Sao Paulo HIV Clinical Forum - 2022

ARV Therapy:
Just make it simple

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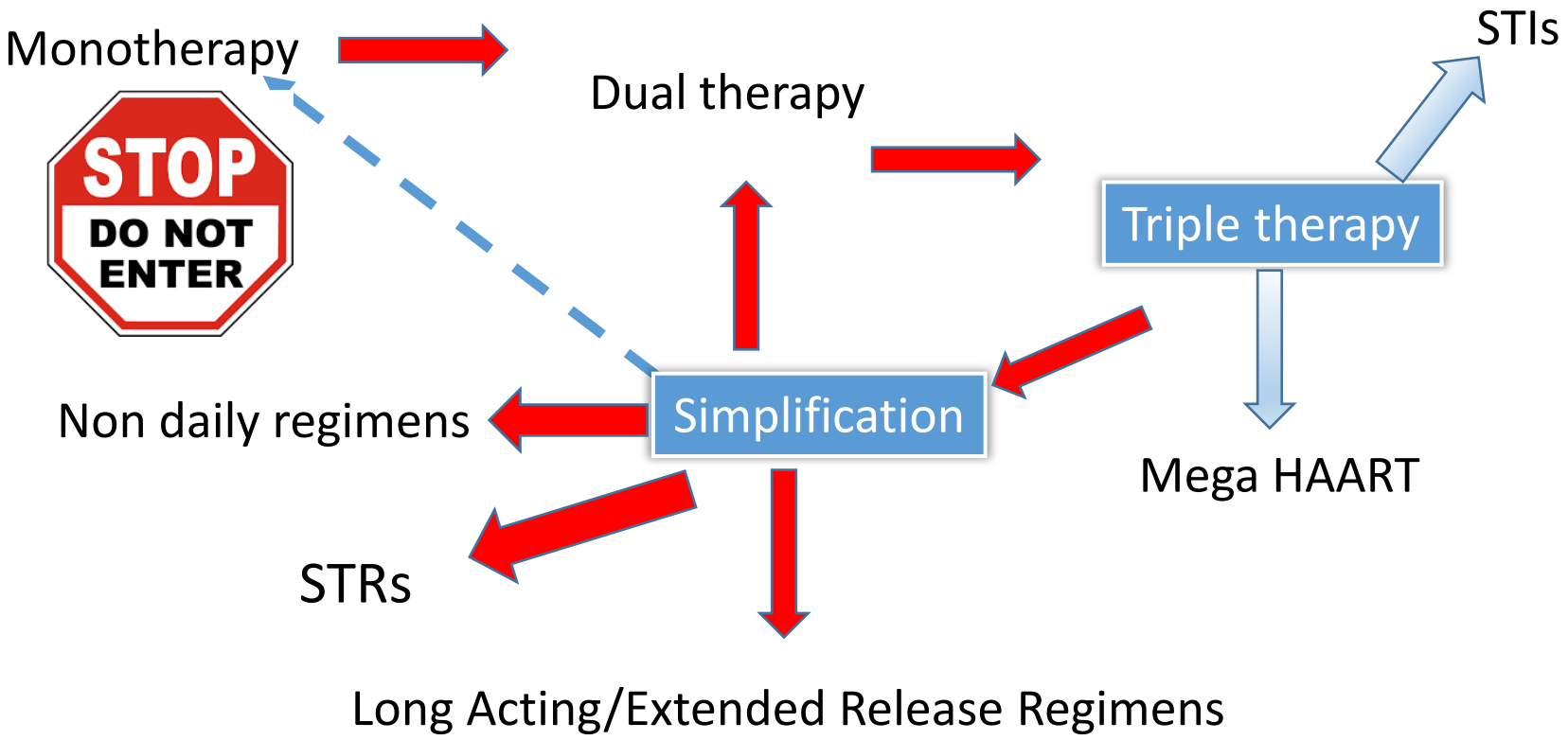
Treatment Strategies: A long way……



Reasons to Consider an ART Switch During Viral Suppression

Appropriate[1]

- To simplify a regimen (eg, reduce pill burden or dosing frequency)
- To enhance tolerability or decrease toxicity
- Aging & comorbidities
- To prevent or mitigate DDIs
- To eliminate food/fluid requirements
- To allow for optimal ART use during pregnancy or where pregnancy may occur
- To reduce costs

Inappropriate

- To use the "newest" regimen
- To reduce costs at the price of a toxicity or intolerance risk for your patient

"Clinicians should always review possible AEs or tolerability issues with current ARV regimens. Just because the viremia is suppressed, it should not be assumed that the PLWH is well adapted and tolerating the current regimen" (EACS)

DHHS Guidelines. .

Principles of Regimen Switching in Virologically Suppressed Pts

Drug Resistance:

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

Safety:

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

Comorbidity:

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

DHHS ART Guidelines. May 2018.

DHHS Guidelines: Switch Strategies NOT Recommended

- As a result of unacceptable efficacy and/or tolerability, including risk of VF and drug resistance in some cases, several switch strategies are specifically NOT RECOMMENDED

Do NOT Switch to:

- **Boosted PI or INSTI monotherapy**
- **DTG monotherapy**
- **RTV-boosted ATV + RAL**
- **Maraviroc + boosted PI**
- **Maraviroc + RAL**

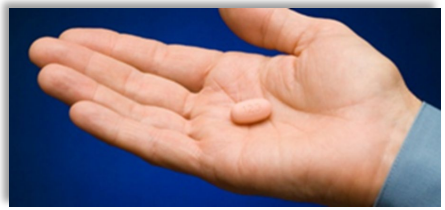
Two different manners of switching….

Reducing drug burden in HAART: Why would you do that?

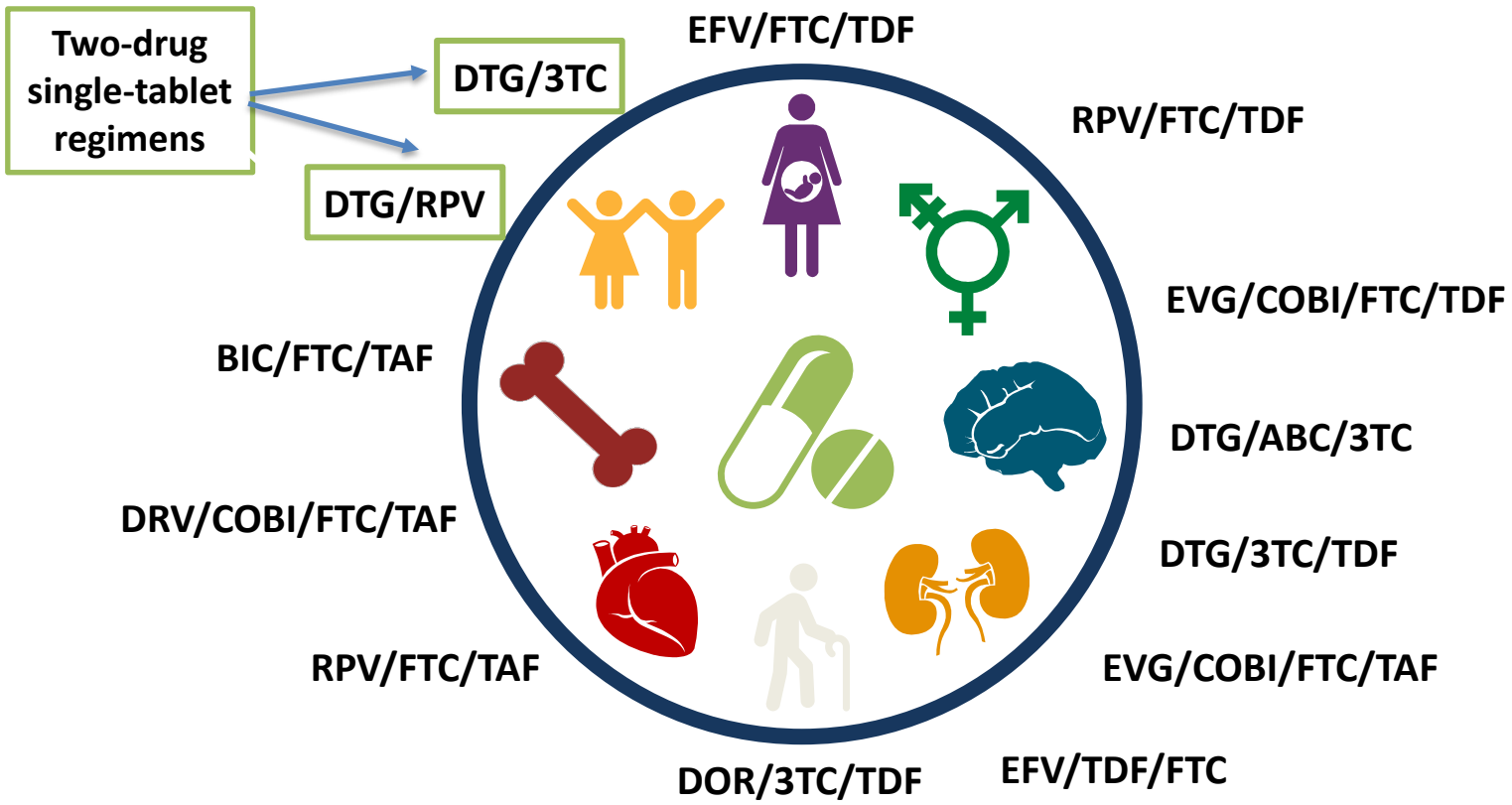
- ✓ To reduce ARV exposure making treatment safer without sacrificing virologic control
- ✓ To reduce pill burden/improved patient adherence and quality of life
- ✓ To reduce drug-drug interactions
- ✓ To reduce cost
- ✓ Potential for longer-term success
  - ✓ Downstream options with "spared" class in case of first-regimen failure

Tools aiming to reduce drug burden

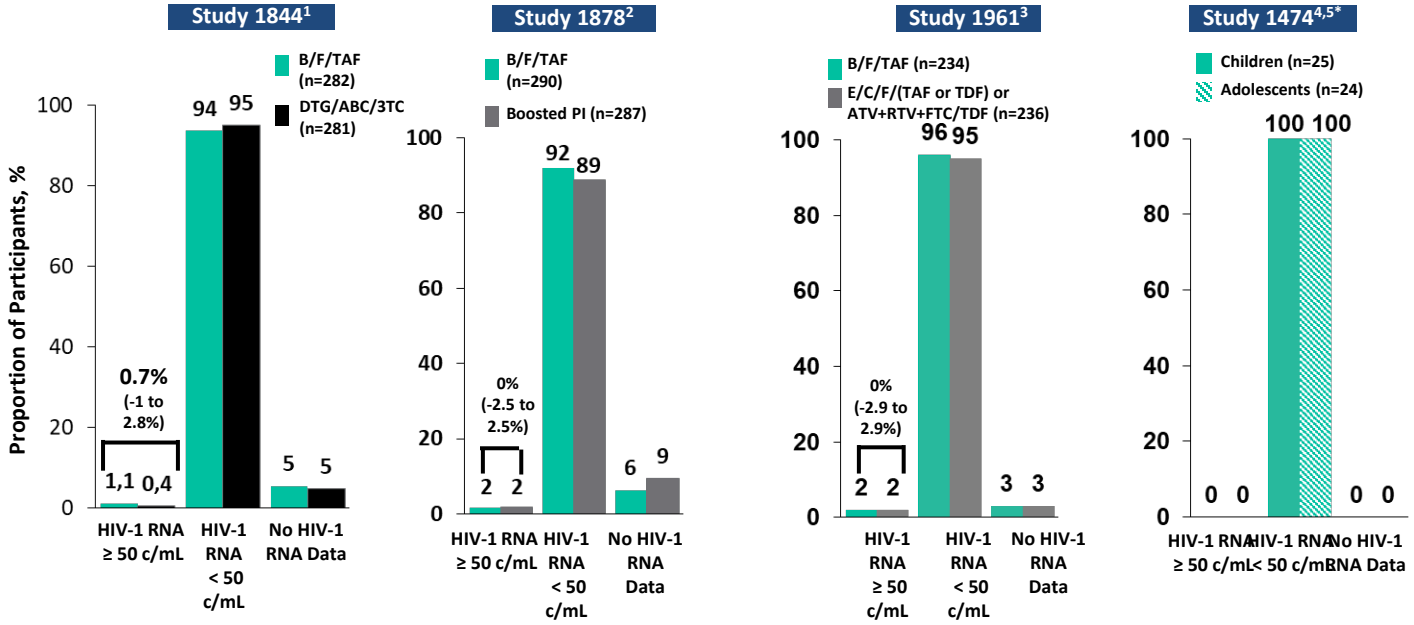
- ✓ Reduce # of doses a day
- ✓ Reduce # of pills
- ✓ Reduce drug dosage
- ✓ Reduce # of drugs
- ✓ Reduce # of days on ART
- ✓ Expand dosing interval



Reducing # of pills/doses a day: Oral Fixed-Dose Combinations



Resultados Virológicos (FDA Snapshot)



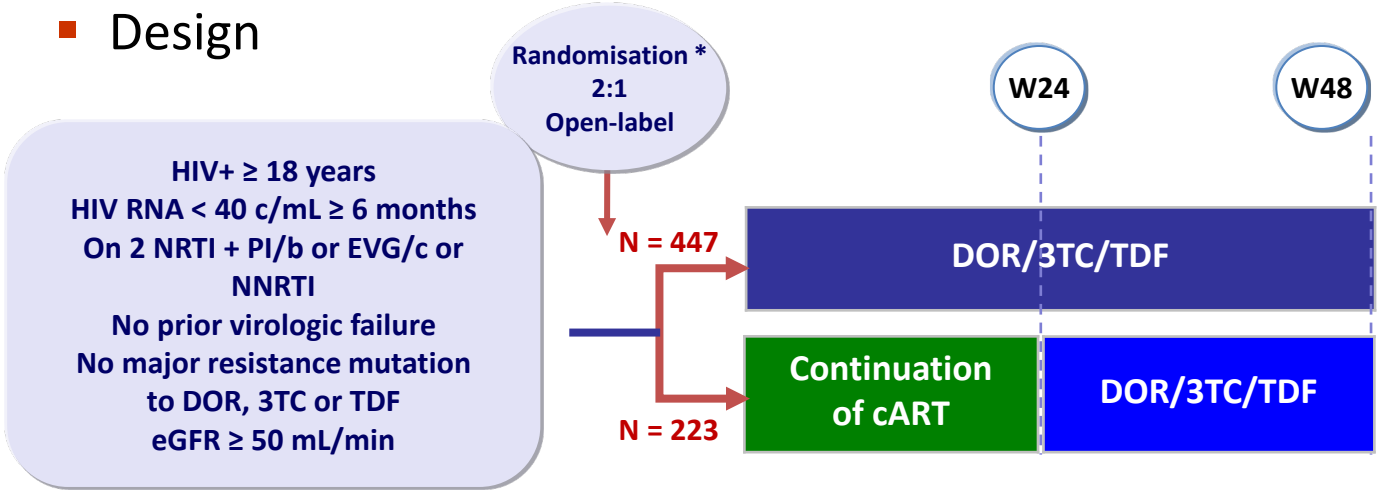
El cambio a B / F / TAF tiene una eficacia no inferior en los estudios de pacientes virológicamente suprimidos, en adultos , en mujeres (S48) y en pediatría (S24) *

*Study 1474 is a single-arm study – adolescent and children primary outcomes are from Week 24

1. Molina JM, et al. *Lancet* HIV 2018;5:e357–65
2. Daar E, et al. *Lancet* HIV 2018;5:e347–56.
3. Kityo C, et al. CROI 2018. Boston, MA. Poster 500
4. Gaur A, et al. CROI 2018. Boston, MA. Poster 844.
5. Cotton M, et al. AIDS 2018. Amsterdam, Netherlands. Oral WEAB0205

DRIVE-SHIFT Study: Switch to DOR/3TC/TDF

- Design

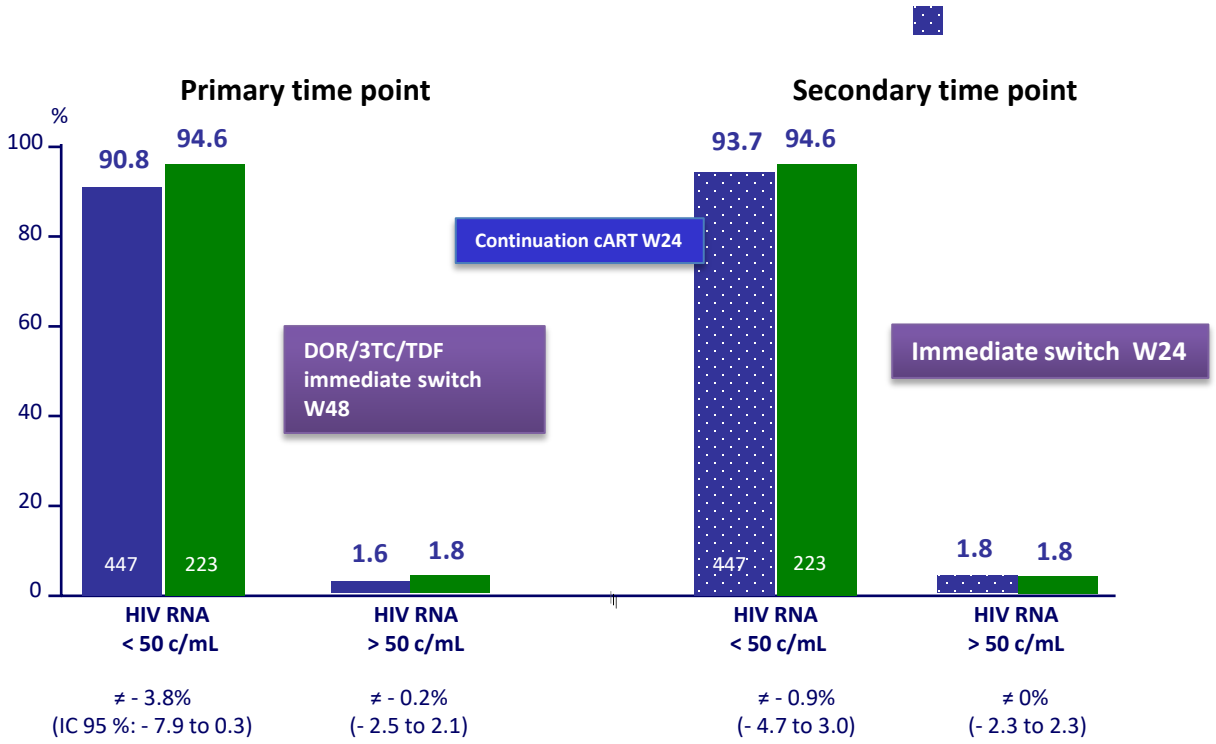


- **Endpoints**
  - Primary: % of patients maintaining HIV RNA < 50 c/mL (ITT-snapshot) ; non-inferiority of DOR/3TC/TDF at W48 (and at W24) compared to continuation of cART at W24 if lower margin of a two-sided 95% CI for the adjusted difference = - 8%
  - Secondary : % of patients with HIV RNA ≥ 50 c/mL: non-inferiority of DOR/3TC/TDF at W48 (and at W24) compared to continuation of cART at W24, non-inferiority margin of 4%

Johnson M, JAIDS 2019

DRIVE-SHIFT Study: Switch to DOR/3TC/TDF

Primary endpoint: efficacy at 2 different time points, ITT Snapshot

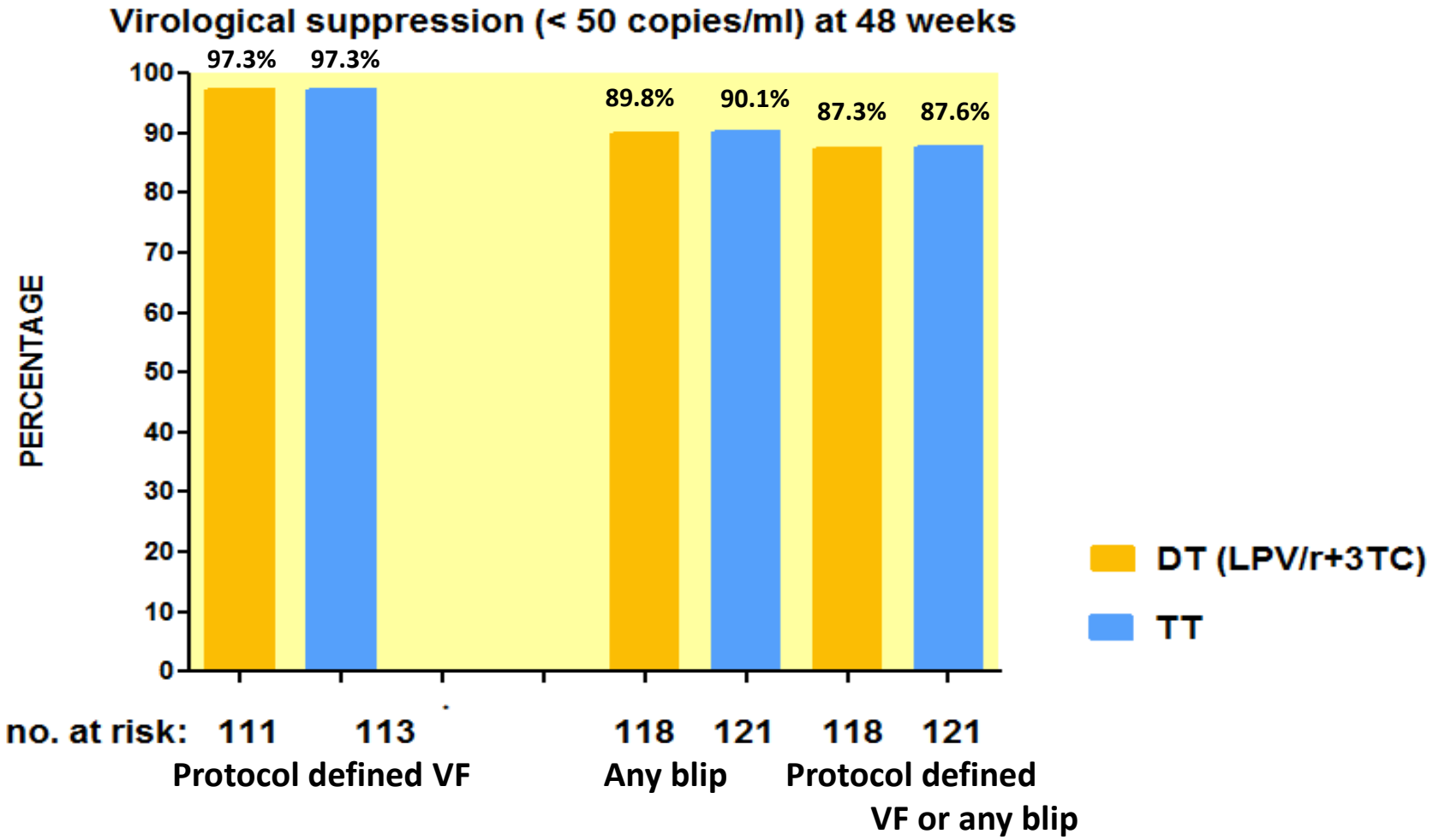


Johnson M, JAIDS 2019

No emergence of resistance to DOR, 3TC or TDF

All 24 participants with baseline NNRTI mutations (K103N, Y181C, G190A) remained suppressed

OLE: Main endpoints



Difference (95% CI)
0.05% (-5.3% to + 5.1%)

Difference (95% CI)
-0.25% (- 8.2 to + 7.6%)

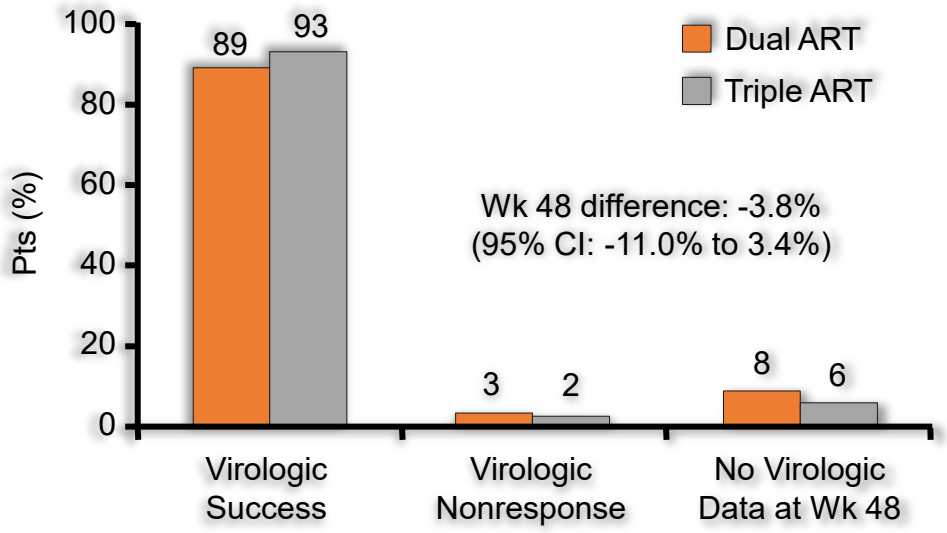
Difference (95% CI)
0.3% (- 8.5 to + 8.3%)

Protocol defined VF: 2 consecutive VL>= 50 copies/ml; **VF or any blip:** any detectable VL >= 50 copies/ml

DUAL-GESIDA Switch study: DRV/RTV + 3TC Dual ART Noninferior to Triple ART at Wk 48

- **Stable regimen: DRV/r + TDF/FTC or ABC/3TC ≥ 2 months**
- **VL < 50 c/mL > 6 months**
- **HBs Ag (-)**

- No resistance detected for 2 pts with resistance data in dual arm
- AE rates similar between arms
- D/c for AEs: 0.8% dual vs 1.6% triple ART (*P* = .55)

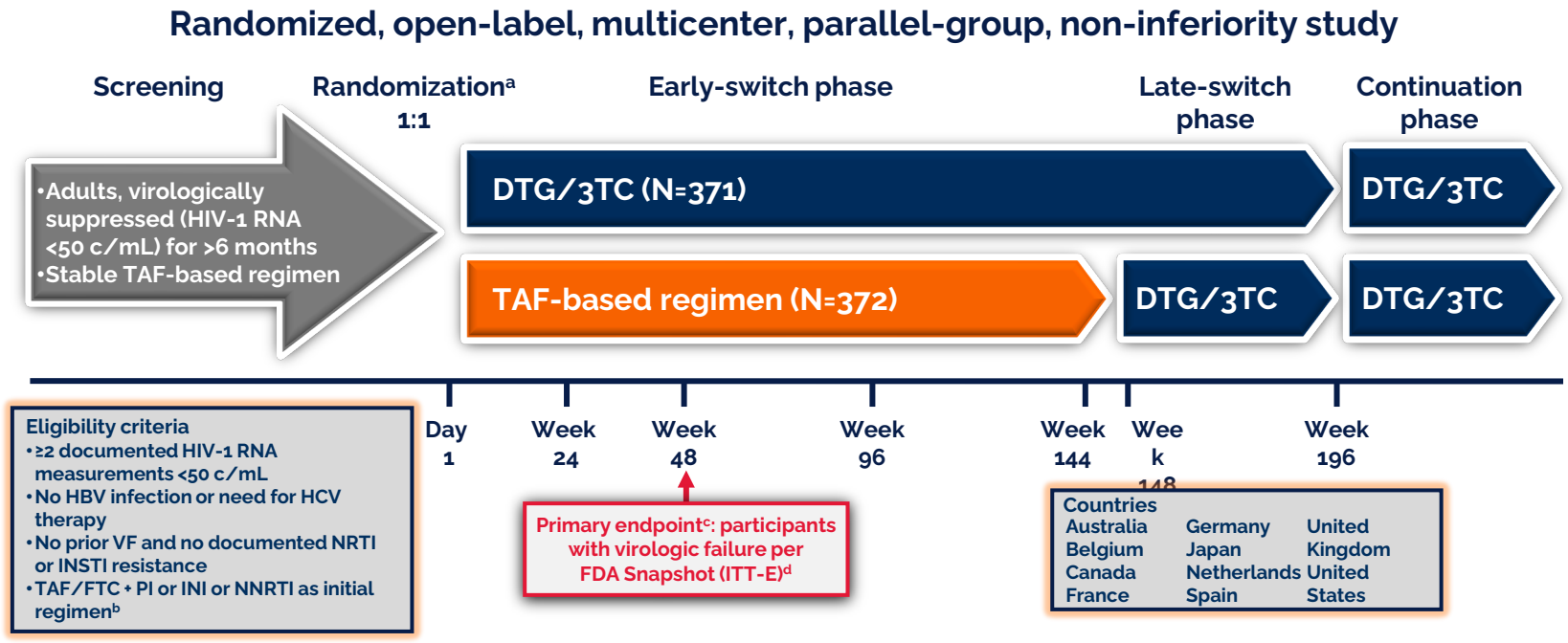


Pts With 1, 2, or 3 Blips,* %	Dual ART	Triple ART	*P* Value
1	8.9	13.2	.31
2	4.5	2.6	.46
3	0.9	0	.31

*Defined as transitory HIV-1 RNA ≥ 50 copies/mL in pts with HIV-RNA < 50 copies/mL at Wk 48.

Pulido F, et al. HIV Glasgow 2016. Abstract O331.

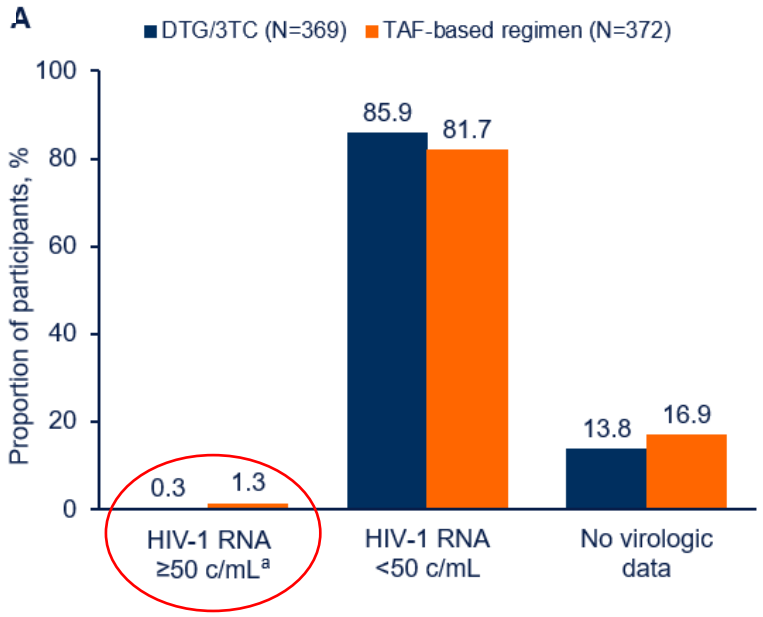
TANGO PHASE III STUDY DESIGN



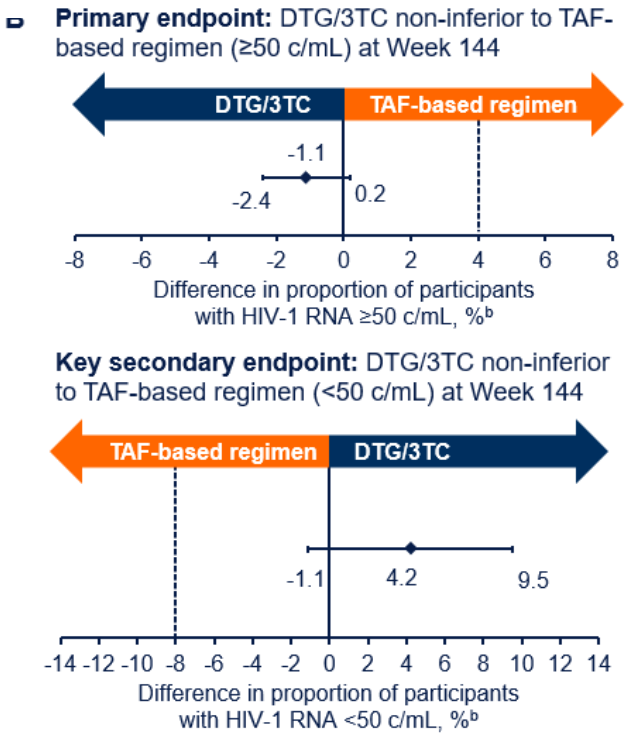
[a]Stratified by baseline third agent class (PI, INI, or NNRTI). [b]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [c]4% non-inferiority margin. [d]Includes participants who changed a background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

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

Efficacy Results



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



Patients with baseline HIV RNA <40 copies/mL and target not detected: Dolutegravir/3TC arm: 90% of patients never had HIV RNA ≥40 copies/mL **over 144 weeks**. Wang R, et al. CROI 2022. Abstract LB-484

van Wyk et al. IAS 2021; Virtual. Poster PEB164.

NO CONFIRMED VIROLOGIC WITHDRAWALS WITH DTG/3TC THROUGH WEEK 48

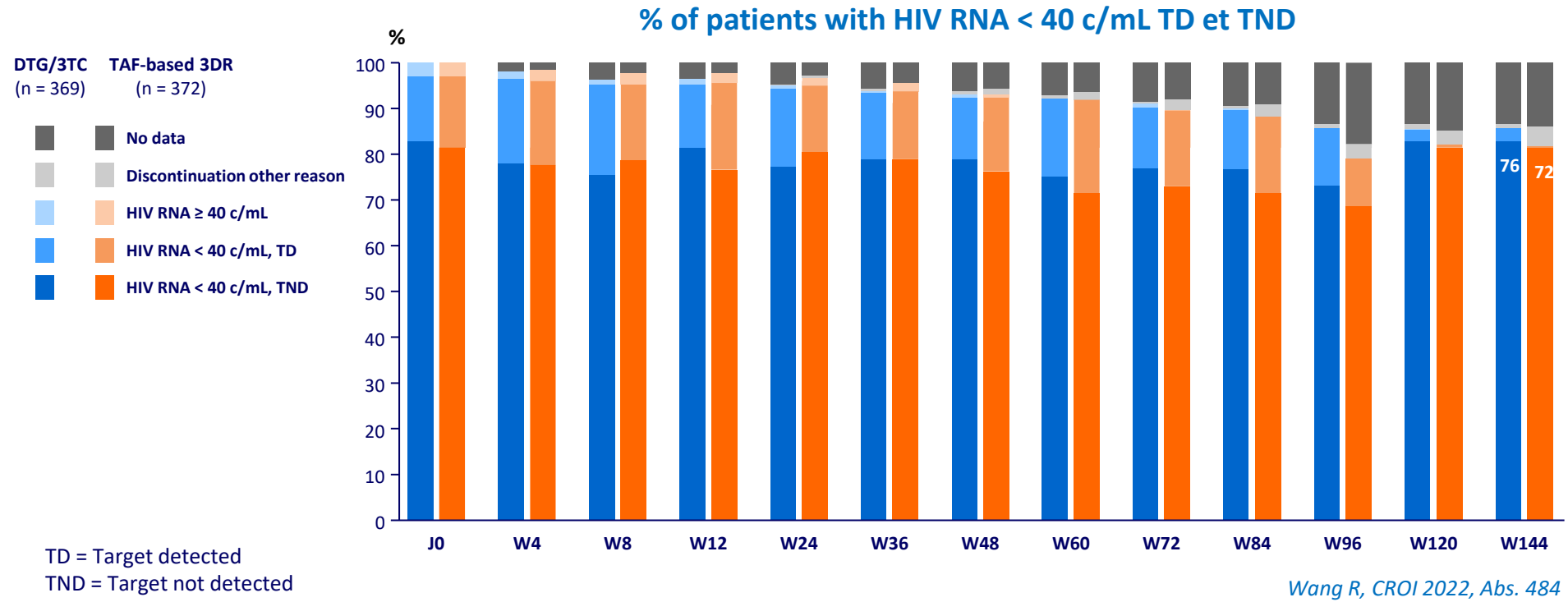
n (%)	DTG/3TC (N=369)	TAF-based regimen (N=372)
Confirmed virologic withdrawal (CVW)[a]	0	1 (<1)[b]
Observed resistance mutation at failure[c]	0	0

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

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

TANGO Study : residual replication at W144

- Randomised clinical trial in HIV+/HBV- patients with pVL < 50 c/mL on ARV : non inferiority of DTG/3TC (n = 369) vs continuation of 3DR with TAF (n = 372)



TD = Target detected
TND = Target not detected

Wang R, CROI 2022, Abs. 484

Adverse events leading to withdrawal

n (%)[a]	DTG + 3TC (N=369)	TAF-based regimen (N=372)
Participants with AEs leading to withdrawal	13 (4)	2 (1)
Anxiety	3 (1)	0
Insomnia	3 (1)	0
Weight increased	2 (1)	1 (<1)
Fatigue	2 (1)	0
Abdominal discomfort	1 (<1)	0
Gastroesophageal reflux disease	1 (<1)	0
Hypoesthesia oral	1 (<1)	0
Nausea	1 (<1)	0
Paraesthesia oral	1 (<1)	0
Drug hypersensitivity	1 (<1)	0
Gunshot wound[b]	1 (<1)	0

n (%)[a]	DTG + 3TC (N=369)	TAF-based regimen (N=372)
Diffuse large B-cell lymphoma[b]	1 (<1)	0
Lung adenocarcinoma[b]	1 (<1)	0
Disturbance in attention	1 (<1)	0
Hypoesthesia	1 (<1)	0
Paraesthesia	1 (<1)	0
Depression	0	1 (<1)
Irritability	1 (<1)	0
Suicidal ideation[b]	1 (<1)	0
Suicide attempt[b]	0	1 (<1)
Genital hypoesthesia	1 (<1)	0
Genital paraesthesia	1 (<1)	0
Pruritus	1 (<1)	0

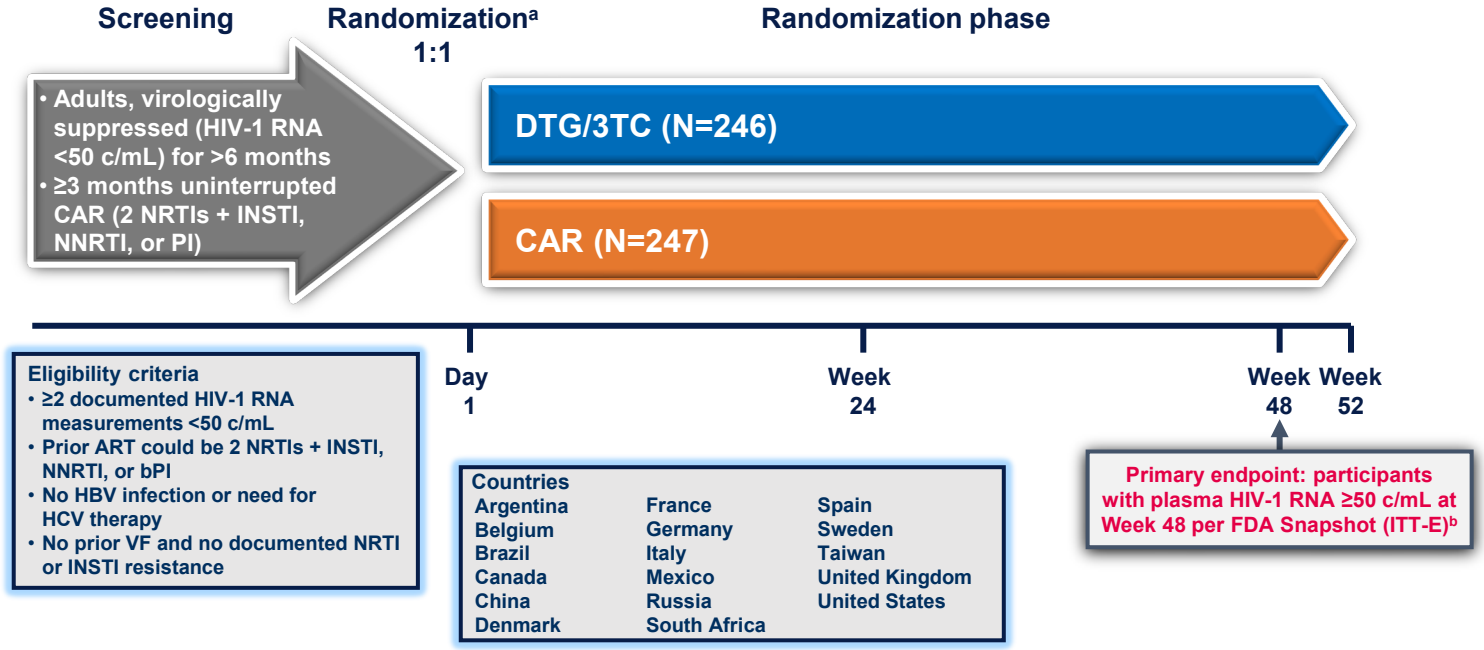
- Adjusted mean increase from BL in weight: +0.8 kg in both arms

[a]Participants may have had more than 1 AE leading to withdrawal. [b]AE not related to study treatment.

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

SALSA Phase III Study Design

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

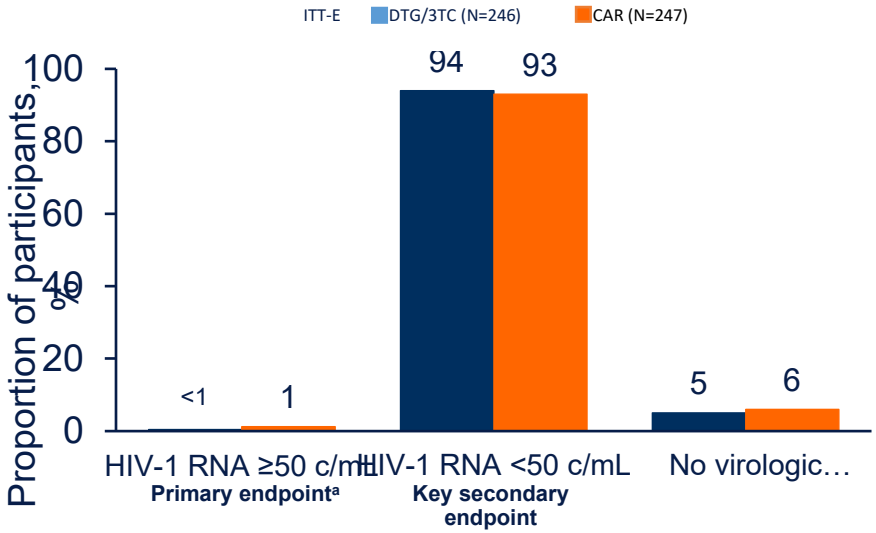


Llibre et al. IAS 2021; Virtual. Slides OALB0303.

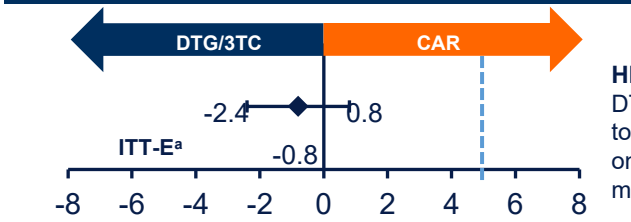
[a]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]5% non-inferiority margin.

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

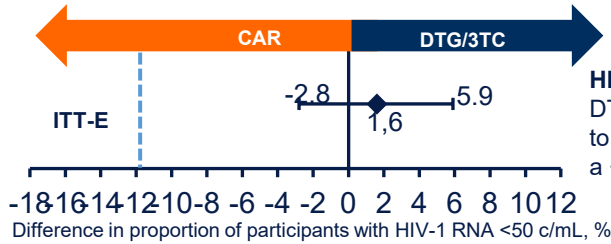
Virologic outcomes (Snapshot analysis)



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.

Confirmed Virologic Withdrawals Through Week 48

Confirmed virologic withdrawal (CVW), n (%)	DTG/3TC (N=246)	CAR (N=247)
Week 48	0	0

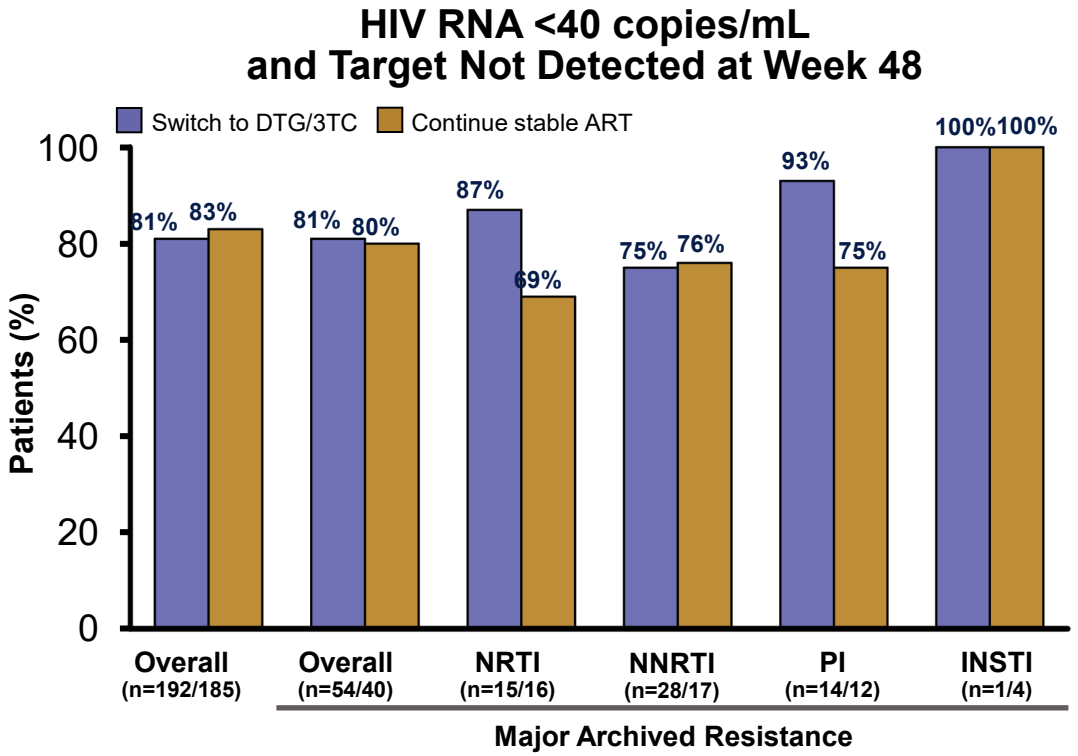
- Zero resistance mutations were observed as zero participants met confirmed virologic withdrawal criteria

Confirmed virologic withdrawal criteria defined as one assessment of HIV-1 RNA ≥200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL.

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

SALSA Trial: Switch to Dolutegravir/3TC in Treatment-Experienced Patients With Archived Resistance

- Switching to dolutegravir/3TC was non-inferior to continuing TAF-based regimen
  - Virologic failure (5% margin)
  - HIV RNA <50 copies/mL (12% margin)
- HIV RNA <40 copies/mL and target not detected
  - Similar responses with switching to dolutegravir/3TC and continuing stable ART despite baseline archived proviral resistance



Underwood M, et al. CROI 2022. Abstract 481.

Adverse Events Leading to Withdrawal Through Week 48: Safety Population

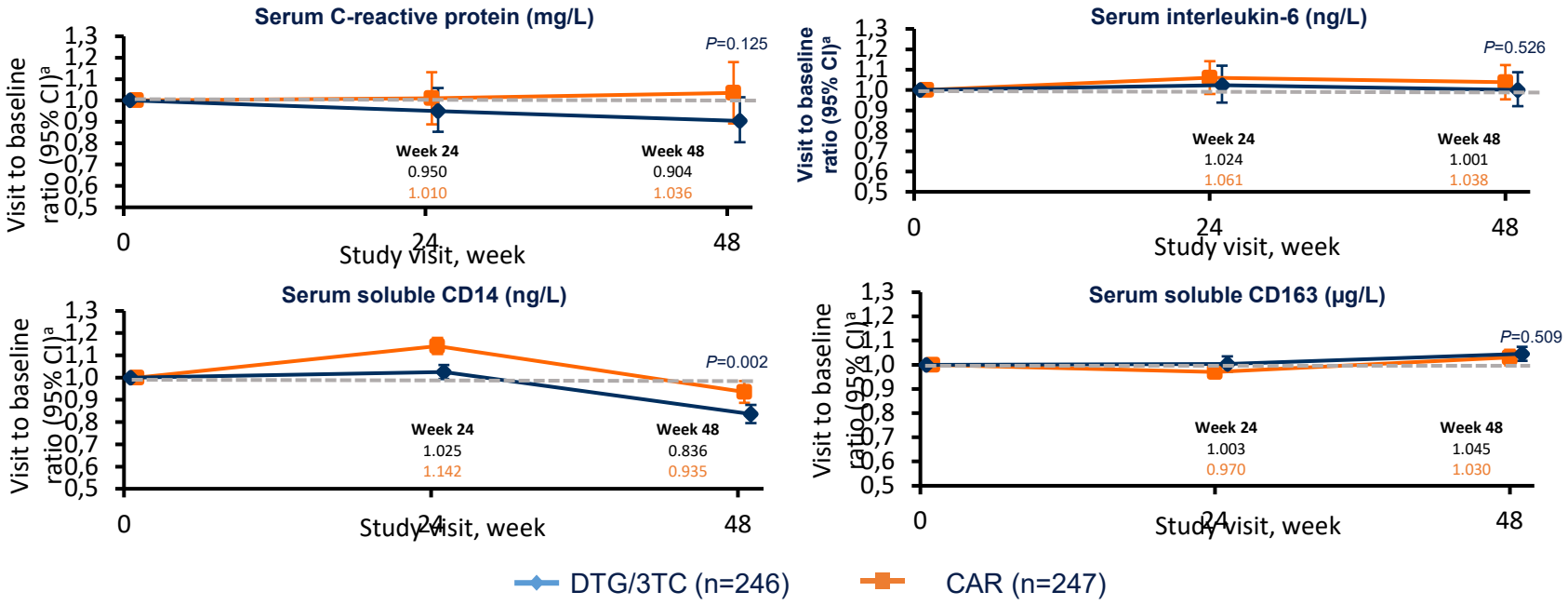
n (%)	DTG/3TC (N=246)	CAR (N=247)
AEs leading to withdrawal from the study	5 (2)	3 (1)
Psychiatric	3 (1)	1 (<1)
Insomnia	2 (<1)	0
Alcohol abuse	1 (<1)	0
Anxiety	1 (<1)	0
Suicidal ideation	0	1 (<1)
Gastrointestinal disorders	0	1 (<1)
Colitis ulcerative[a]	0	1 (<1)
General disorders and administration site conditions	1 (<1)	0
Death[a]	1 (<1)	0
Injury, poisoning, and procedural complications	0	1 (<1)
Post-procedural complication[a]	0	1 (<1)
Investigations	1 (<1)	0
Weight increased	1 (<1)	0

[a]Considered unrelated to study treatment.

- Adjusted mean change in weight from baseline to Week 48 was 2.1 kg in the DTG/3TC group and 0.6 kg in the CAR group
- Adjusted mean change in BMI from baseline to Week 48 was 0.7 kg/m^2 in the DTG/3TC group and 0.2 kg/m^2 in the CAR group

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

Change in Inflammatory Biomarkers at Week 48: Safety Population



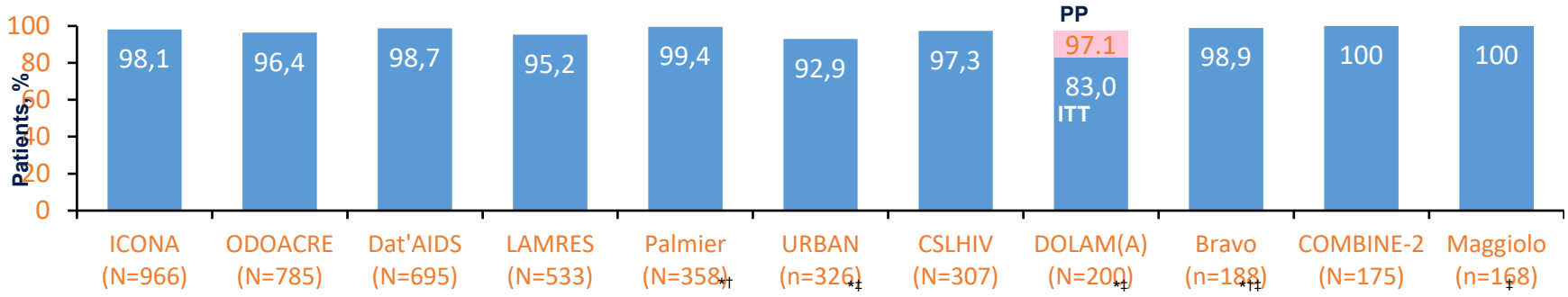
MMRM analysis was not performed for D-dimer due to high proportion of participants with D-dimer < LLQ in both treatment groups. Baseline geometric mean values (DTG/3TC group; CAR group): C-reactive protein (1.34; 1.27), interleukin-6 (1.73; 1.68), soluble CD14 (1.55 × 10^6; 1.46 × 10^6), and soluble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

Effectiveness Outcomes Reported in Treatment-experienced Patients Who Switched to DTG + 3TC in Real-world Studies

Reported effectiveness outcomes vary between studies (stated below chart)



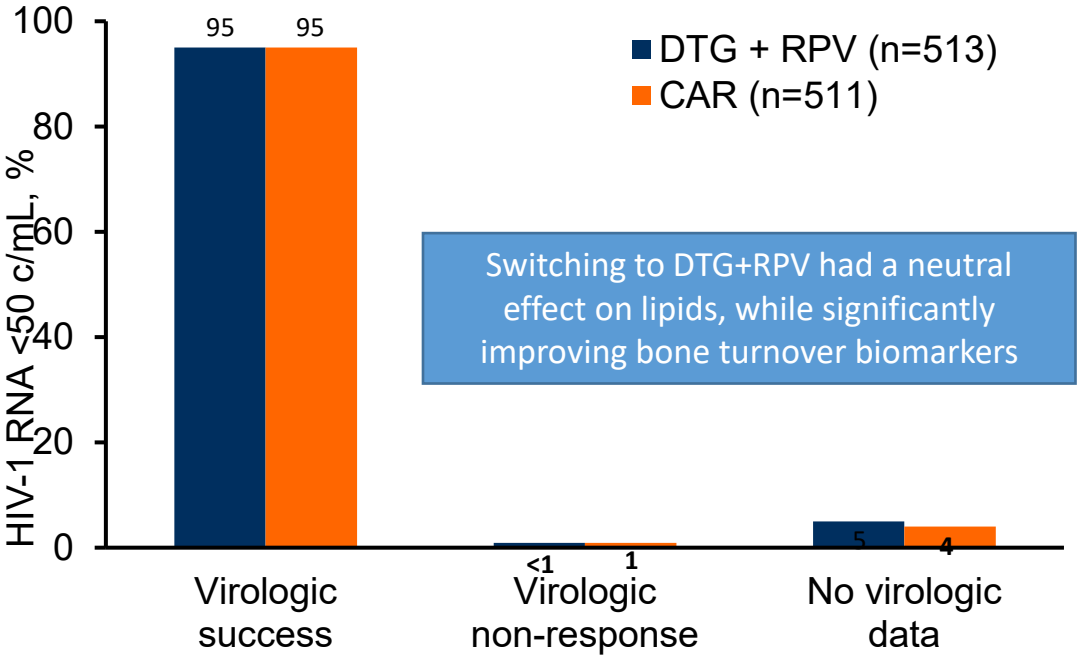
	ICONA (N=966)	ODOACRE (N=785)	Dat'AIDS (N=695)	LAMRES (N=533)	Palmier (N=358)*†	URBAN (n=326)*‡	CSLHIV (N=307)	DOLAM(A) (N=200)*‡	Bravo (n=188)*†‡	COMBINE-2 (N=175)	Maggiolo (n=168)‡
Timepoint	1,505 PYFU[1]	2,014.7 PYFU, up to Week 240[2]	Median FU 1.2 years[3]	2 years[4]	Week 48[5]	1 year[6]	1 year[7]	Week 48[8]	Week 24[9]	96 weeks[10]	5 years[11]
Effectiveness outcome	Remained free of VF§	Estimated probability of maintaining viral suppression§	Remained free of VF§	Probability of remaining free of VF§	Remained free of VF§	Achieved/ maintained viral suppression (MEX)	Estimated probability of remaining free of VF§	VL <50 c/mL (PP, ITT)	VL <50 c/mL (MEX)	Remained free of VF§	Remained free of VF (MEX)§

TANGO
SALSA

Data are only included for 'lead' studies with N≥100 patients treated with DTG + 3TC; potential overlap between patient cohorts cannot be ruled out
***Patients viraemic at BL:** Palmier n=15; URBAN n=7; DOLAM(A) n=8; Bravo n=16; †Data are available at a later timepoint for Bravo (n=66 at Week 48) and Palmier (n=82 at Week 96) but are not included as the number of patients is below the threshold to be included on this slide; ‡**Patients excluded** due to missing data or not being treated per protocol: URBAN n=10, DOLAM(A) n=29; Bravo n=100; Maggiolo n=50;
§Definitions of VF: ICONA, COMBINE-2 and Palmier, confirmed HIV-1 RNA > or
≥50 c/mL; ODOACRE, confirmed HIV-1 RNA ≥50 c/mL or single HIV-1 RNA ≥1,000 c/mL; Dat'AIDS and LAMRES, confirmed HIV-1 RNA >50 c/mL or single HIV-1 RNA >200 c/mL; CSLHIV, confirmed HIV-1 RNA >50 c/mL or single HIV-1 RNA >50 c/mL followed by treatment modification or single HIV-1 RNA >1,000 c/mL; Maggiolo, not specified. Viral suppression in URBAN was defined as HIV-1 RNA <50 c/mL in visit window 9–15 months or 50–200 c/mL with subsequent HIV-1 RNA <50 c/mL
FU, follow up; **ITT,** intention-to-treat; **PP,** per protocol; **PYFU,** person-years of follow-up

SWORD Studies: Snapshot Outcomes at Week 48 (Pooled)

Virologic outcomes

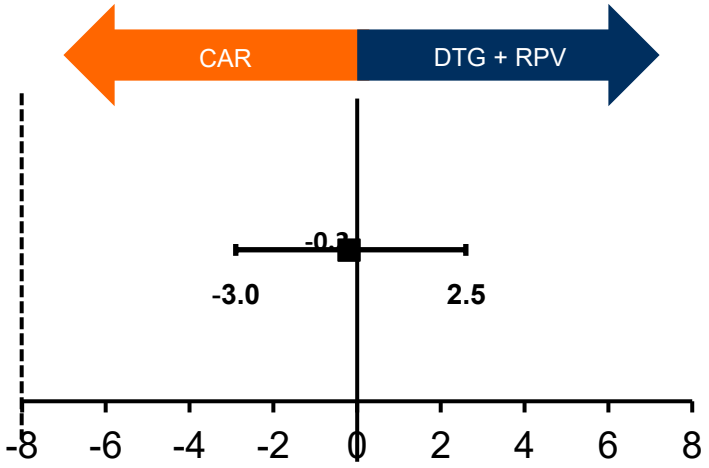


Switching to DTG+RPV had a neutral effect on lipids, while significantly improving bone turnover biomarkers

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

Inclusion criteria
- **On stable CAR ≥6 months before screening**
- **1st or 2nd ART with no change in prior regimen due to VF**
- **Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening**
- **HBV negative**

Adjusted treatment difference (95% CI)[a]



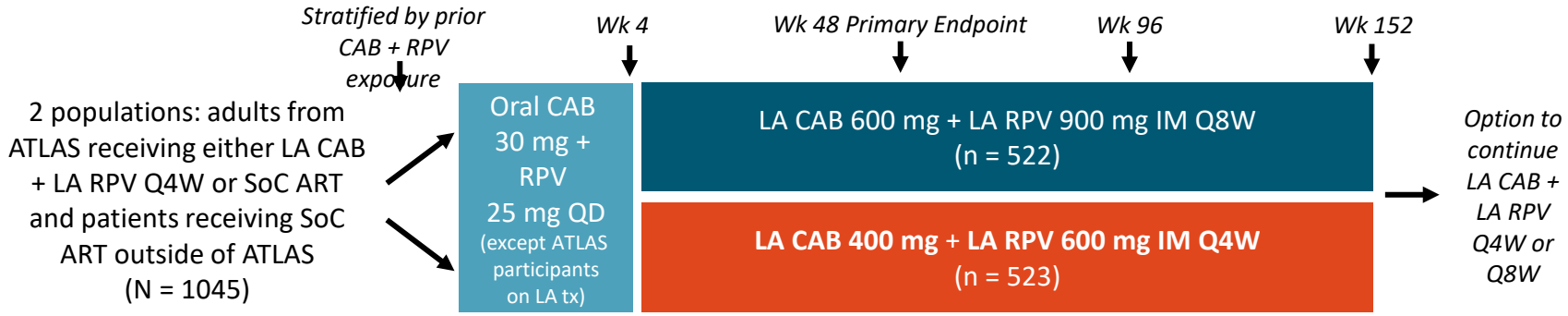
DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48

One subject on DTG + RPV meeting virologic withdrawal criteria had an NNRTI resistance-associated mutation (K101K/E)
No INI resistance-associated mutations were identified

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

ATLAS-2M: LA CAB + RPV Q8W vs Q4W

- Multicenter, randomized, open-label phase IIIb noninferiority trial

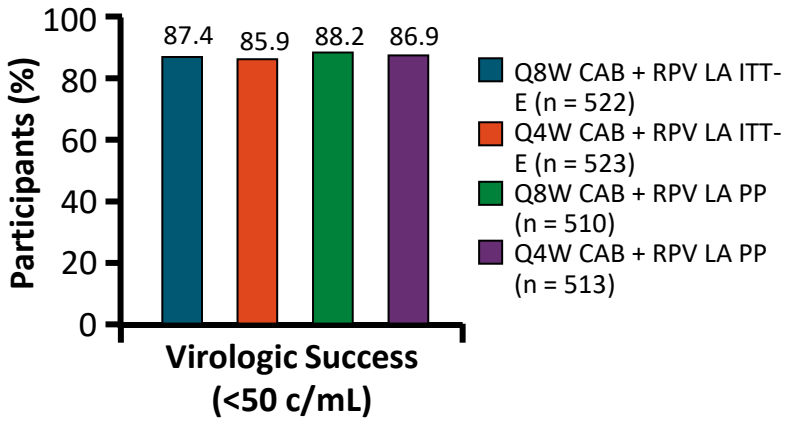


- Primary endpoint: HIV-1 RNA ≥50 c/mL at Wk 48 by FDA snapshot in ITT-E
  - Q8W found to be noninferior to Q4W at Wk 48
- Secondary/other Wk 152 endpoints: plasma HIV-1 RNA ≥50 or <50 copies/mL at Wk 152 by FDA snapshot in ITT-E, CVF incidence, viral resistance in patients with CVF, safety and tolerability, treatment satisfaction

Overton. Lancet. 2021;396:1994. Overton. CROI 2022. Abstr 479. NCT03299049.

Slide credit: clinicaloptions.com

ATLAS-2M: Wk 152 Outcomes



Outcome	Q8W (n = 522)	Q4W (n = 523)
CVF, n (%)	11 (2)	2 (<1)
RPV RAMs, n/N	9/11	1/2
INSTI RAMs, n/N	8/11	2/2

- LA CAB + RPV well tolerated
  - 99% of ISRs were grade 1/2; median duration was 3 days
  - 8 (2%) Q8W and 13 (3%) Q4W withdrew due to ISRs
- Patient satisfaction scores significantly favored Q8W vs Q4W dosing at Wk 24, 48, and 152

Overton. Lancet. 2021;396:1994. Overton. CROI 2022. Abstr 479.

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U.S. DHHS ART Guidelines (February 24, 2021)
www.clinicalinfo.hiv.gov

- Panel recommends monthly IM CAB + IM RPV as an optimization strategy for people with HIV currently on oral ART with documented viral suppression ≥3 months (AI), who—
  - have no baseline resistance to either medication
  - have no prior virologic failures
  - do not have active HBV infection (unless also receiving an oral HBV active regimen)
  - are not pregnant and are not planning on becoming pregnant
  - are not receiving medications with significant drug interactions with CAB and RPV

- Before initiation of the IM injection, patients should receive oral CAB and oral RPV for 28 days as an oral lead-in to assess tolerance.
- Approved as **every-2-mo injections** since February 2022

"Direct to Inject": Switching to LA CAB + RPV Without an Oral Lead-in

- FLAIR extension study[1]
  - Participants receiving DTG/ABC/3TC achieving virologic suppression (HIV-1 RNA <50 copies/mL) could switch to monthly LA CAB + RPV at Wk 100
  - Switchers elected to start with (n = 121) or without (n = 111) oral CAB + RPV lead-in

Outcome, n (%)	Direct to Inject (n = 111)	Oral Lead-in (n = 121)
HIV-1 RNA <50 copies/mL	110 (99.1)	113 (93.4)
HIV-1 RNA ≥50 copies/mL	1 (0.9)	1 (0.8)
▪ Discontinued for lack of efficacy	1 (0.9)	-
▪ Data in window not below threshold	--	1 (0.8)
No virologic data	0	7 (5.8)
▪ Discontinued due to AE	--	2 (1.7)
▪ Discontinued for other reason	--	5 (4.1)*

*Burden of travel, prohibited medication use, participant relocation, burden of procedures/intolerability of injections, and pregnancy.

- As of March 2022, the oral lead-in is optional according to the FDA approved prescribing information.[2]

1. Orkin. Lancet HIV. 2021;8:e668.
2. Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension PI.

Conclusions

- HAART efficacy is reaching its ceiling
- New goals: Patient-centered rather than virus-centered
- Two types of switch indications: Reactive and proactive
- BIC and DRV-based STRs good options for simplification
-
- Some 2-drug ART regimens are potent, convenient, well-tolerated and have a high barrier to resistance. RT inhibition seems to be crucial (DTG + 3TC, boosted PI + 3TC, DTG + Ril)
- Long-acting regimens in progress: **Oral**, **IM**, SC, implantable
- Simplified HAART might be the SOC in the next future

Muito obrigado pela atenção