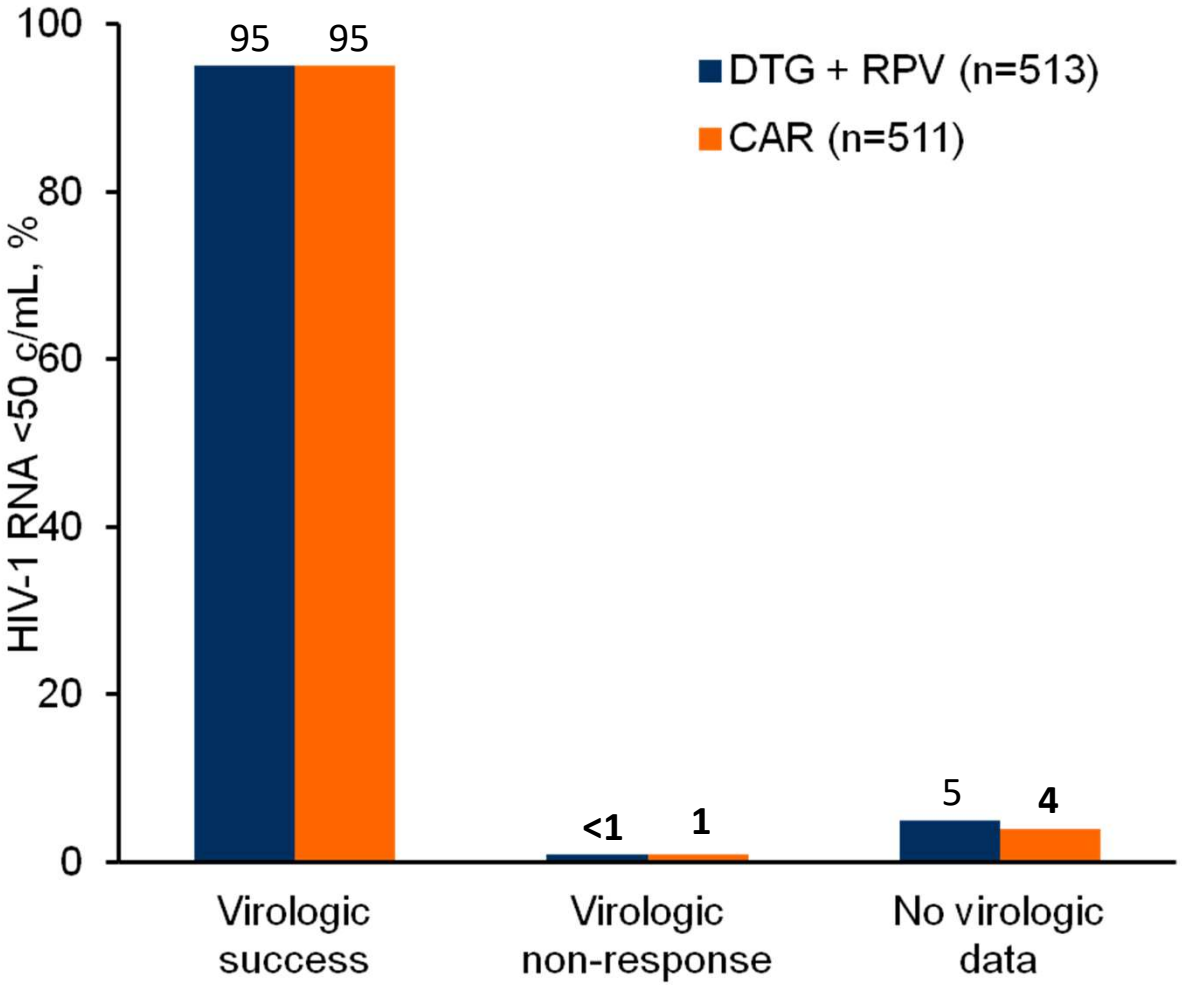
Options under investigation (some phase 2/3 studies)

- Coming during the talk….(no spoiler)

SWORD: DTG + RPV

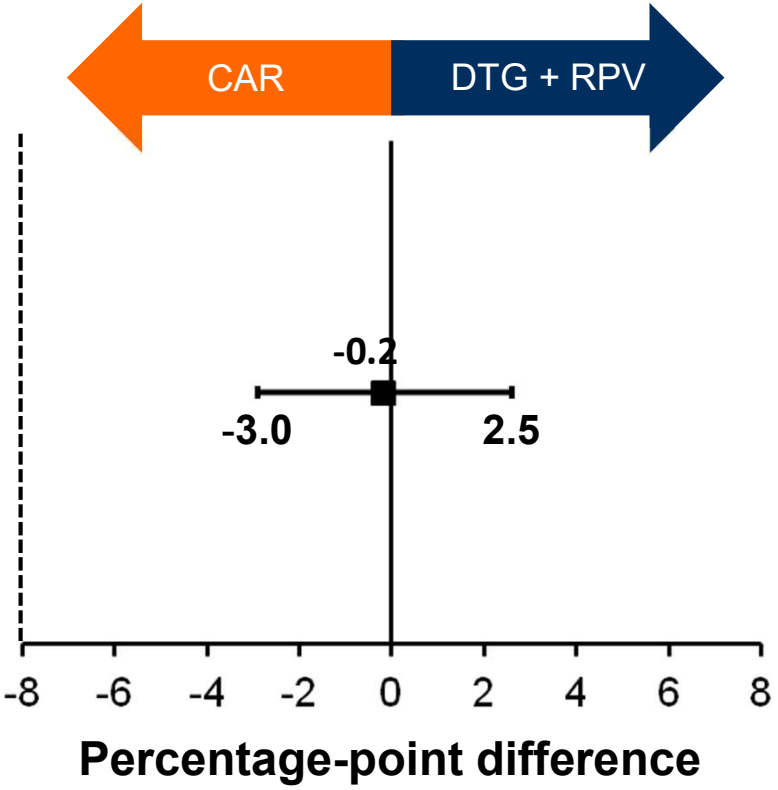
Snapshot Outcomes at Week 48 (Pooled)

Virologic outcomes



[a]Adjusted for age and baseline 3rd agent.

Adjusted treatment difference (95% CI)[a]



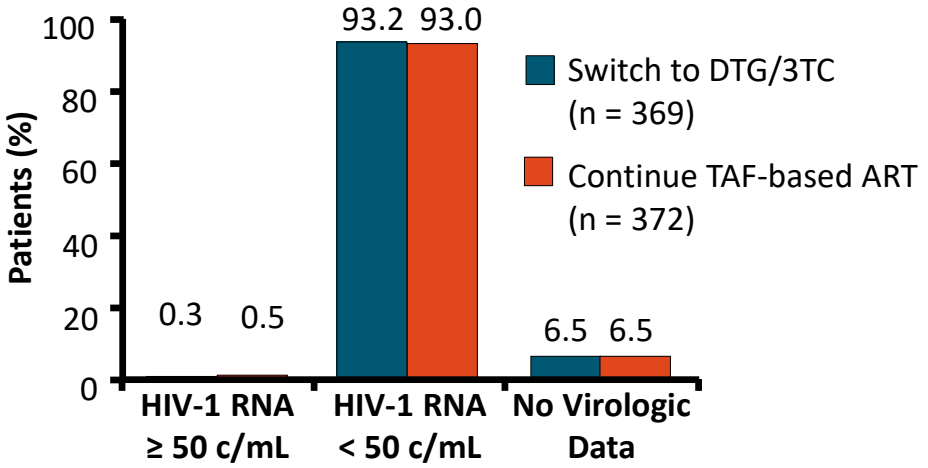
DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48

Llibre et al. CROI 2017; Seattle, WA. Abstract 2421.

TANGO: Switch to DTG/3TC vs Continuing TAF-Based 3-Drug or 4-Drug Regimen

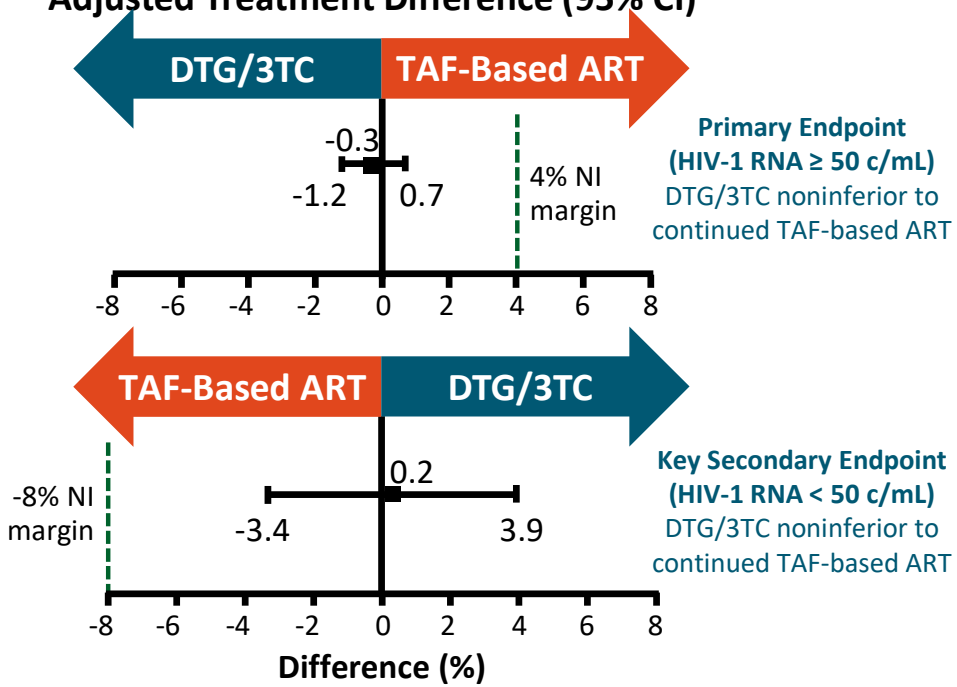
- International, randomized, open-label phase III noninferiority study in adults with HIV-1 RNA < 50 c/mL for > 6 mos on TAF-based ART

Virologic Outcomes by FDA Snapshot (ITT-E) at Wk 48



- No CVW in DTG/3TC arm, CVW in 1 (< 1%) patient in TAF-based ART arm; no resistance detected at failure
- All 7 patients (4 in DTG/3TC group, 3 in TAF-based ART group) with proviral M184V/I mutation at baseline maintained HIV-1 RNA < 50 c/mL at Wk 48

Adjusted Treatment Difference (95% CI)*



*Adjusted for baseline third agent class.

van Wyk. IAS 2019. Abstr WEAB0403LB.

TANGO study 48w: no differences in PCR and D-dímer (n= 369)

Parameter	Treatment	n/N	Baseline Geometric Mean (95% CI)[a]	Visit to baseline (95% CI)[b]	Treatment ratio (95% CI)[c]	*P* value[d]
Blood D-dimer, nmol/L FEU	**DTG/3TC**	**334/369**	**1.69 (1.59, 1.79)**	**0.968 (0.920, 1.019)**	**0,973 (0.907, 1.044)**	**0.440**
	TAF-based regimen	334/371	1.66 (1.58, 1.76)	0.995 (0.948, 1.044)		
Serum hs-CRP, mg/L	**DTG/3TC**	**342/369**	**1.37 (1.23, 1.53)**	**1.012 (0.911, 1.124)**	**0.934 (0.811, 1.075)**	**0.341**
	TAF-based regimen	342/371	1.30 (1.16, 1.46)	1.083 (0.986, 1.190)		
Serum IL-6, ng/L	**DTG/3TC**	**343/369**	**1.64 (1.52, 1.78)**	**0.990 (0.909, 1.078)**	**1.163 (1.045, 1.293)**	**0.006**
	TAF-based regimen	340/371	1.67 (1.54, 1.80)	0.852 (0.800, 0.907)		
Serum sCD14, ng/L	**DTG/3TC**	**343/369**	**1606.5 (1573.1, 1640.6)**	**0.953 (0.933, 0.973)**	**0.971 (0.942, 1.000)**	**0.048**
	TAF-based regimen	343/371	1578.6 (1546.4, 1611.4)	0.982 (0.962, 1.002)		
Serum sCD163, ng/L	**DTG/3TC**	**342/369**	**660.9 (630.5, 692.7)**	**0.916 (0.889, 0.943)**	**1.013 (0.974, 1.054)**	**0.508**
	TAF-based regimen	342/371	642.0 (615.3, 670.0)	0.904 (0.881, 0.927)		

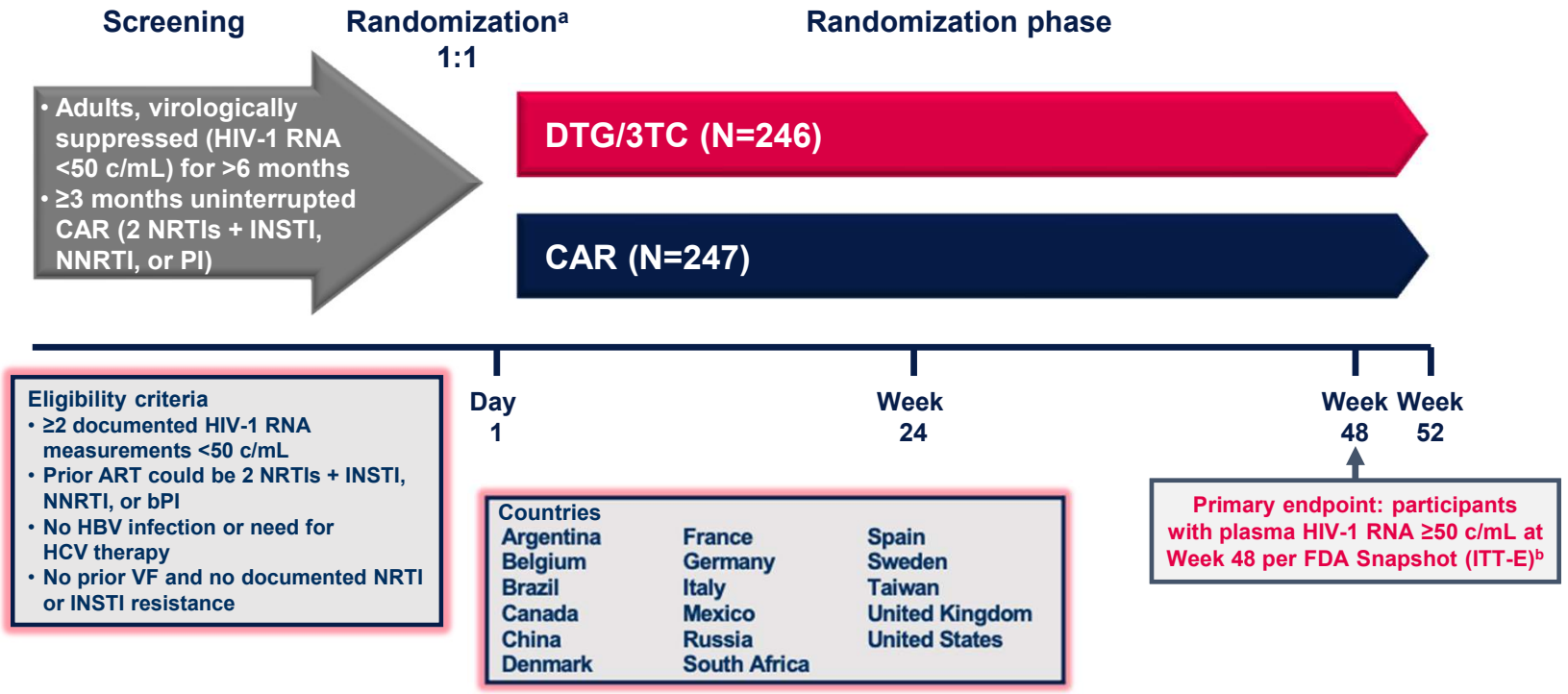
DTG, dolutegravir; FEU, fibrinogen equivalent unit; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; MMRM, mixed model repeated measures; sCD14, soluble CD14; sCD163, soluble CD163; TAF, tenofovir alafenamide; 3TC, lamivudine. [a]Ratio is the estimated adjusted ratio (Week 48 to baseline) in each group calculated using MMRM applied to change from baseline in loge-transformed data adjusting for the following: treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, body mass index (continuous), smoking status, hepatitis C virus coinfection status, loge-transformed baseline biomarker (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Treatment ratio is DTG/3TC to TAF-based regimen. [c]*P* value for

Small effect on inflammatory markers with no differences in D-dimer or usPCR , and with differences in diferent directions in IL-6 and sCD14

Adapted from van Wyk J, Ajana F, Bisshop F, et al. Clin Infect Dis, ciz1243, https://doi.org/10.1093/cid/ciz1243

SALSA Phase III Study Design

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

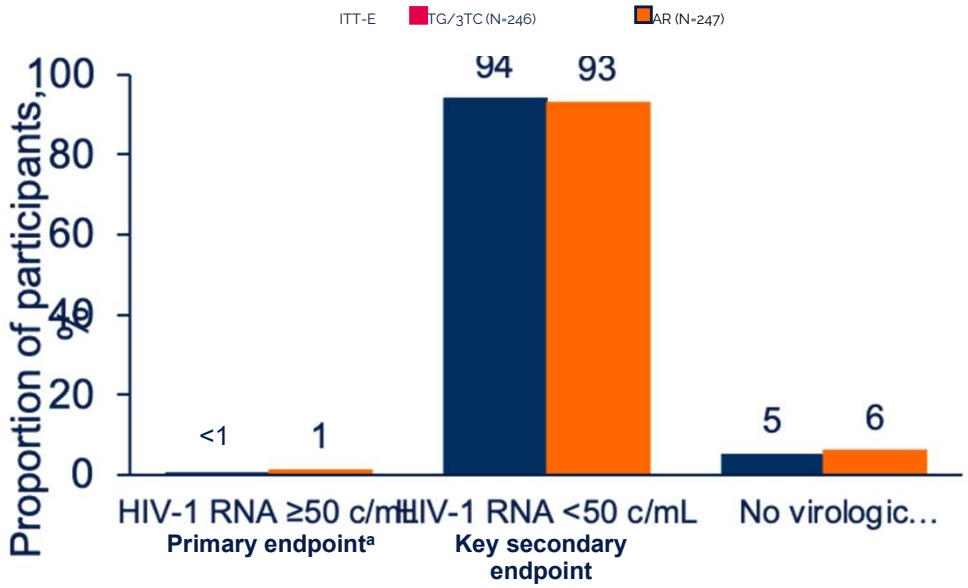


Llibre et al. IAS 2021; Virtual. Slides OALB0303.

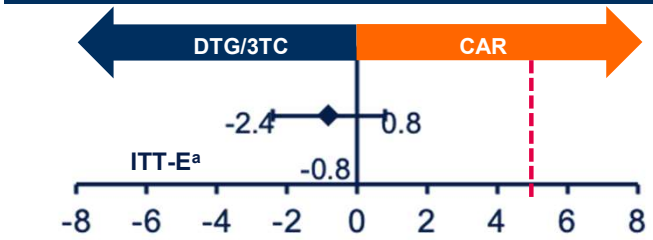
[a]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]5% non-inferiority margin.

DTG/3TC Is Non-Inferior to CAR at Week 48

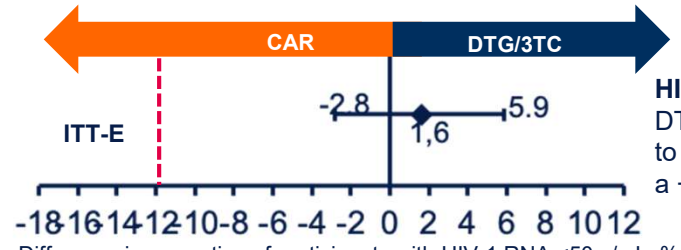
Virologic outcomes (Snapshot analysis)



Adjusted treatment difference (95% CI)[b]



HIV-1 RNA ≥50 c/mL
DTG/3TC is non-inferior to CAR at Week 48 based on a 5% non-inferiority margin



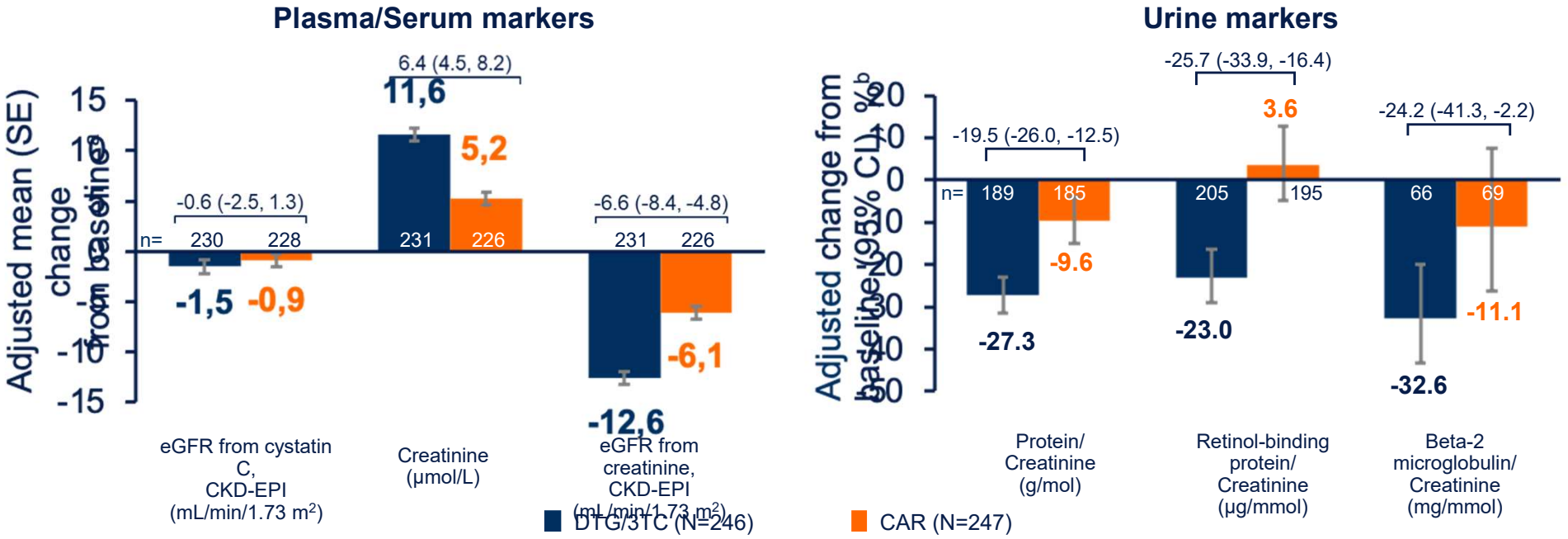
HIV-1 RNA <50 c/mL
DTG/3TC is non-inferior to CAR at Week 48 based on a −12% non-inferiority margin

- In the per-protocol population, 1/222 (0.5%) in the DTG/3TC group and 3/234 (1.3%) in the CAR group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.8%; 95% CI, −2.5% to 0.9%)

Llibre et al. IAS 2021; Virtual. Slides OALB0303.

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − CAR) adjusting for baseline third agent class.

Change in Renal Biomarkers at Week 48: Safety Population

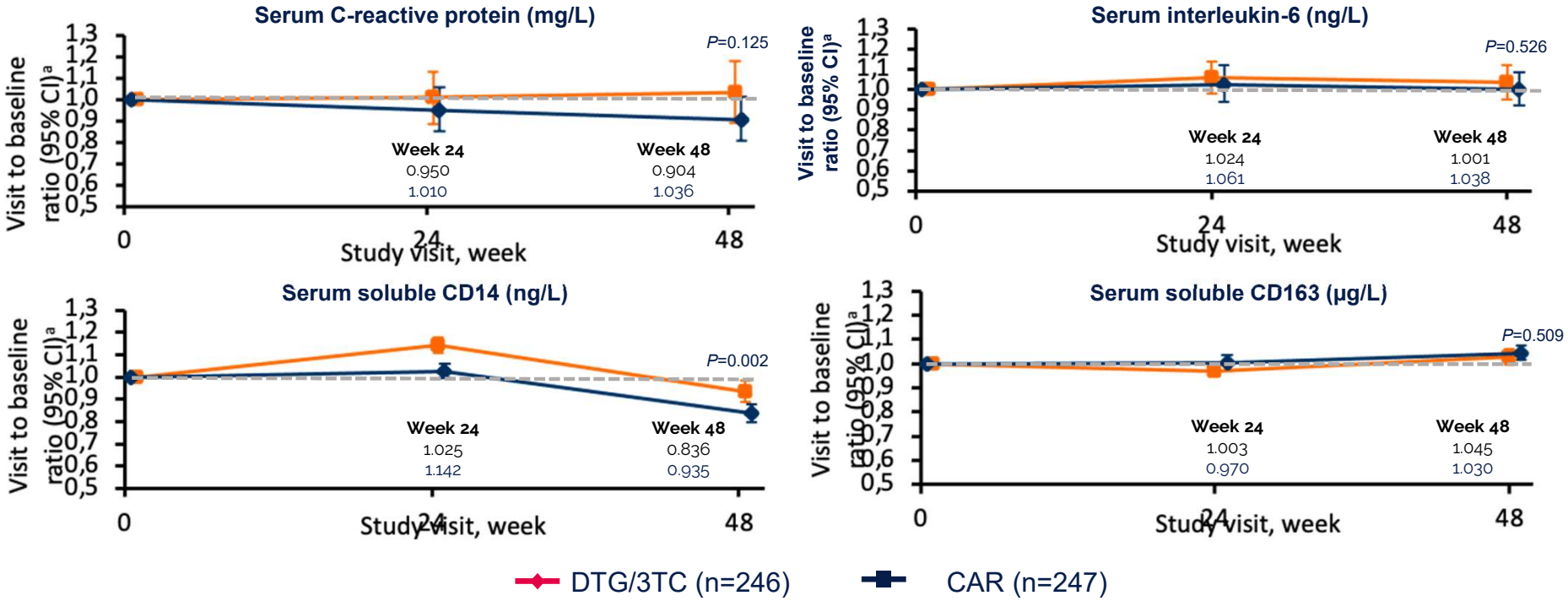


- Similar small changes in eGFR from cystatin C were observed in both treatment groups; decreases in eGFR by creatinine were observed in both treatment groups, with a greater decrease with DTG/3TC
- Improvements in markers for proximal tubular renal function were observed with DTG/3TC

Adjusted mean treatment difference (95% CI) displayed above treatment groups.
[a]Estimated mean change from baseline at Week 48 in each group calculated from MMRM adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), presence of diabetes mellitus, presence of hypertension, baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Based on estimated geometric means ratio of Week 48 vs baseline. Based on the same model as plasma/serum markers except adjusting for $\log_e$-transformed baseline biomarker value. n = number of participants with non-missing data at baseline and Week 48.

Llibre et al. IAS 2021; Virtual. Slides OALB0303.

Change in Inflammatory Biomarkers at Week 48: Safety Population



MMRM analysis was not performed for D-dimer due to high proportion of participants with D-dimer < LLQ in both treatment groups. Baseline geometric mean values (DTG/3TC group; CAR group): C-reactive protein (1.34; 1.27), interleukin-6 (1.73; 1.68), soluble CD14 (1.55×10^6; 1.46×10^6), and soluble CD163 (538.18; 541.70).

[a]Ratio is the estimated adjusted ratio (Week 144 to baseline) in each group calculated using MMRM applied to change from baseline in $\log_e$-transformed data adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), smoking status, HCV co-infection status, $\log_e$-transformed baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

Llibre et al. IAS 2021; Virtual. Slides OALB0303.

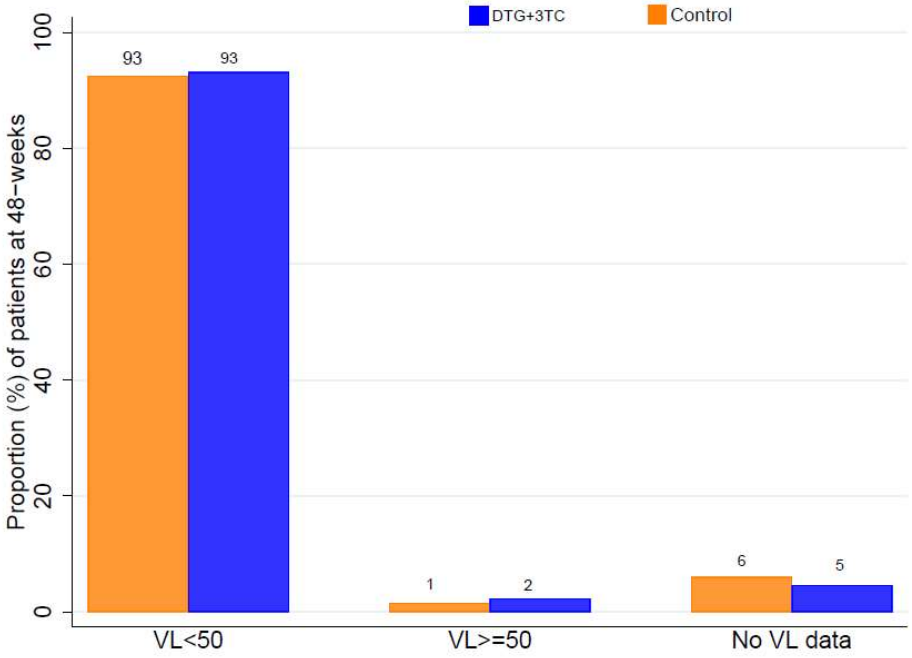
Differences in weight change according to previous ART regimens

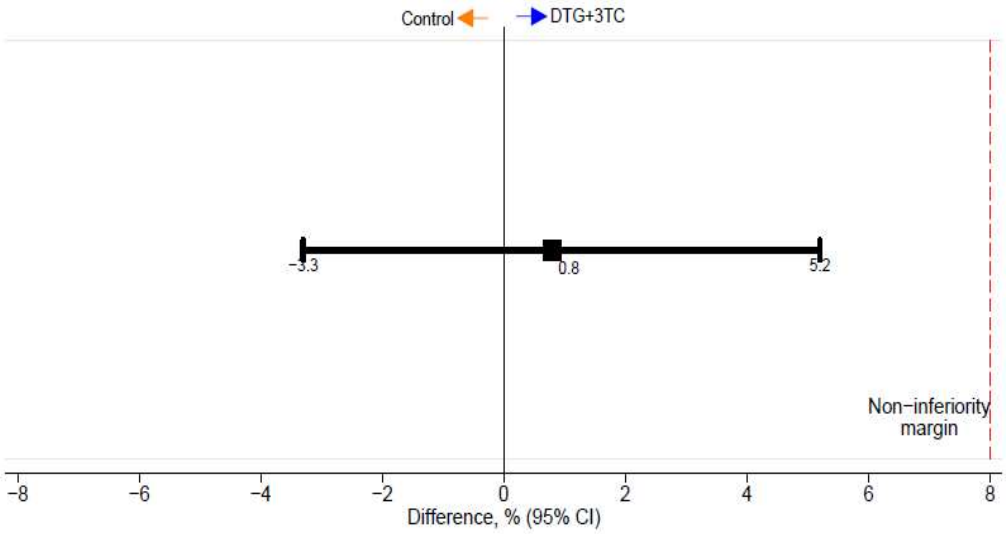
Weight Gain after Switching to DTG/3TC: Lessons from TANGO and SALSA

Study	Weight change (kg): DTG/3TC vs. CAR	Demographics	Baseline TDF use	Baseline EFV use
TANGO	0.81 vs. 0.76 kg	8% female 23% ≥50 yr 21% non-white	0%	<1.5%
SALSA	2.1 vs. 0.6 kg	39% female 39% ≥50 yr 41% non-white	44%	32%

- **Potential reasons more weight gain seen with DTG/3TC in SALSA than in TANGO**
  - Higher risk population: greater proportion female, non-white, > age 50
  - Higher proportion were on medication that may attenuate weight gain (TDF, EFV withdrawal of those medicines may have led to greater weight gain

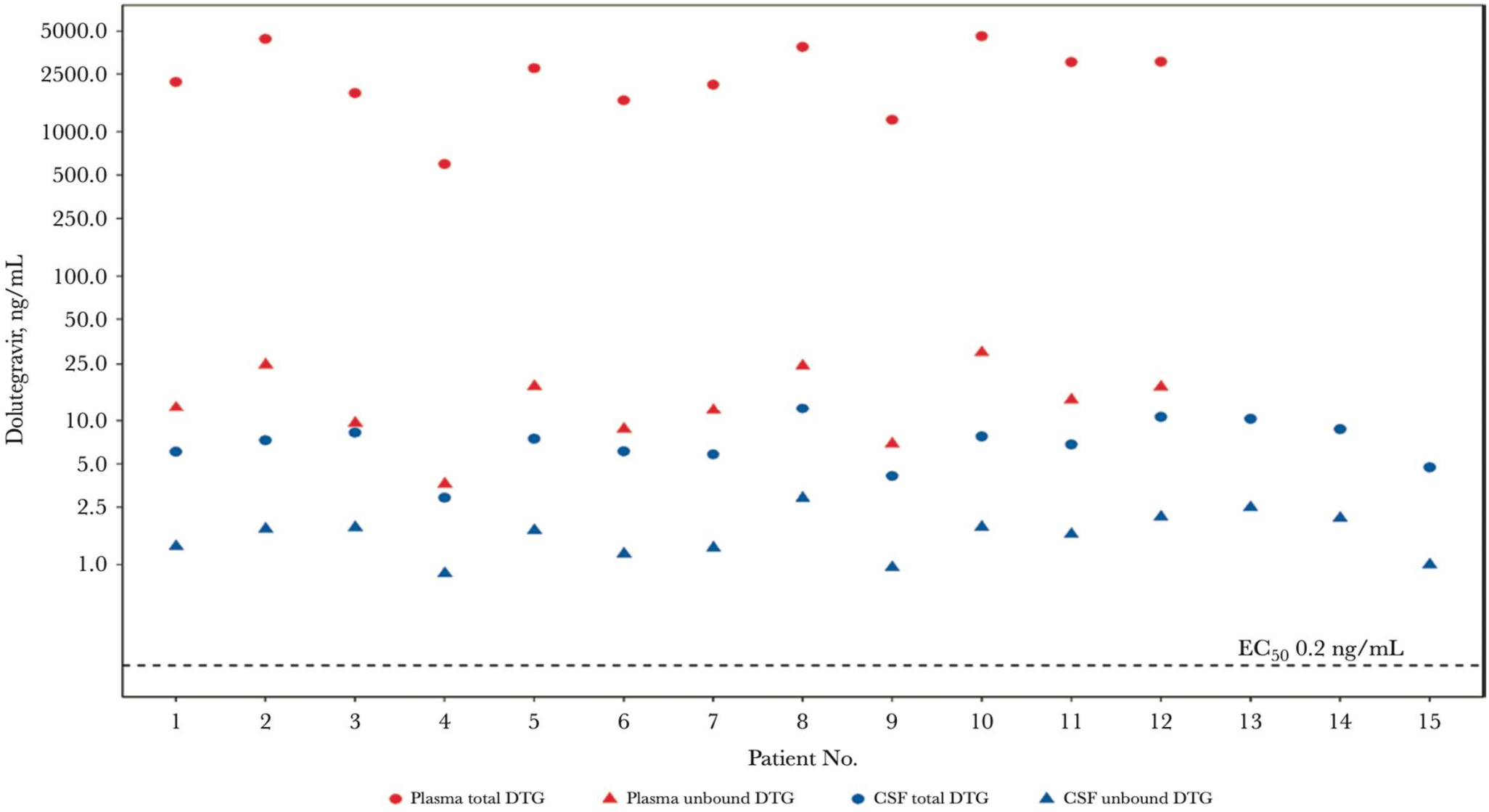
Efficacy of DTG/3TC after switching from several ART regimens in stable pts: the DOLAM Study





Rojas J, et al. Lancet HIV (in press)

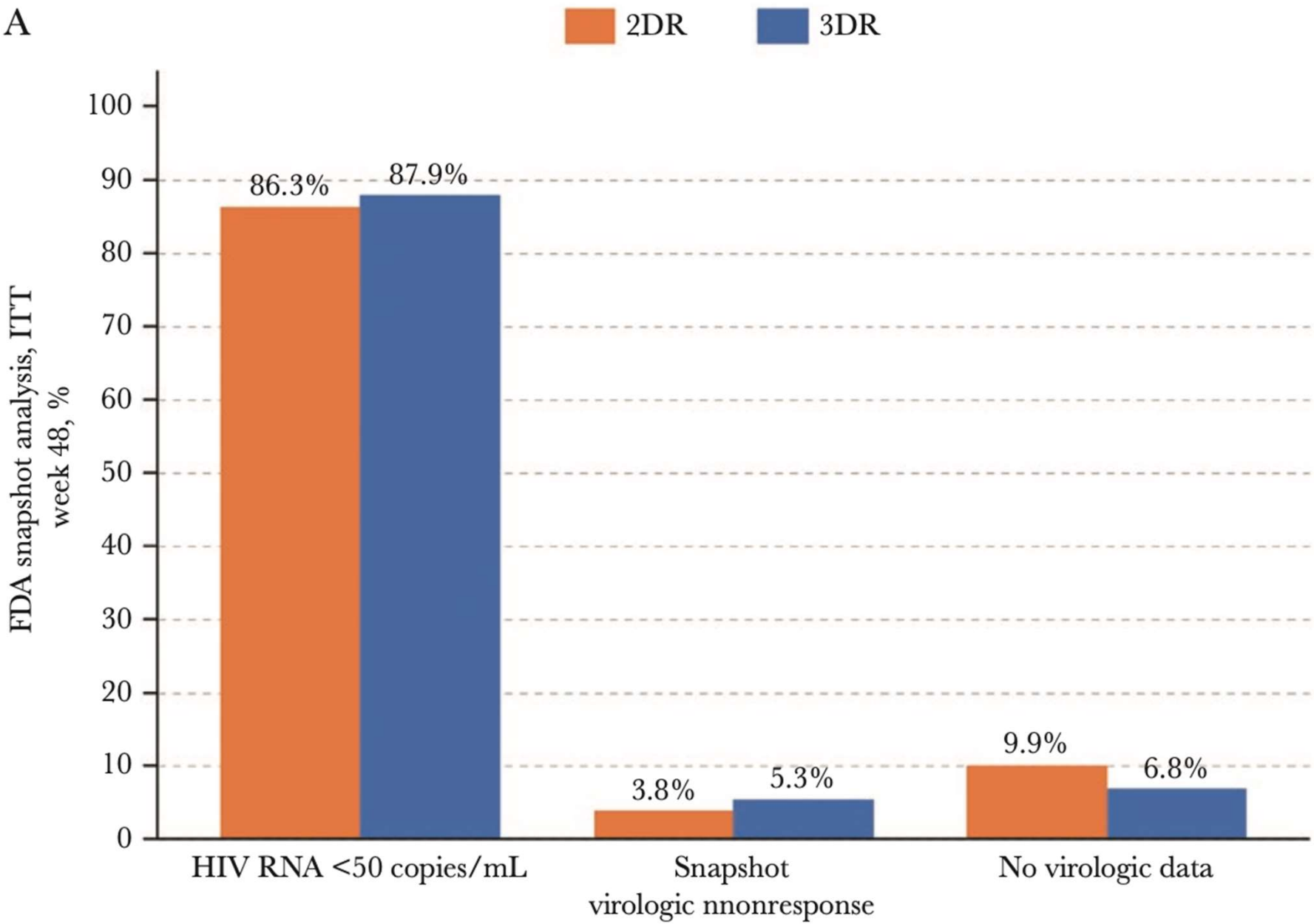
Viral Efficacy, inflammatory markers and drug concentration in CSF of patients switching to DTG/3TC (a substudy of the DOLAM study)



At 48w, viral suppression maintained, no changes in inflammatory markers (sTREM-2, YKL-40, NFL)

Tiraboschi J, et al. J Infect Dis 2020

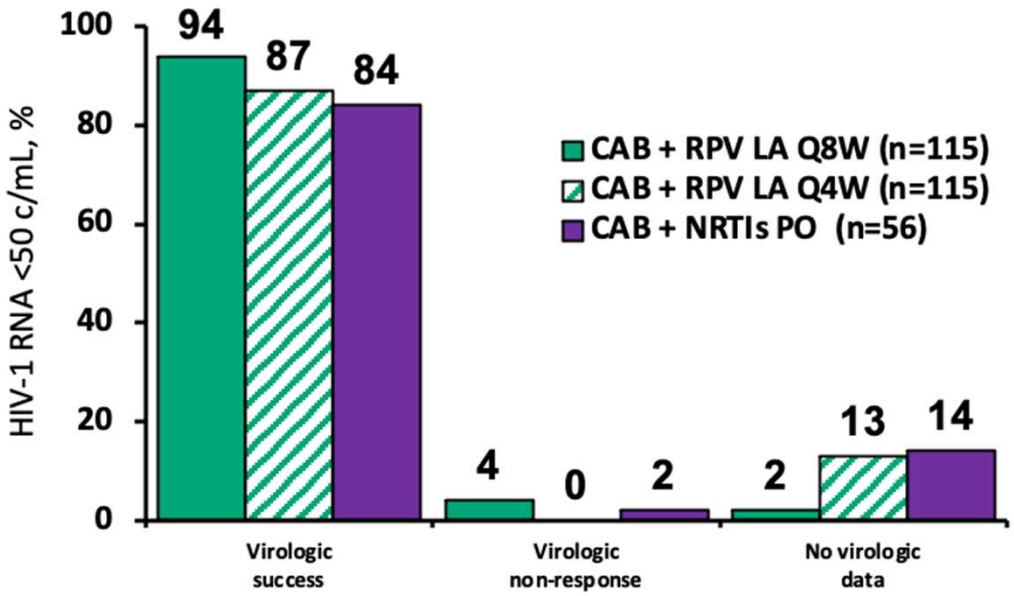
DUALIS: DTG + DRVr in virologically suppressed patients



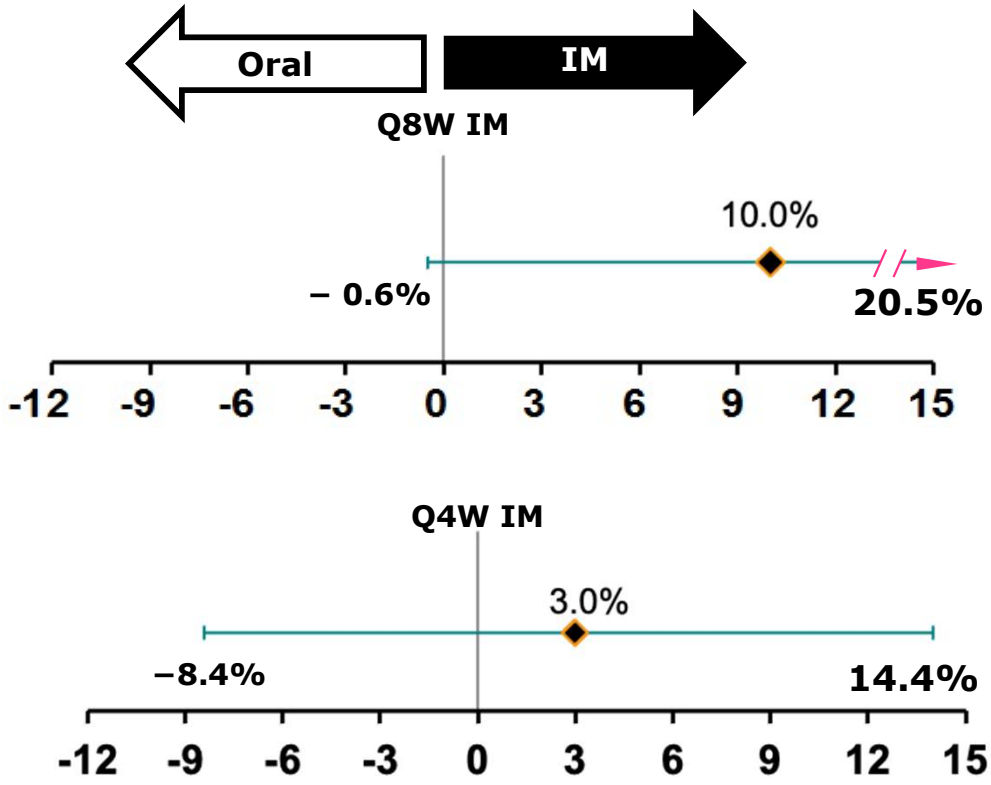
Spinner Ch, et al. Open Forum Infect Dis 2020

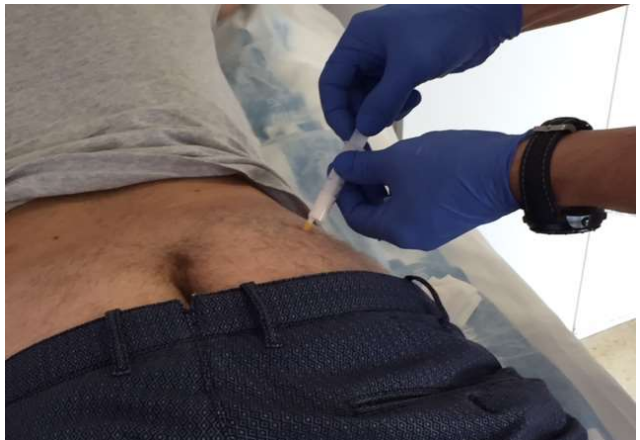
LATTE-2:Comparable Response Across Arms ITT-ME (Snapshot) Week 96 VL <50c/mL

Virologic outcomes



Treatment differences (95% CI)

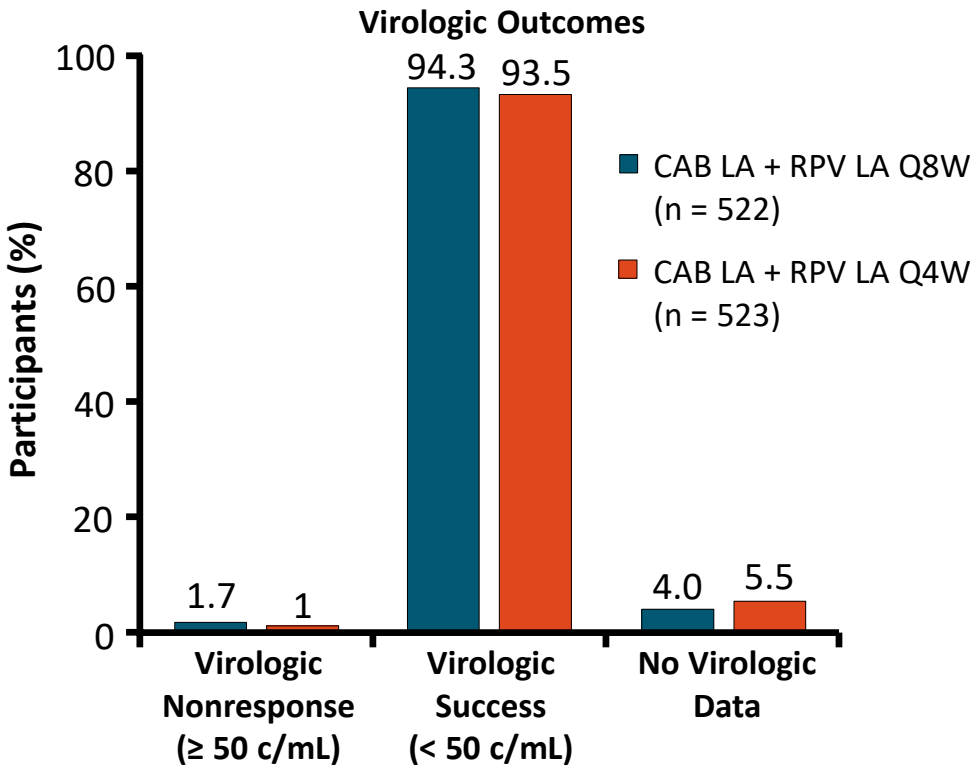




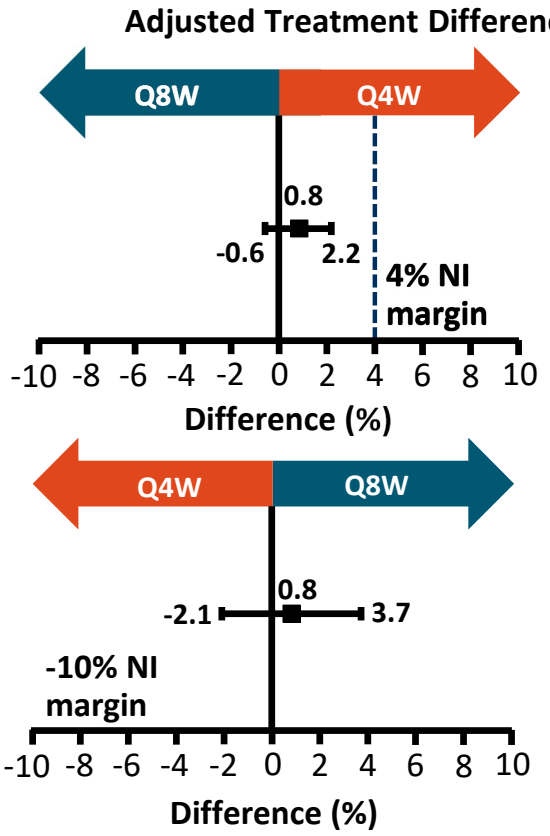
Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB

Eron et al. IAS 2017; Paris, MOAX0205LB.

ATLAS-2M: Virologic Outcomes at Wk 48 in ITT-E by FDA Snapshot



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



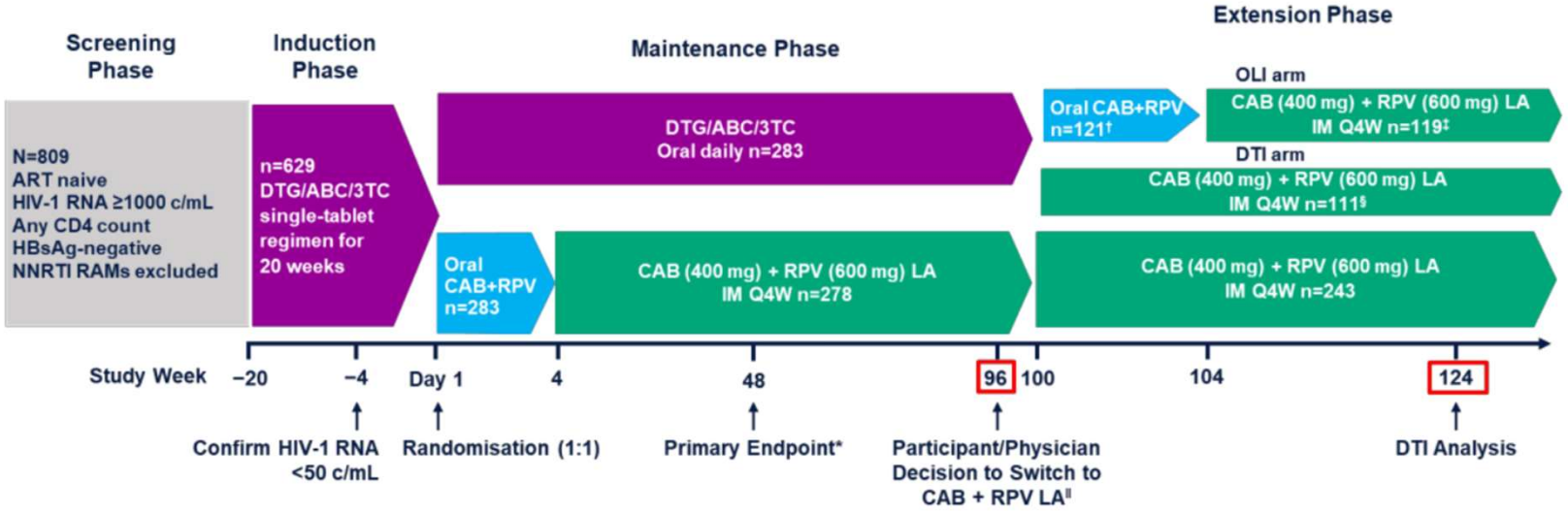
Primary endpoint (HIV-1 RNA ≥ 50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W

Key secondary endpoint (HIV-1 RNA < 50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W

Overton. CROI 2020. Abstr 34.

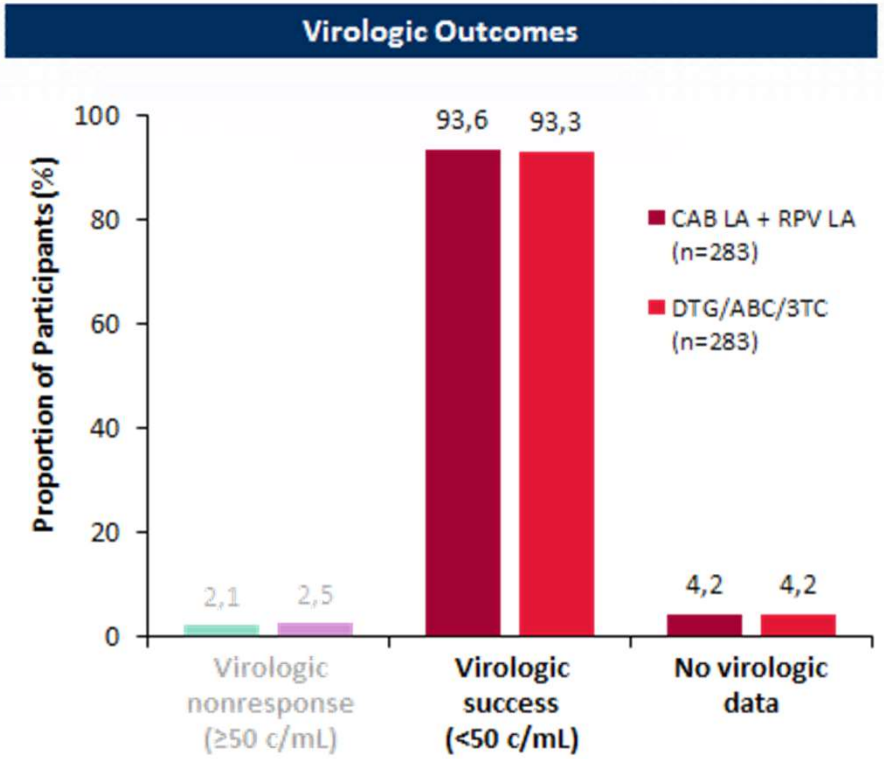
Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study

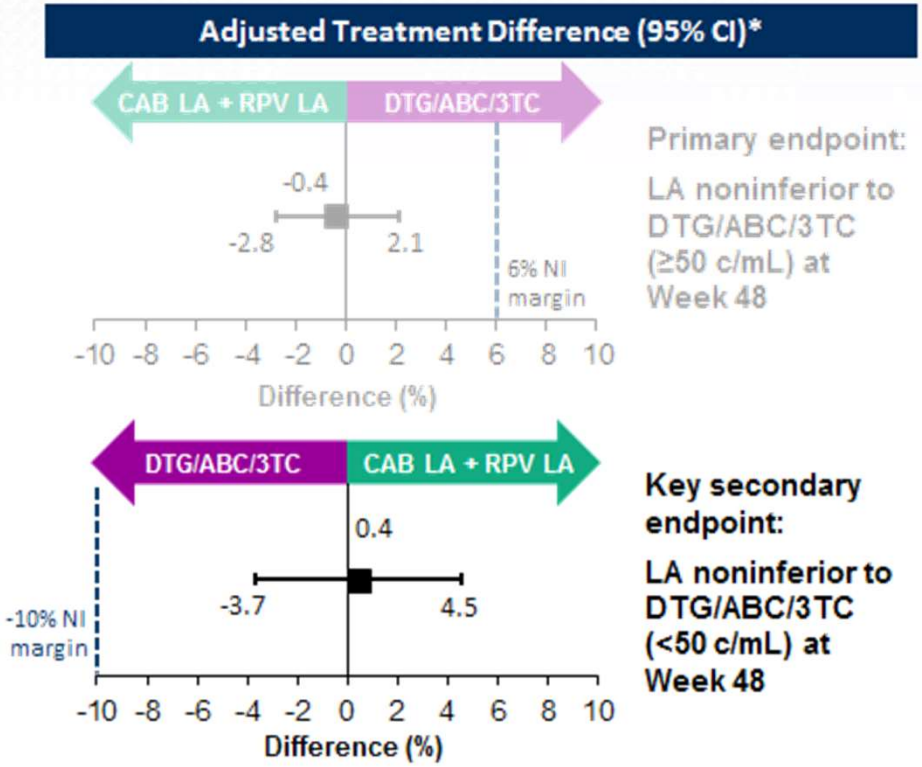
Chloe Orkin, Enrique Bernal Morell, Darrell H S Tan, Harold Katner, Hans-Jürgen Stellbrink, Elena Belonosova, Rebecca DeMoor, Sandy Griffith, Shanker Thiagarajah, Rodica Van Solingen-Ristea, Susan L Ford, Herta Crauwels, Parul Patel, Amy Cutrell, Kimberly Y Smith, Kati Vandermeulen, Eileen Birmingham, Marty St Clair, William R Spreen, Ronald D'Amico



Orkin C, et al. Lancet HIV 2021; 8: e668-78

FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E:
Noninferiority Achieved for Primary and Secondary Endpoints





3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

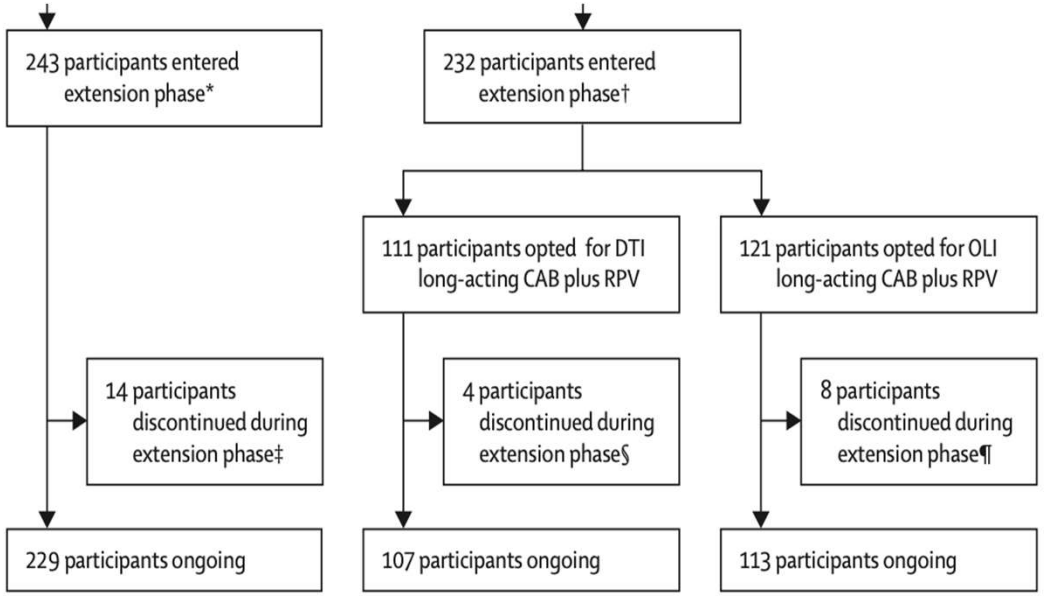
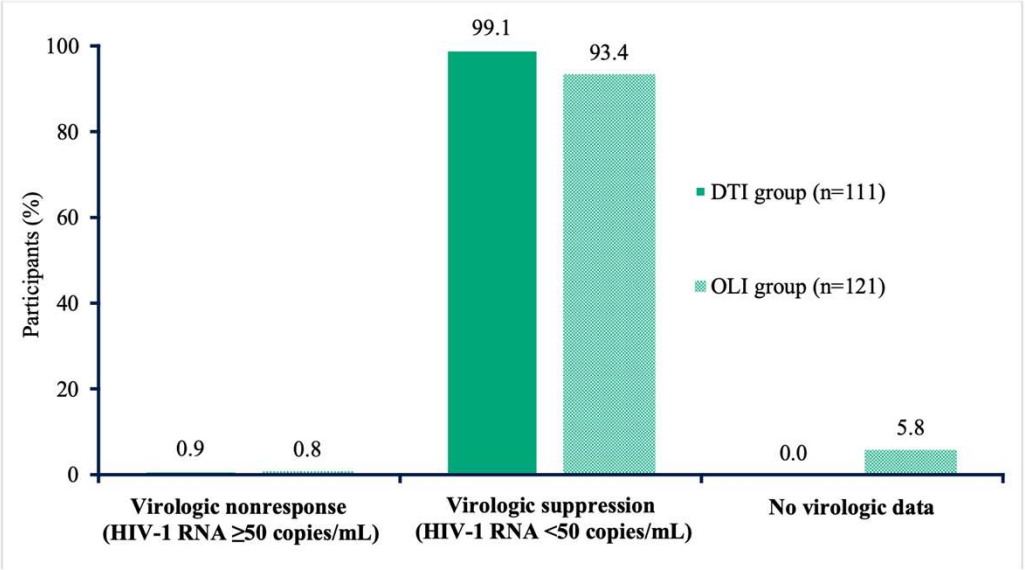


Figure S2. Snapshot efficacy outcomes at Week 124 for the extension switch population after 24 weeks* of CAB+RPV LA



Reassessing oral lead-in for injectable long-acting HIV therapy

**Josep M Llibre, Paul E Sax*

Lancet HIV 2021

London, October 28, 2021

ViiV: Injections to be initiated with or without an Oral lead-in period

Resistance to CAB + RPV

WHO FAILS WITH RESISTANCE ON LA CAB + RPV

Parameter	Final Model Or (95% CI), p-value
RPV RAM(s) at baseline	37.24 (8.44->99), p<0.001
Log_2 of *post hoc* Week 8 RPV trough concentration	4.17 (1.59-11.11), p=0.004
Baseline HIV-1 subtype A6/A1	6.59 (1.82-25.26), p=0.005
BMI (kg/m^2) at baseline	1.13 (1.03-1.25), p=0.014

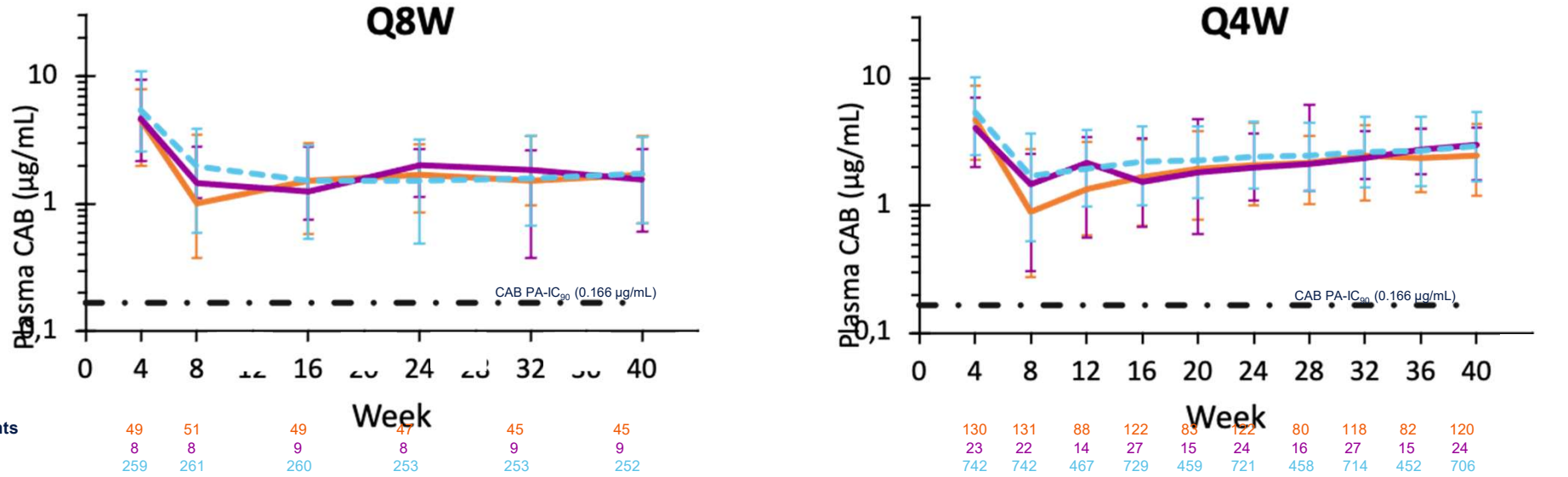
Sensitivity and specificity of at least two baseline factors is optimal

	PPV	NPV	Sensitivity	Specificity
Two or more factors	26%	99.6%	69%	97.5%
Any one factor	<1%	98%	8%	74%

Source: Margolis DA, Schapiro JM, Perno CF, et al. HIV Drug Therapy Glasgow, 1-4 October, 2020, Virtual

Longer Needle Lengths Were Associated With Higher CAB Troughs in the BMI ≥30 kg/m^2 Group Early in Treatment

Median (5th and 95th percentile)* plasma CAB troughs through Week 40 in participants with BMI ≥30 kg/m^2

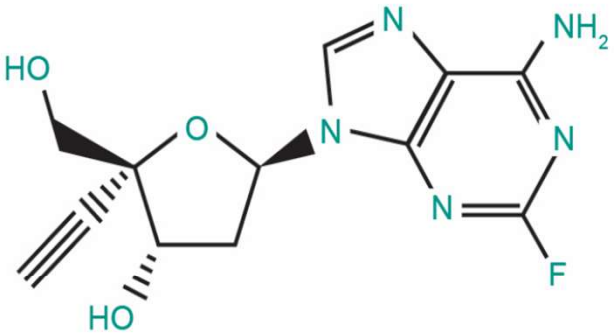


- Use of longer 2-inch needles resulted in higher median CAB trough concentrations for participants with BMI ≥30 kg/m^2
- Longer 2-inch needles are recommended to accommodate individual body habitus and in participants with BMI ≥30 kg/m^2 to ensure appropriate administration into gluteal muscle†

*Data beyond Week 40 were not available at time of analysis.
†The majority (78%, n=3889/4970) of injections in participants with BMI ≥30 kg/m^2 were administered with needles <1.6 inches in length vs. the recommended longer 2-inch needle due to issues with procurement.
BMI, body mass index; CAB, cabotegravir; PA-IC$_{90}$, protein-adjusted 90% inhibitory concentration; Q4W, every 4 weeks; Q8W, every 8 weeks.

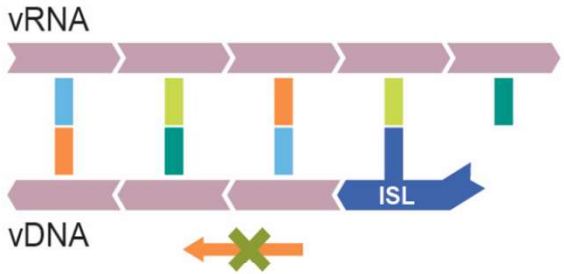
Elliot et al. EACS 2021; Virtual. Presentation BPD1/8.

Islatravir (ISL) Has Multiple Mechanisms of Action[1-3]



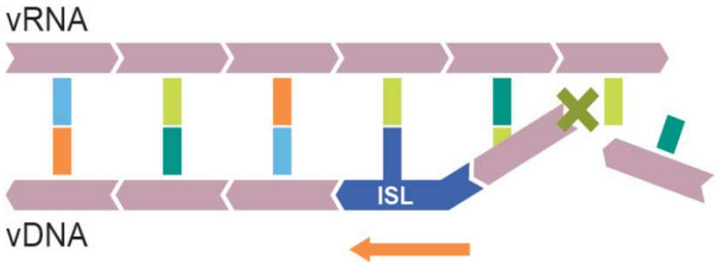
Multiple mechanisms contribute to the high potency of ISL against HIV-1 (including drug-resistant variants) and its high barrier to resistance

Translocation Inhibition



- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination

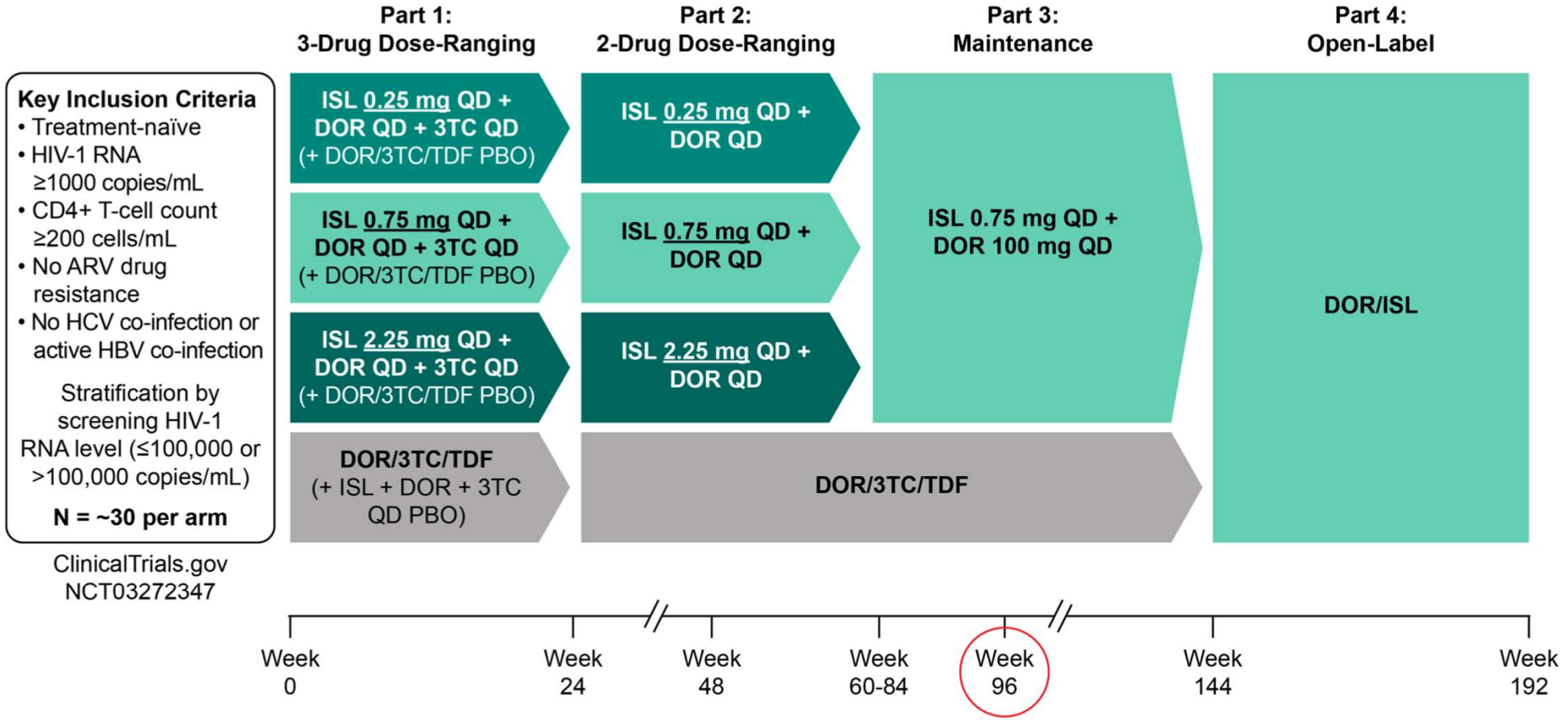


- ISL changes vDNA structure such that nucleotide incorporation is prevented
- Because ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- **Viral replication is inhibited**

ISL, islatravir; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.

1. Kawamoto et al. *Int J Biochem Cell Biol* (2008) 40:2410-2420. 2. Michailidis et al. *J Biol Chem* (2014) 289:24533-24548; 3. Salie et al. *PNAS* (2016) 113:9274-9279.

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



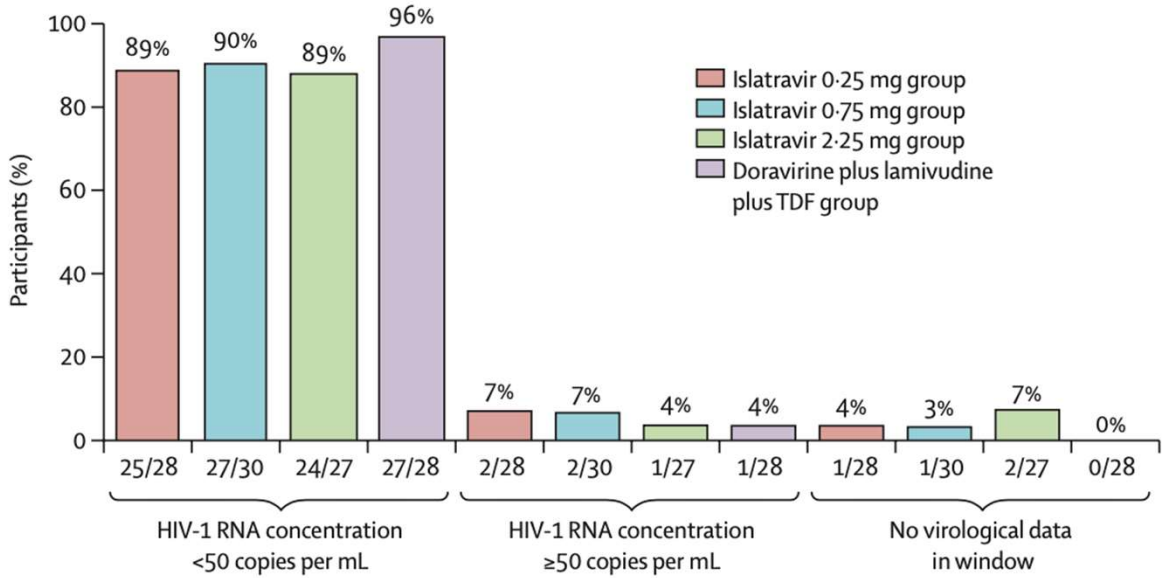
ClinicalTrials.gov
NCT03272347

3TC, lamivudine; ARV, antiretroviral; DOR, doravirine; HBV, hepatitis B virus; HCV, hepatitis C virus; ISL, islatravir; PBO, placebo; QD, once daily; TDF, tenofovir disoproxil fumarate

[a]Participants who were virologically suppressed (HIV-1 RNA <50 copies/mL) at Week 20 and did not meet any viral failure criteria were eligible to enter Part 2 at Week 24. Participants with HIV-1 RNA ≥50 copies/mL at Week 20 remained in Part 1 until eligible to enter Part 2.

McComsey et al. Abstract presented at: IAS Conference on HIV Science; July 18-21, 2021. Virtual. Abstract # A-IAS2021-01017.

Virologic outcome after entering part 2 (ISLA+DOR after VL < 50 copies/mL)



Interpretation Treatment regimens containing islatravir and doravirine showed antiviral efficacy and were well tolerated regardless of dose. Doravirine in combination with islatravir has the potential to be a potent two-drug regimen that warrants further clinical development.

ARTICLES
https://doi.org/10.1038/s41591-021-01479-3

nature medicine

Check for updates

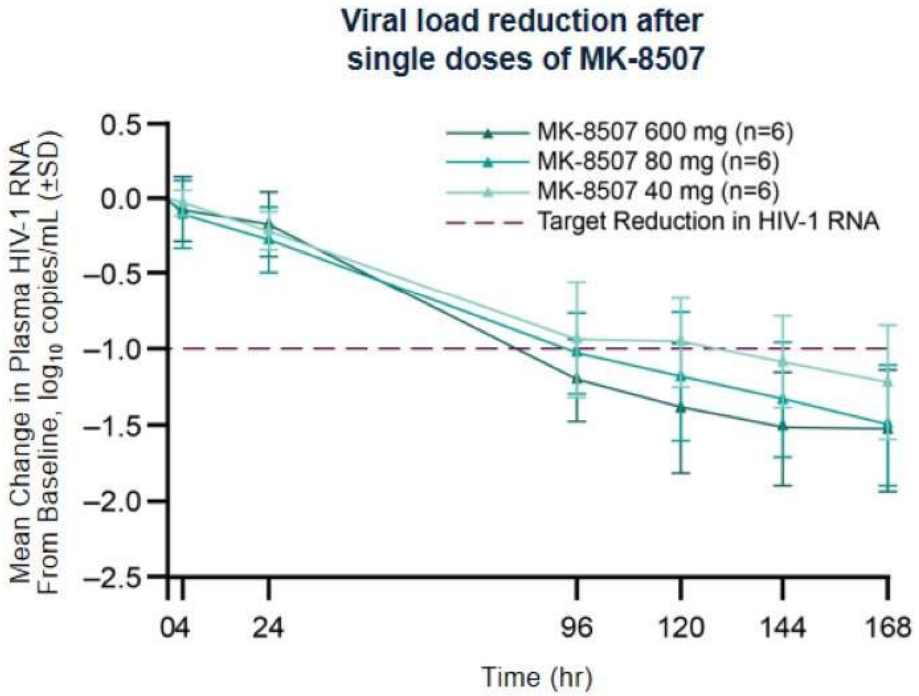
Safety and pharmacokinetics of islatravir subdermal implant for HIV-1 pre-exposure prophylaxis: a randomized, placebo-controlled phase 1 trial

Randolph P. Matthews[1]✉, Munjal Patel[1], Stephanie E. Barrett[1], Liesbeth Haspeslagh[2], Tom Reynders[2], Saijuan Zhang[1], Sylvie Rottey[3], Adrian Goodey[1], Ryan C. Vargo[1], Jay A. Grobler[1], S. Aubrey Stoch[1] and Marian Iwamoto[1]

NATURE MEDICINE | VOL 27 | OCTOBER 2021 | 1712–1717 |

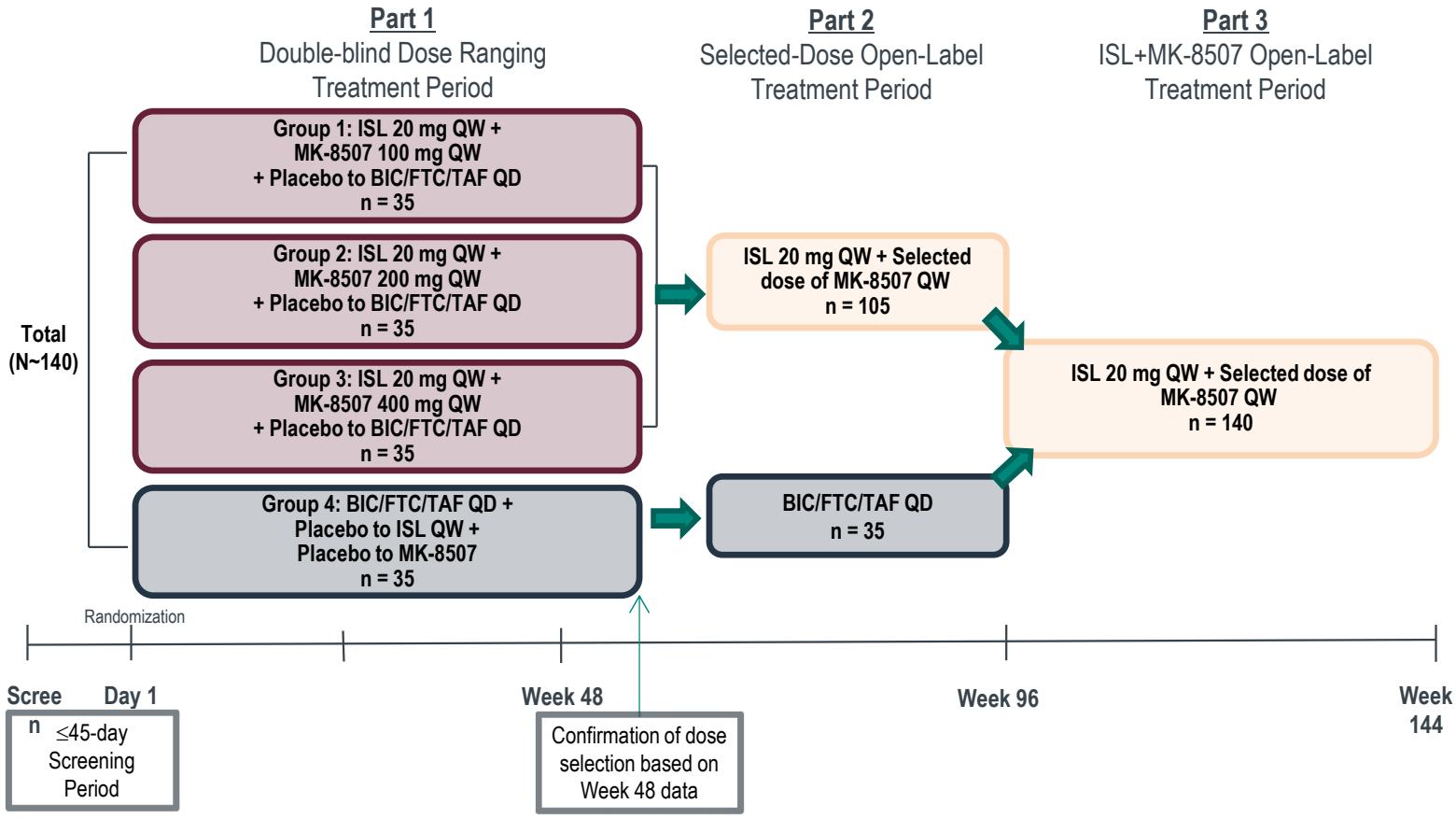
MK-8507, a once-weekly NNRTI for HIV-1 treatment

- In vitro IC_{50} (100% NHS)=51.3nM
- Mean plasma $t_{1/2}$ ~70 hours in humans supports once-weekly dosing
- Generally well tolerated with single doses up to 1200 mg and 3x weekly doses up to 400 mg
- Single oral doses of MK-8507 as low as 40 mg reduced mean plasma HIV-1 RNA levels >1 log for up to 7 days in treatment-naïve PLWH
- Phase 2 study of MK-8507 in combination with islatravir is planned (NCT04564547)



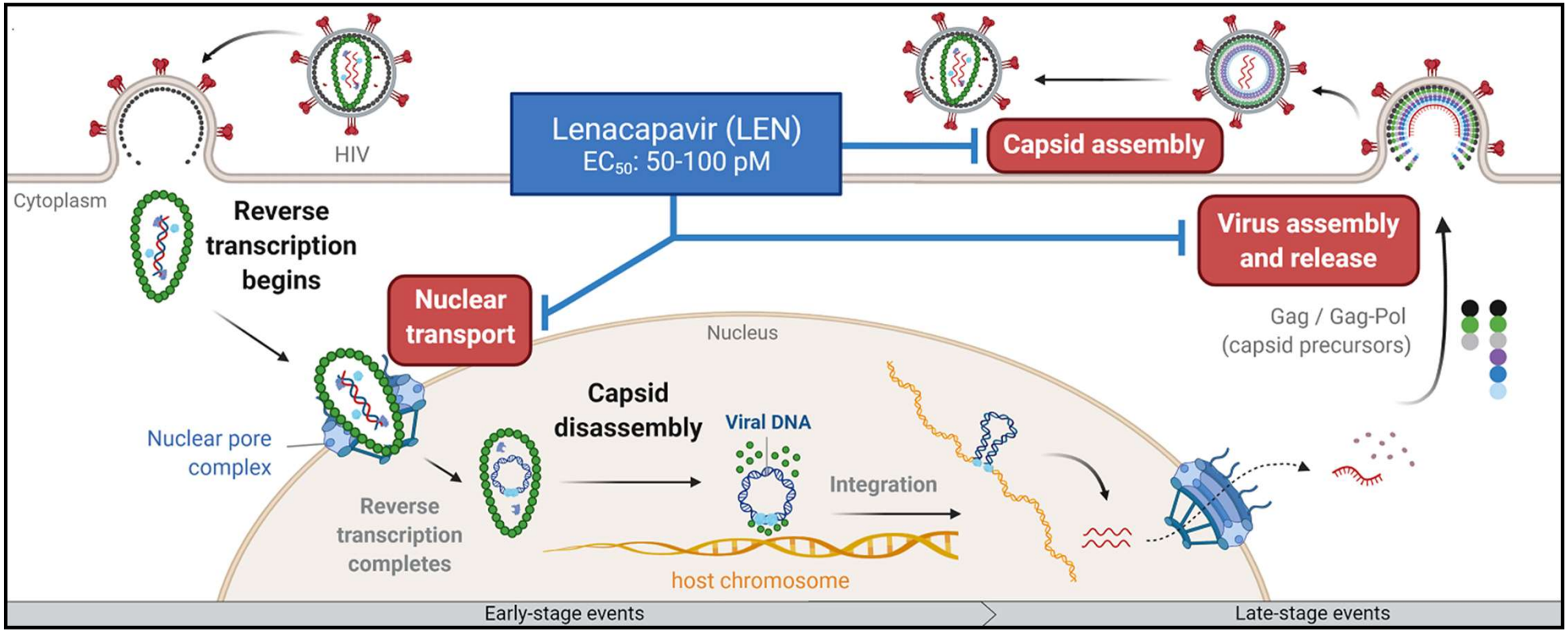
IC_{50}, half-maximal inhibitory concentration; NHS, normal human serum; PLWH, people living with HIV

Protocol 013: Dose Ranging, Switch Study of ISL/MK-8507 QW



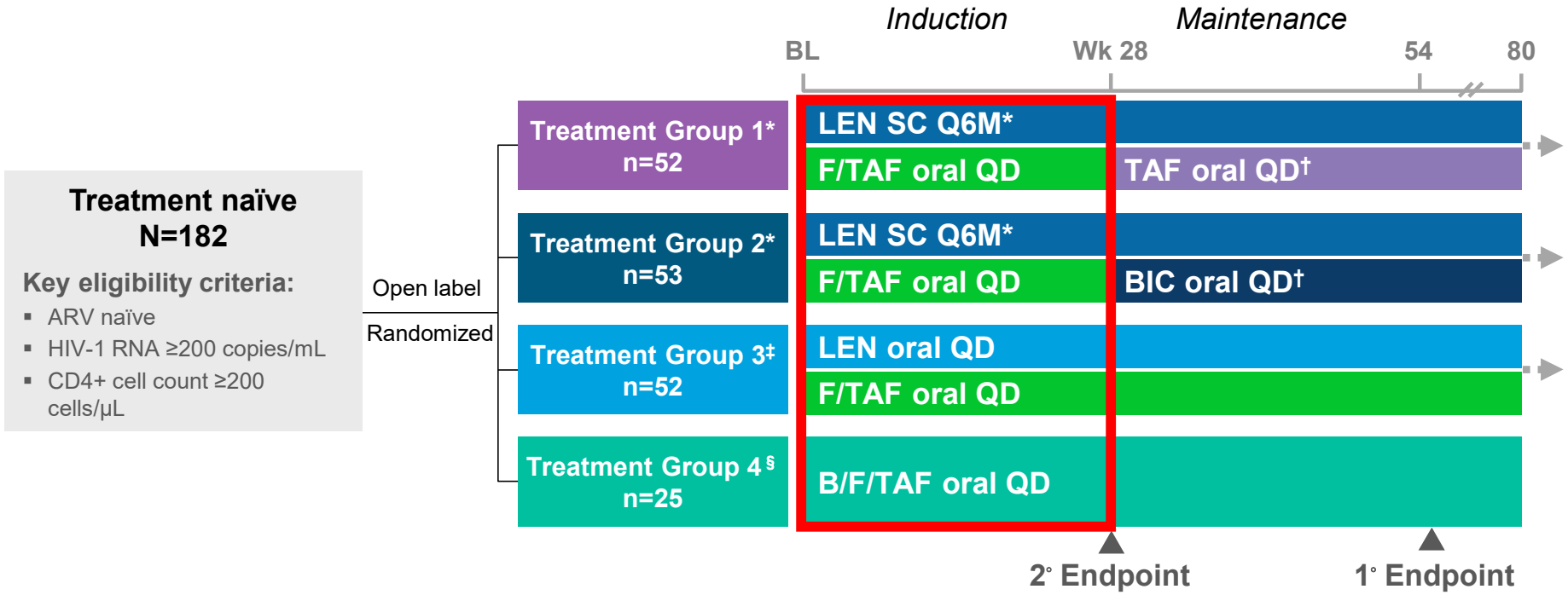
https://clinicaltrials.gov/ct2/show/NCT04564547 (accessed 26 October 2020)

LEN Targets Multiple Stages of HIV Replication Cycle



Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

Study Design



- DMC recommended continuation of study, based on Week 16 results (i.e. abstract data)

*LEN oral lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/TAF 200/25 mg; †Participants in TG 1 and 2 will need HIV-1 RNA results <50 copies/mL at Wks 16 and 22 to initiate either TAF 25 mg or BIC 75 mg at Wk 28; those with HIV-1 RNA ≥50 copies/mL will discontinue study at Wk 28; ‡LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; §B/F/TAF 50/200/25 mg.
ARV, antiretroviral; BIC, B, bictegravir; BL, baseline; DMC, data monitoring committee; QD, once daily; Q6M, every 6 months; TG, treatment group; Wk, Week.

March 15, 2021 6:45 am ET

Collaboration to Focus on Oral and Injectable Formulations of Lenacapavir and Islatravir

Agreement Brings Together Potentially Complementary Medicines in Late-Stage Development with the Goal to Provide Innovative, Long-Acting Treatments in HIV

Foster City, Calif. and Kenilworth N.J. – March 15, 2021 – Gilead Sciences, Inc. (Nasdaq: GILD) and Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that they have entered into an agreement to co-develop and co-commercialize long-acting treatments in HIV that combine Gilead's investigational capsid inhibitor, lenacapavir, and Merck's investigational nucleoside reverse transcriptase translocation inhibitor, islatravir, into a two-drug regimen with the potential to provide new, meaningful treatment options for people living with HIV.

Conclusiones

- El cambio/simplificación continúa siendo una estrategia relevante en pacientes en TAR virológicamente suprimidos, para mejorar la adherencia y la tolerabilidad, reducir el número de fármacos y/o de comprimidos, así como el coste del tratamiento.

- Las pautas de 2 fármacos –orales e inyectables en un futuro cercano (aún no aprobada en España)- se han convertido en una muy buena opción para un número creciente de pacientes.

- En los próximos años tendremos nuevas opciones de fármacos de acción prolongada, que ayudarán a mantener el éxito a largo plazo del TAR, facilitando la adherencia y mejorando la calidad de vida de las personas que viven con el VIH.


Gracias!