14th Residential Course
on Clinical Pharmacology
of Antiretrovirals

Turin, 16-18 January 2019

Two drugs regimens for HIV infection

TRIALS EVALUATION

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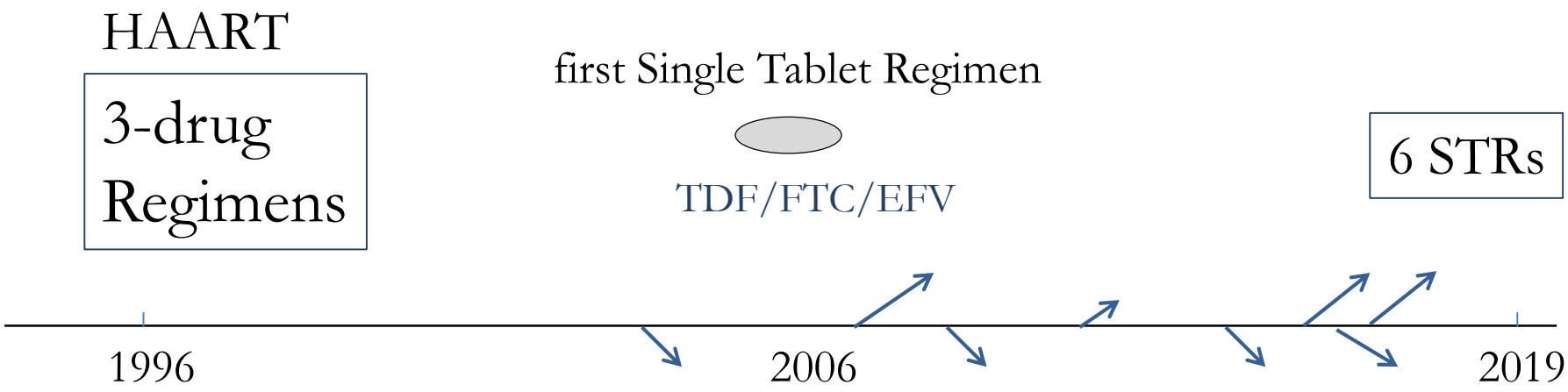
ASST Papa Giovanni XXIII

DISCLOSURES

Diego Ripamonti has received advisory fees, speaker fees, travel and education from:

- ViiV
- Janssen
- Merck
- Gilead
- BMS

HAART in history



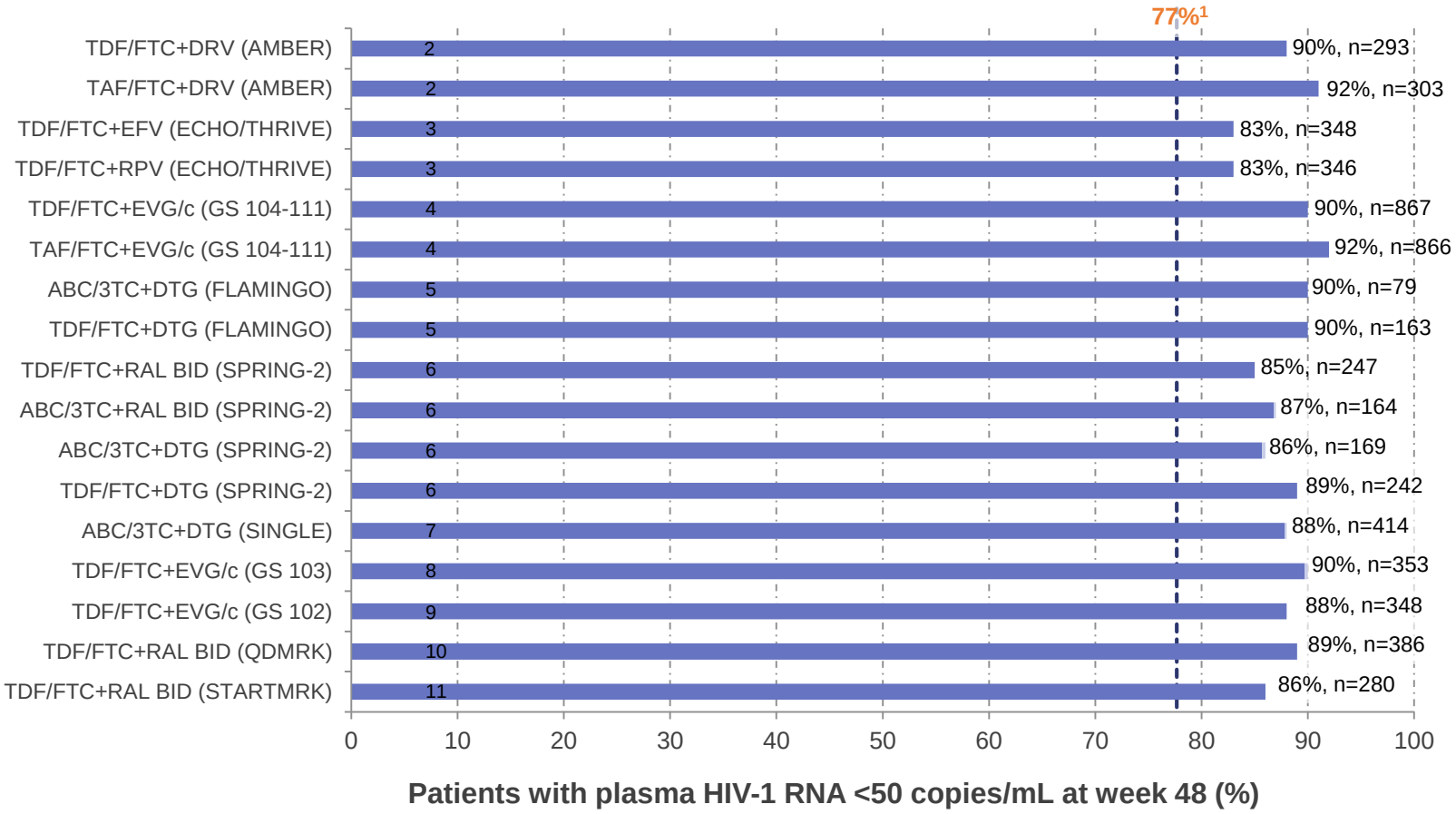
- multiple pills
- multiple doses

- TDF/FTC/EFV
- ABC/3TC/DTG
- TAF/FTC/RPV
- TAF/FTC/EGV-c
- TAF/FTC/BIC
- TAF/FTC/DRV-c

The history of HIV pharmacology is important to understand the current debate on dual vs triple?

Treatment response

Mean response rates (48-weeks) of initial regimens continue to rise from 77%[1] (2005–2010) to approximately 90% today



1. Lee FJ et al. PLoS ONE 2014;9:e97482; 2. Eron J, EACS 2017, Abs. PS8/2; 3. Molina JM et al. Lancet. 2011 Jul 16;378(9787):238-46; 4. Wohl D et al. CROI 2015;abst 113LB; 5. Clotet B et al. Lancet 2014;383:2222–2231; 6. Raffi F et al. Lancet 2013;381:735–43; 7. Walmsley SL et al. N Engl J Med 2013;369:1807–1818; 8. DeJesus E et al. Lancet 2012;379:2429–2438; 9. Sax PE et al. Lancet 2012;379:2439–48; 10. Eron JJ Jr et al. Lancet Infect Dis 2011;11:907–915; 11. Lennox JL et al. Lancet 2009;374:796–806

How many drugs are needed to control the HIV replication?

KEY POINTS

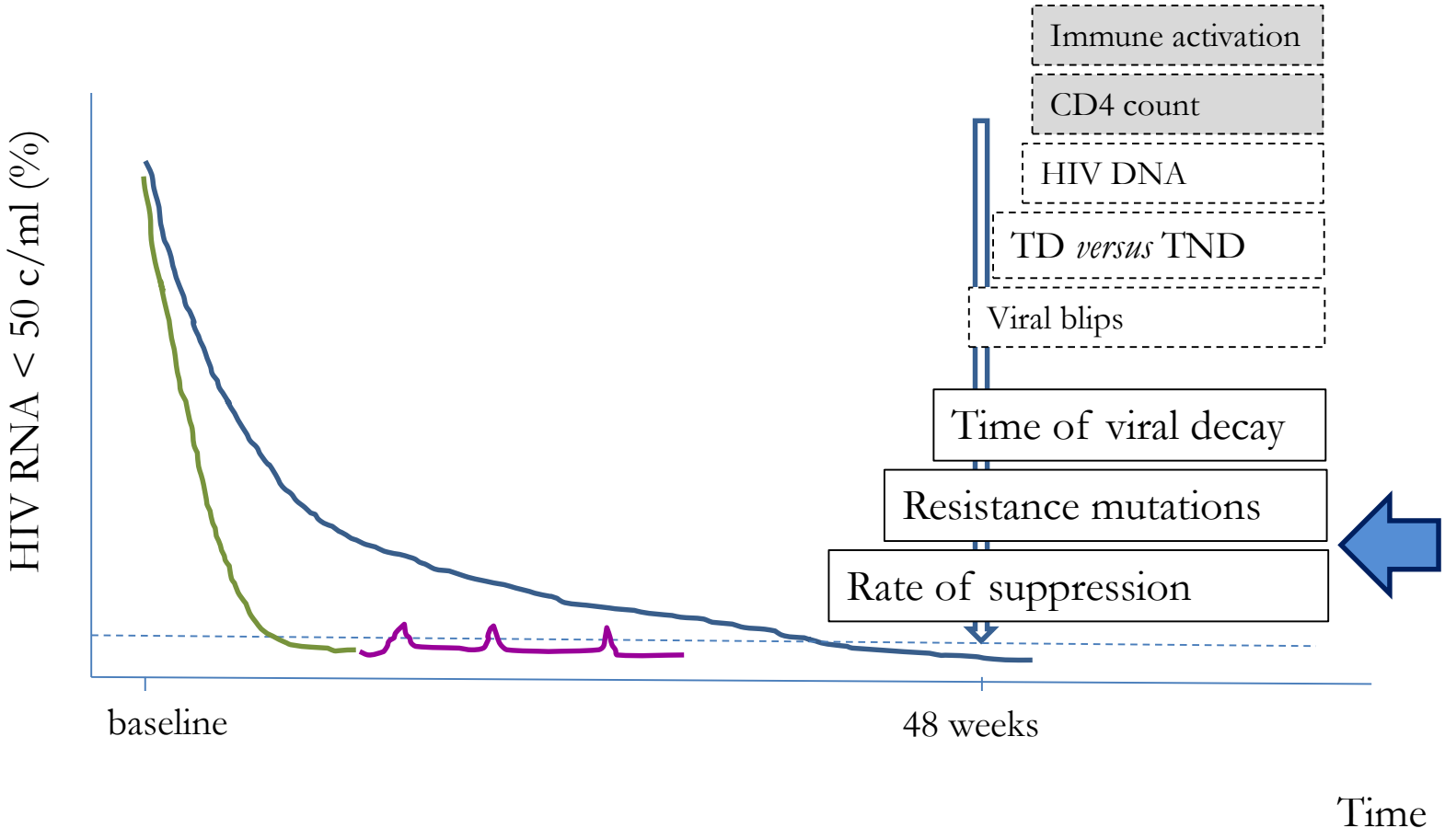
- ✓ Triple regimen does not mean «any triple combination»
- ✓ Dual regimen does not mean «any dual combination»

- ➢ HAART is the standard regimen for HIV infection
- ➢ Toxicity and costs issues were the initial drivers of LDRs

Are the dual regimens comparable to Triple Therapy?

Treatment response evaluation

Proportion of patients with HIV RNA below 50 copies/ml



Dual therapy

Boosted–PI + 3TC (4 trials)

Dolutegravir + Rilpivirine(2 trials)

Dolutegravir + 3TC (2 trials)

Dual regimens in HIV infection

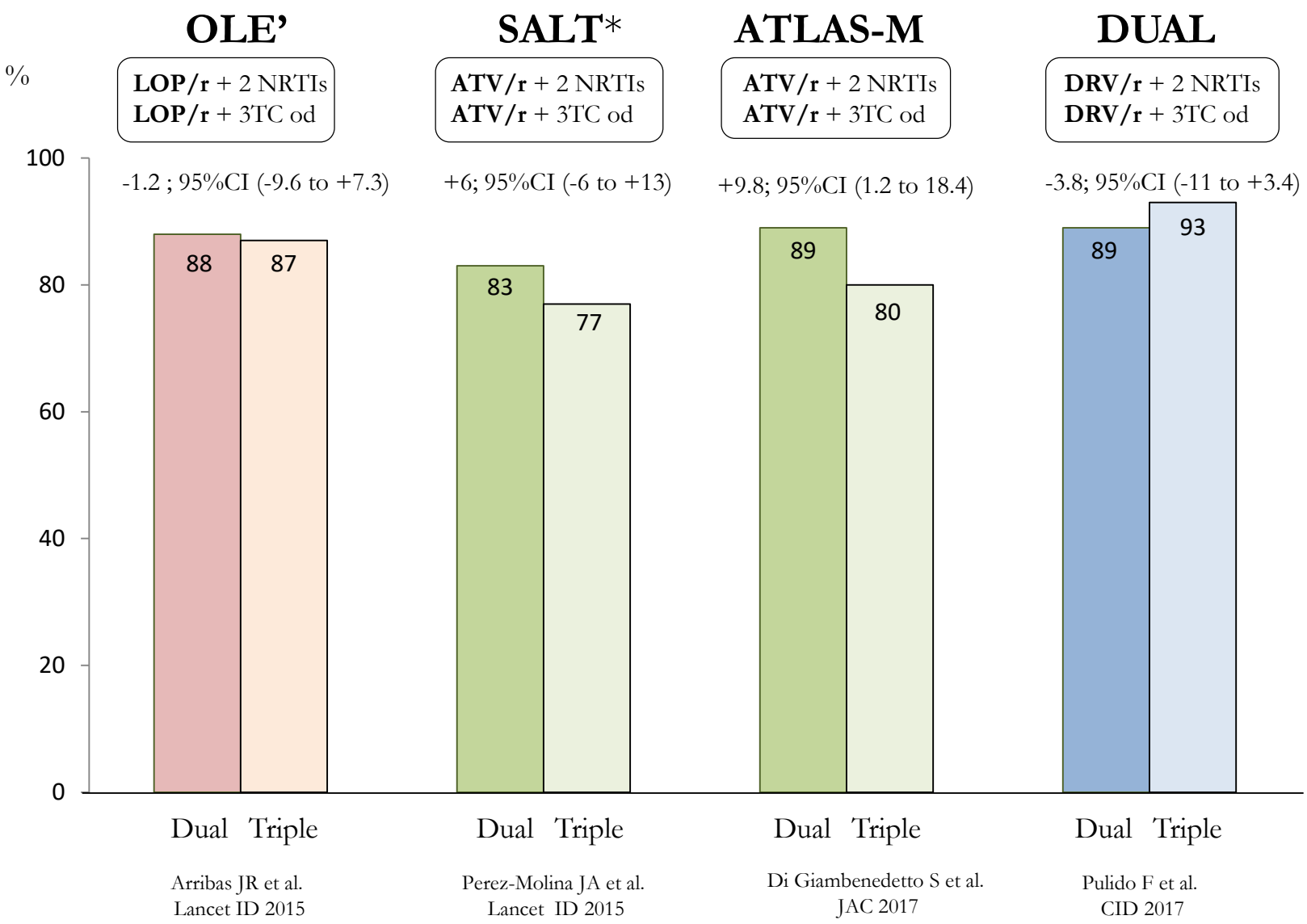
Regimen	Study	Design	from	Number of pts	Non inferiority	F-up weeks	Resistance profile
LOP/r + 3TC ATV/r + 3TC ATV/r + 3TC DRV/r + 3TC	OLE SALT* ATLAS-M DUAL	switch	bPI	**1051**	yes	48 96 96 48	1 1 0 1
DTG + RPV	SWORD 1-2	switch	any	**1024**	yes	48-96	3
DTG + 3TC	GEMINI 1-2	naive	-	**1433**	yes	48	0

* 33% from NNRTI-based rx

Arribas JR et al. Lancet ID 2015;
Di Giambenedetto S et al. JAC 2017;
Llibre JM et al. Lancet 2018;391:839-849;
Perez-Molina JA et al. Lancet ID 2015;
Pulido F. et al. CID 2017;65:2112-2118;
Cahn P et al. Lancet 2018. November

Dual therapy with boosted-PI + 3TC

Switch, randomized, non-inferiority (-12%) trials: HIV RNA < 50 c/ml at week 48 (ITT analysis, Snapshot).

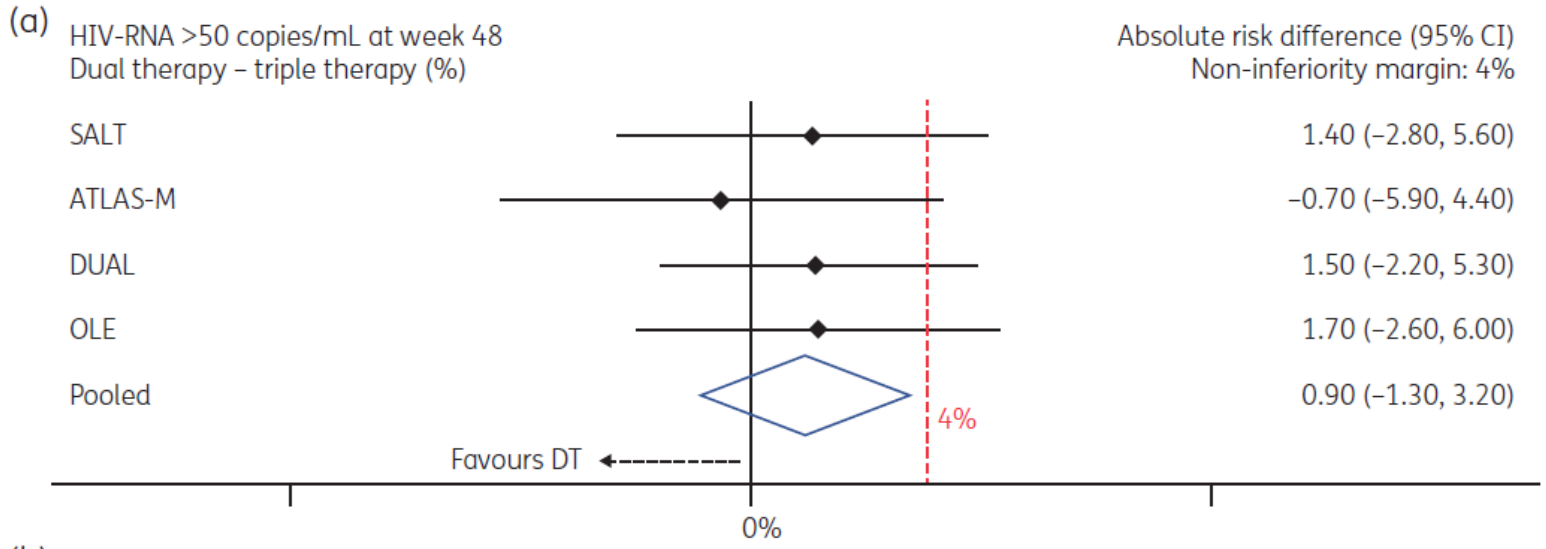


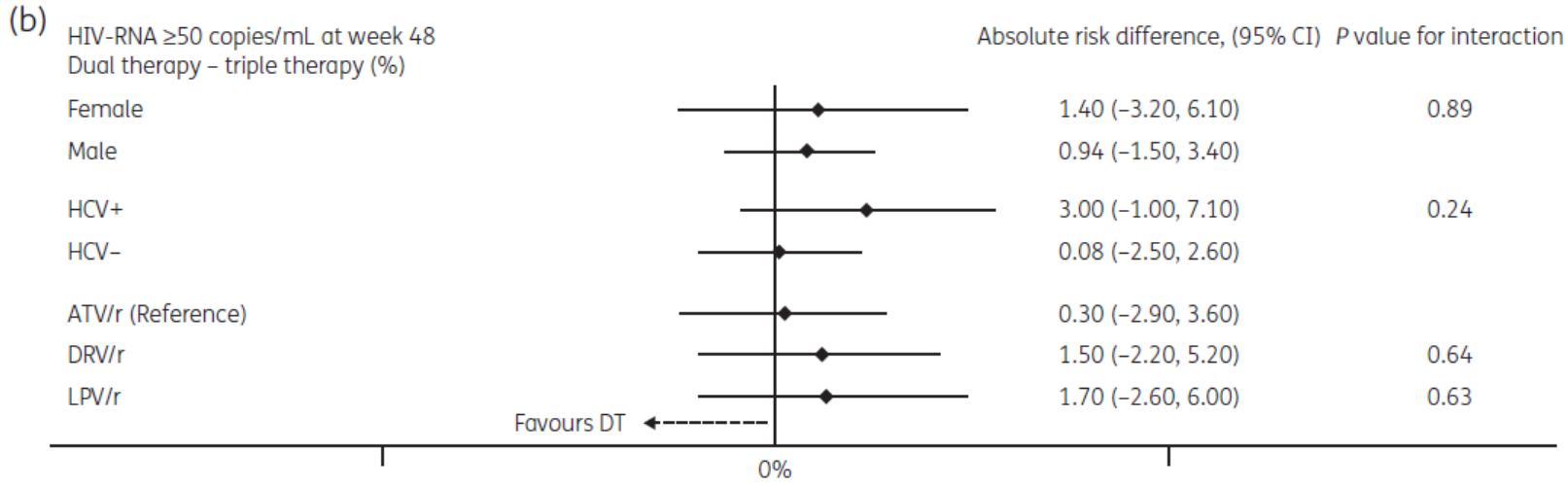
* PP population

Metanalysis of boosted PI + 3TC studies

Switch trials: HIV RNA < 50 c/ml,
Randomized, non-inferiority (-12%)
Total patients: **1051**, 48-week data

4% on DT vs 3.04% on TT had virological failure at week 48 (0.9%; 95% CI -1.2 to 3.1)



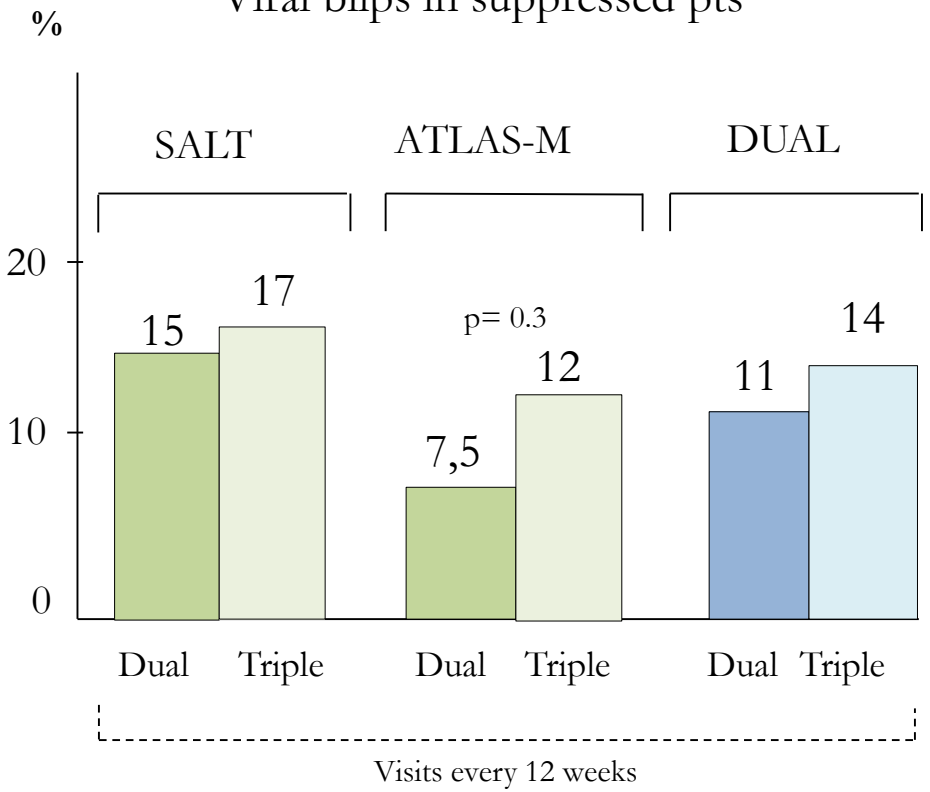


Perez-Molina JA et al. JAC 2018;73:2927-2935.

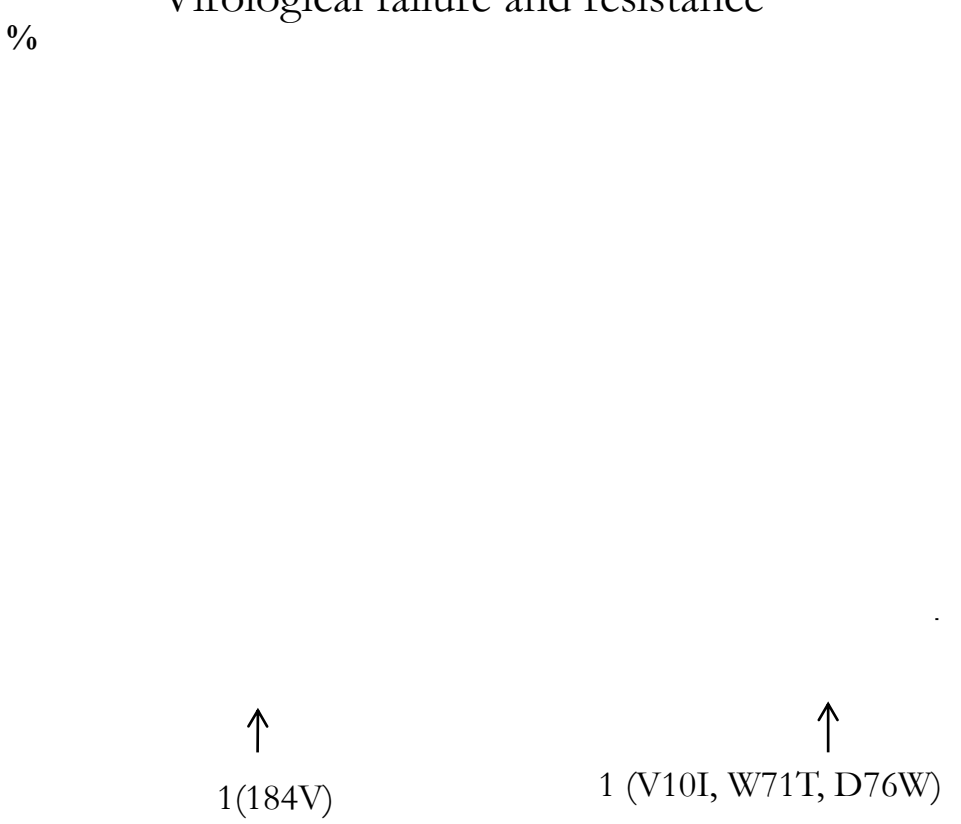
Viral blips & failure in boostedPI + 3TC

48 week-data from randomized, non-inferiority (-12%), switch studies.

Viral blips in suppressed pts



Virological failure and resistance



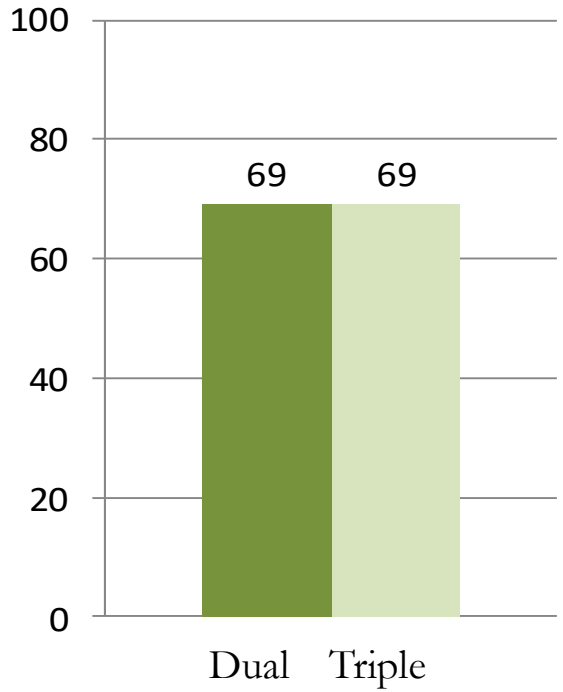
In OLE study, 1 pt failed in DT with 184V, 103A (present in previous saved sample)

1. Perez-Molina JA et al. Lancet ID 2015; 2. Di Giambenedetto S et al. JAC 2017 3. Pulido F et al. CID 2017;

ATV/r + 3TC: 96 week data

(ITT analysis, S=F, snapshot)

SALT

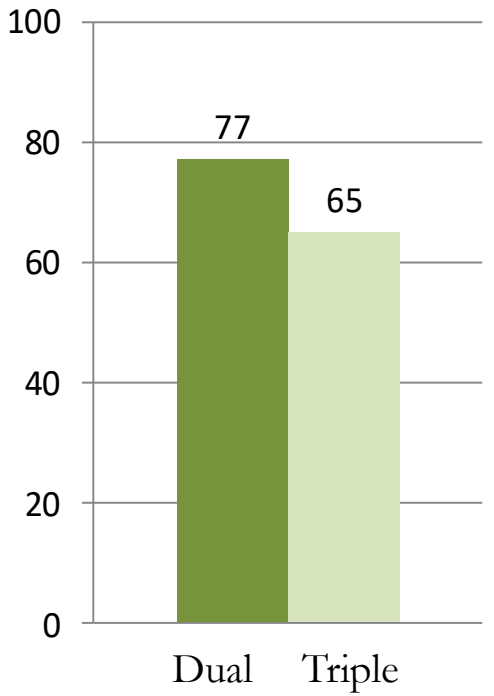


One patient taking ATV/r + 2NUCs with (M184V and L63P)

Perez-Molina et al. JAC 2017;72:246-253

ATLAS-M

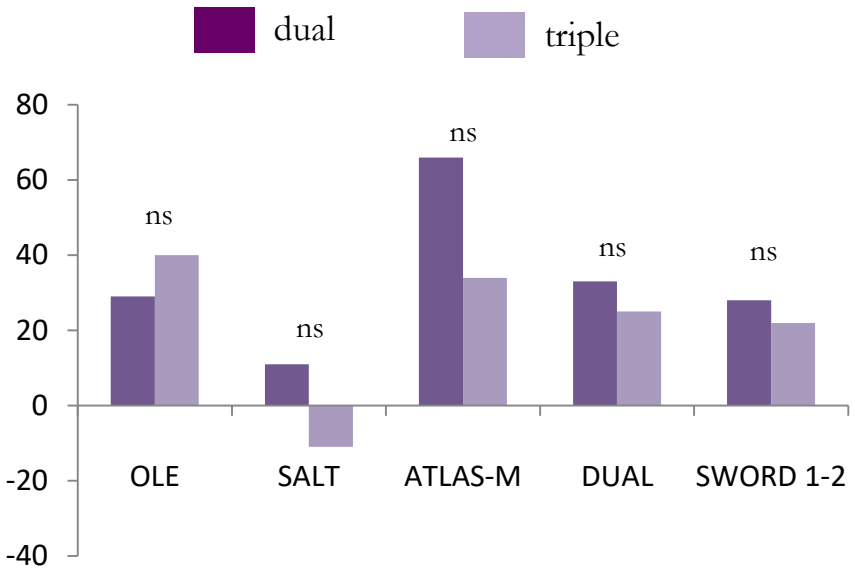
(+12.0%, 95% CI +1.2/+22.8, P = 0.030)



Fabbiani M et al. JAC 2018 Apr 12.

Boosted PI + 3TC: CD4 count and HIV DNA

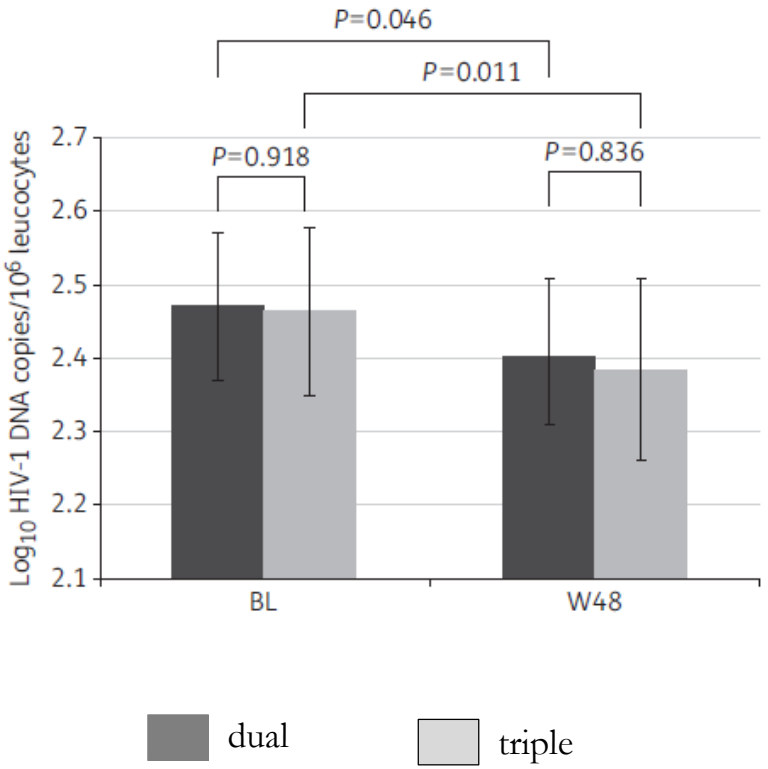
CD4 count increase in Dual *versus* Triple



Perez-Molina JA et al. Lancet ID 2015
Di Giambenedetto S et al. JAC 2017
Pulido F et al. CID 2017
Llibre JM et al. Lancet 2018

HIV DNA evolution in ATLAS-M

(week 48)



Lombardi F et al. JAC 22017;72:2055-2059.

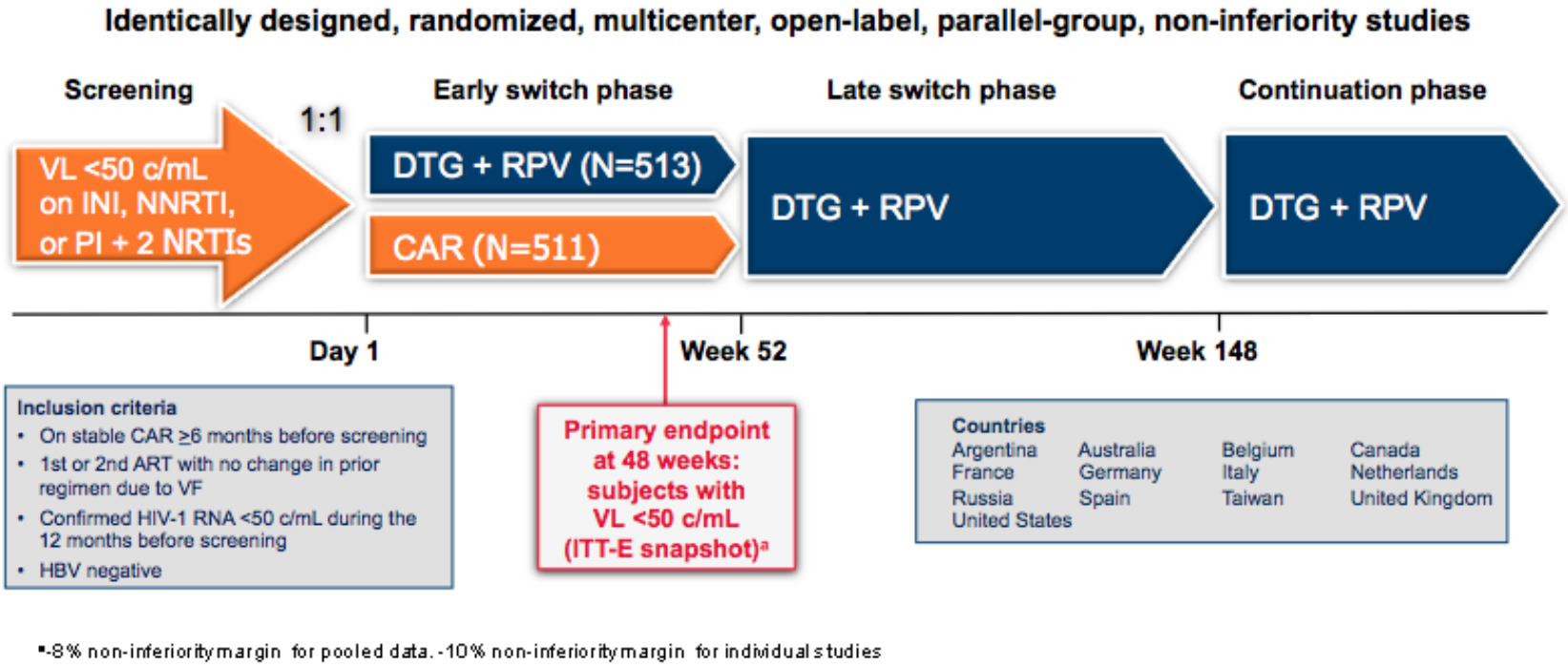
Metanalysis of boosted PI + 3TC studies (48 weeks)

KEY POINTS

- Patients switched mostly from bPI triple therapy
- no HBV coinfection
- **No resistance mutations** to 3TC or PI before switching
- Similar virological failure in DT vs TT (as well as the number of blips)
- Resistance mutations were infrequent (3 patients: 1 on Dual Th, 2 in Triple Th)

- Age, gender, active HCV and type of PI do not affect results
- Similar CD4 count increase and HIV DNA evolution
- Discontinuations were more frequent on triple arm (bone and renal)

SWORD 1 and 2 studies

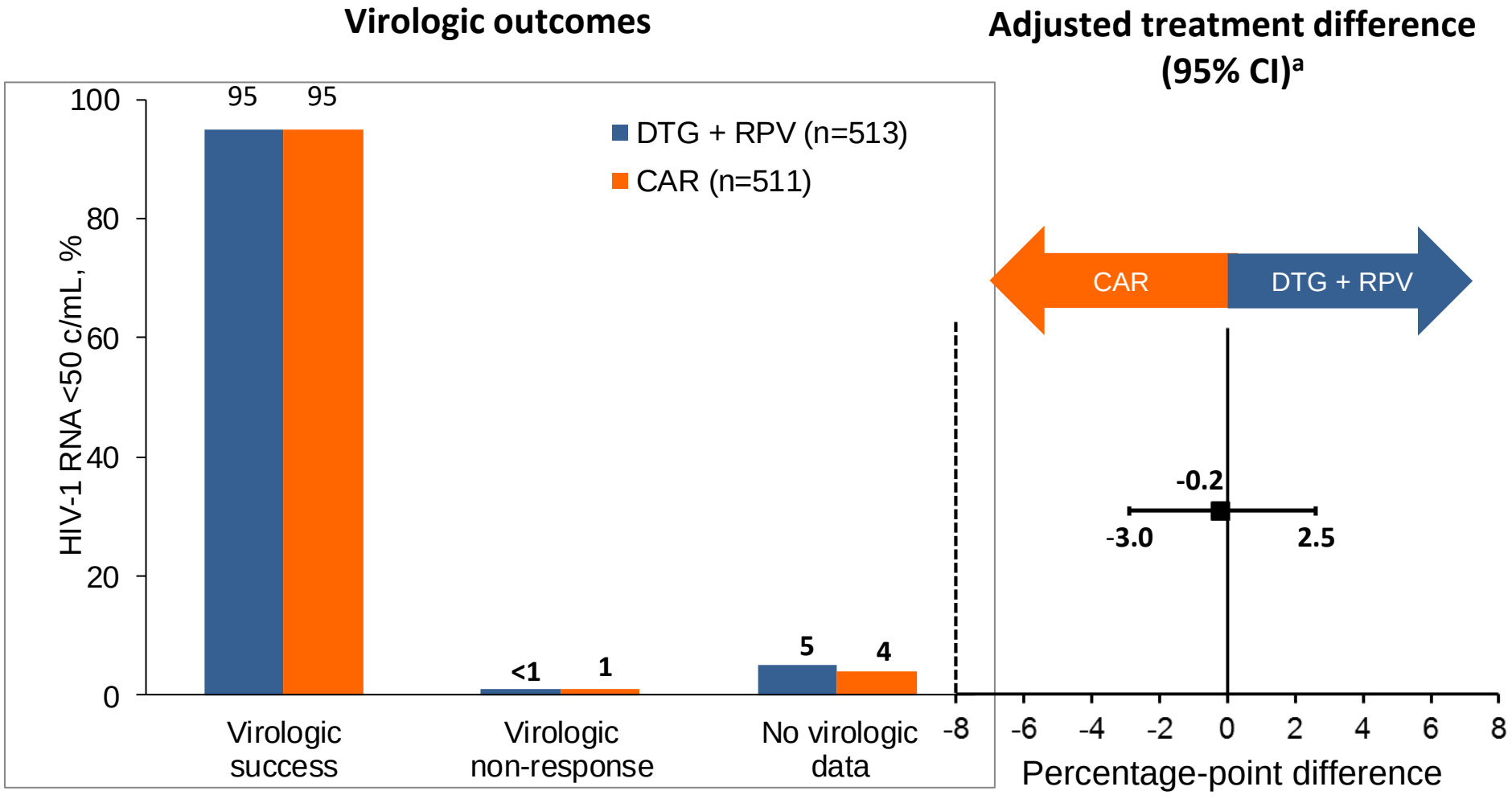


a-8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

- Food & antacids for RPV-based regimens
- Defined history before switching to RPV

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

SWORD 1-2: 48-week data



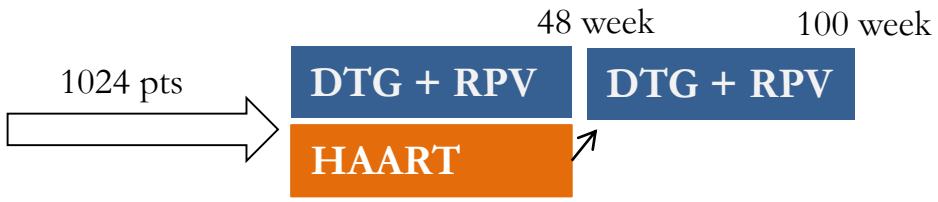
[a]Adjusted for age and baseline 3rd agent.

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

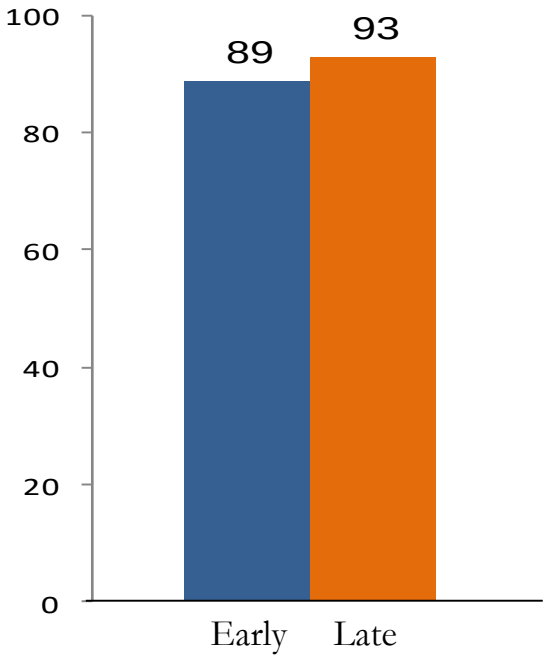
SWORD 1-2: 96-week data

HAART at baseline
from PI: 26%
from NNRTI: 54%
from II: 20%

1024 pts



HIV RNA < 50 c/ml (Snapshot), week 100

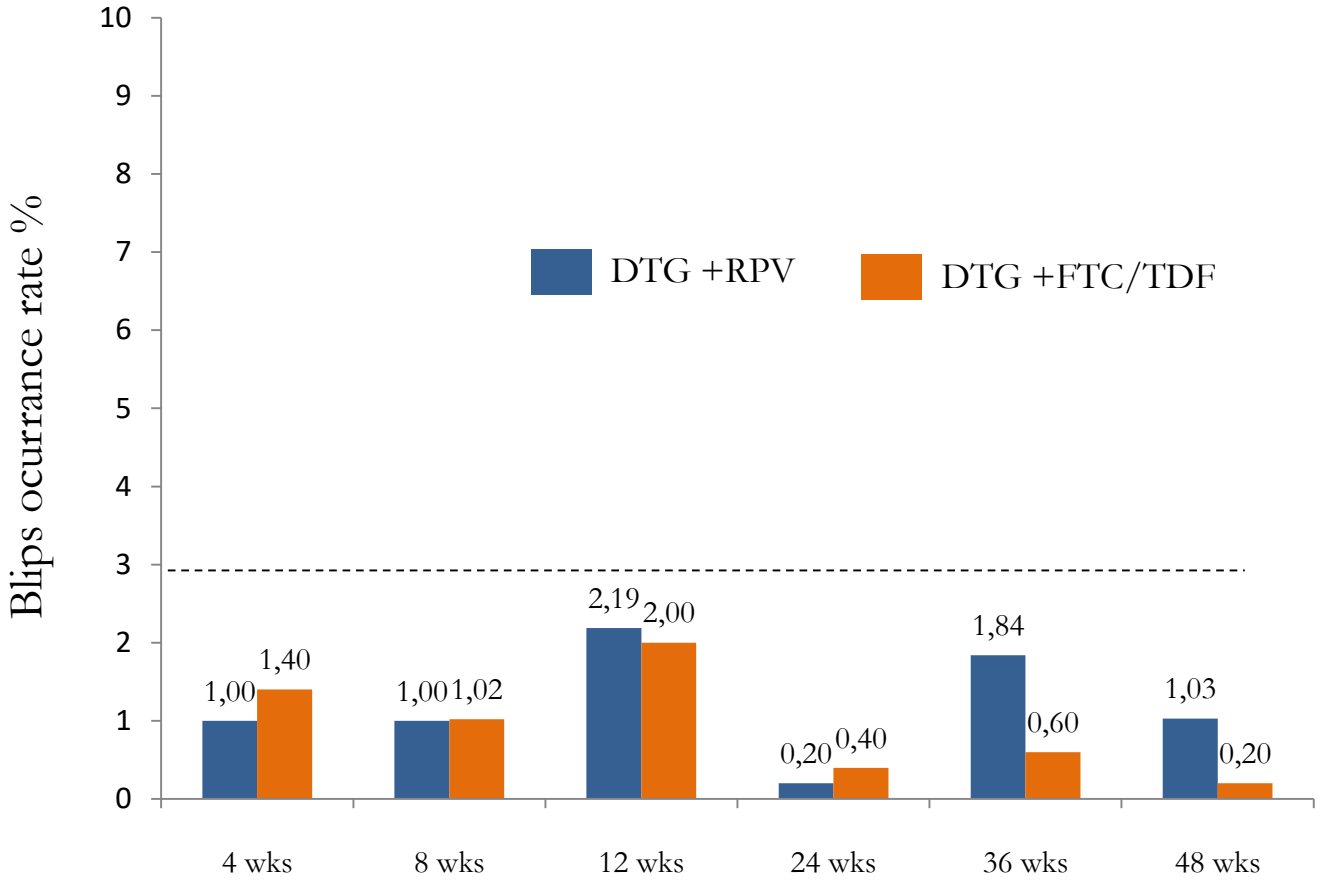


10/990 (1%) confirmed virologic withdrawals through week 100 (**NNRTI resistance** in 3/10, all from early switch arm).

Aboud M et al. AIDS Confer 2018. Abs THPEB047. Llibre JM et al. Lancet. 2018;391:839-849.

Intermittent viremia in SWORD 1-2 studies

Rates of blips (HIV RNA >50 c/ml) by study arm through week 48



Viral blips were not associated to CVW

Wang R et al. HIV Drug therapy 2018, Glasgow UK; Poster 313.

Comparison of Viral Replication Below 50 c/mL for DTG+RPV vs 3-Drug arm in the SWORD 1-2 Studies

Abbott HIV-1 Realtime Assay generates qualitative data for VL <40 c/mL

- HIV-1 RNA present → **TD** (target detected)
- HIV-1 RNA not present → **TND** (target not detected)

Proportions of patients with TND for DTG+RPV and CAR arms through week 48

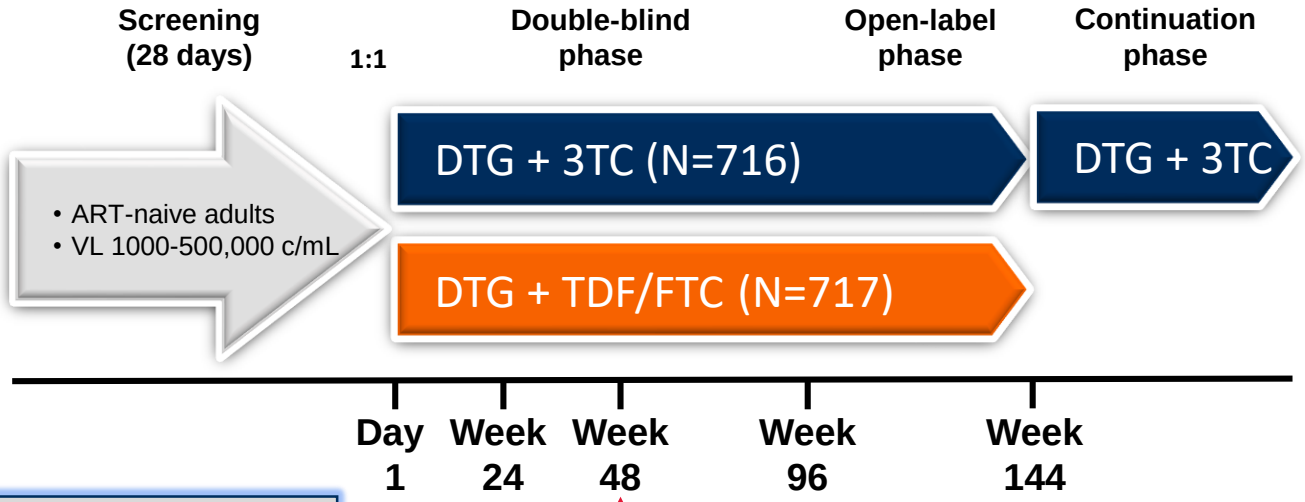
Underwood M et al. HIV Drug Therapy 2018, Glasgow UK; Poster 311.

EFFICACY OF DUAL THERAPY IN NAÏVE PATIENTS

“Stress test” for a dual regimen

GEMINI 1-2, phase III study design

Identically designed, randomized, double-blind, parallel-group, multicenter, non-inferiority studies



Eligibility criteria
- ≤10 days of prior ART
- No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
- No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E Snapshot)[a]

Countries

Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

[a]–10% non-inferiority margin for individual studies.

Cahn P et al. Lancet 2018; November

Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population

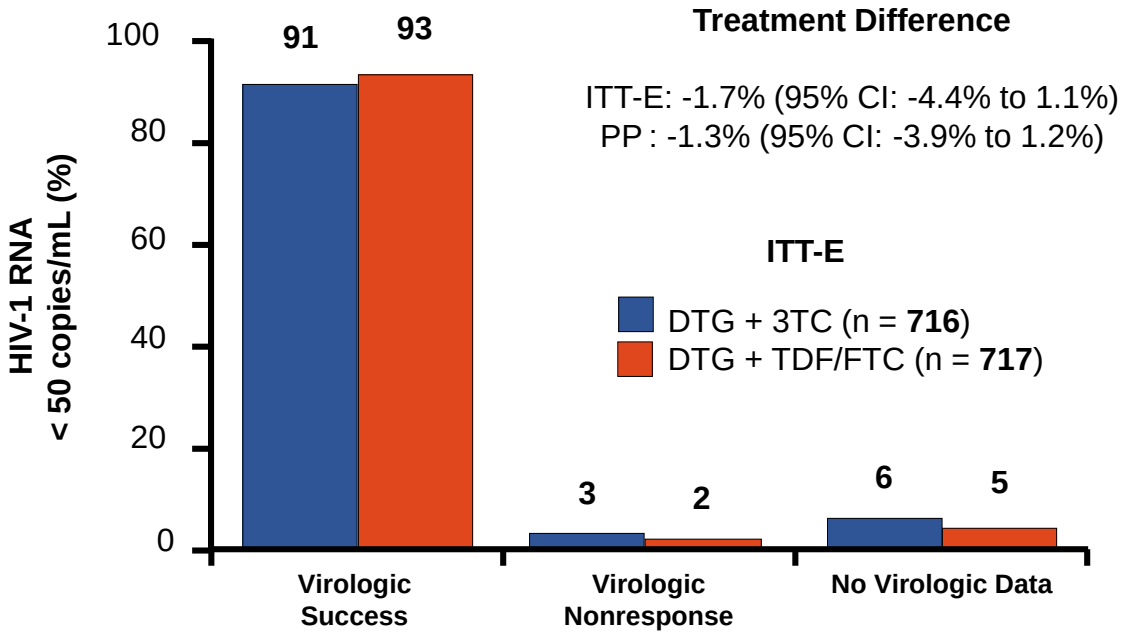
Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
White	480 (67)	497 (69)
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000	140 (**20**)	153 (**21**)
>250,000	51 (7)	46 (6)
>400,000	18 (3)	24 (3)
>500,000[a]	13 (2)	15 (2)
CD4+ cell count, median (range), cells/mm³	427.0 (19-1399)	438.0 (19-1497)
≤200	63 (**9**)	55 (**8**)
>200	653 (91)	662 (92)

[a]Participants were required to have HIV-1 RNA ≤500,000 c/mL at screening. Other than 1 participant enrolled without meeting study entry criteria, these participants had an observed increase in HIV-1 RNA between screening and baseline.

Cahn et al. *Lancet.* 2018 [Epub ahead of print].

Gemini 1- 2: naive patients, 48-week results

"Stress test" for a dual regimen



Baseline characteristics
HIV RNA < 500.000 c/ml: all
HIV RNA > 10^5 c/ml: 20 %
No HBV coinfection
CD4 < 200 cells: 10%

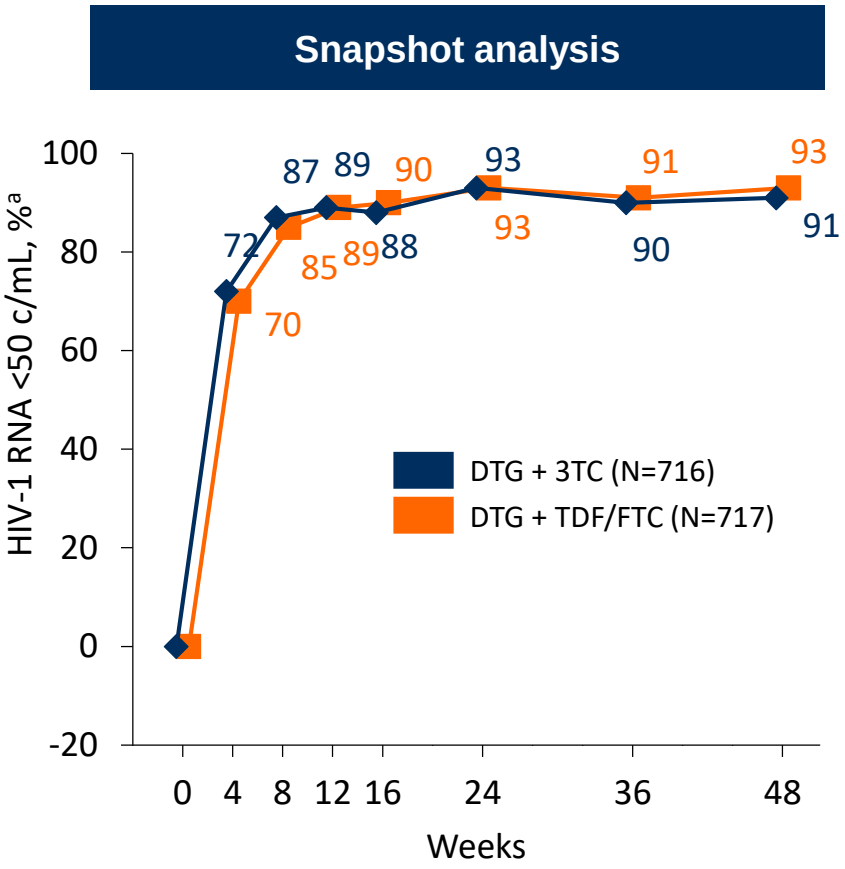
.

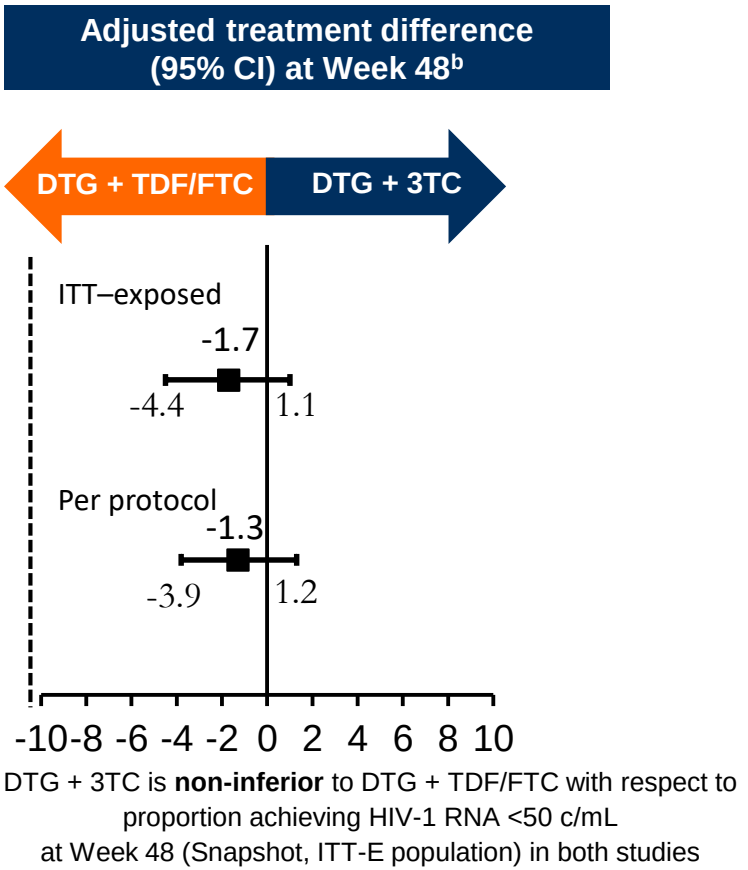
No treatment-emergent mutations

Bone and kidney safety markers better for DTG+3TC

Cahn P et al. Lancet 2018; November

Snapshot Analysis by Visit: Pooled ITT-E Population





DTG + 3TC is **non-inferior** to DTG + TDF/FTC with respect to proportion achieving HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E population) in both studies

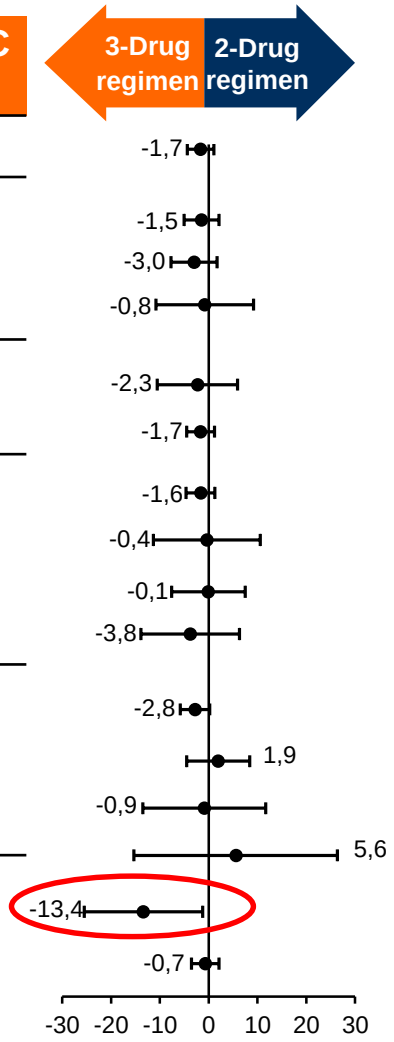
[a]Calculated from a repeated-measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction. [b]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

Figures adapted from Cahn et al. *Lancet*. 2018 [November]

Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Oral Presentation #7.

Snapshot Analysis Outcomes at Week 48 by Subgroups: Pooled ITT–E Population

Variable	Subgroup	DTG + 3TC n/N (%)	DTG + TDF/FTC n/N (%)
	Overall	655/716 (91)	669/717 (93)
Age, y	<35	386/420 (92)	381/408 (93)
	35 to <50	211/231 (91)	216/229 (94)
	≥50	58/65 (89)	72/80 (90)
Sex	Female	100/113 (88)	89/98 (91)
	Male	555/603 (92)	580/619 (94)
Race, n (%)	White	447/480 (93)	471/497 (95)
	African heritage	83/99 (84)	64/76 (84)
	Asian	67/71 (94)	68/72 (94)
	Other	58/66 (88)	66/72 (92)
Baseline HIV-1 RNA, c/mL	≤100,000	526/576 (91)	531/564 (94)
	>100,000	129/140 (92)	138/153 (90)
	>250,000	45/51 (88)	41/46 (89)
	>400,000	16/18 (89)	20/24 (83)
Baseline CD4+ cell count, cells/mm^3	≤200	50/63 (79)	51/55 (93)
	>200	605/653 (93)	618/662 (93)



Orkin et al. HIV Glasgow 2018; Glasgow, UK. Poster P021.

Snapshot Non-Response in Participants With Baseline CD4+ Cell Count ≤200 cells/mm^3

Participant	Snapshot outcome (Week 48)	Clinical Reason for study DC	Study day of DC	Last study VL, c/mL
DTG + 3TC				
1	VL ≥50 c/mL	NA: continued in study	NA	≥50[a,b]
2	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
3	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
4	VL ≥50 c/mL	Protocol-defined virologic withdrawal	205	362
9	VL ≥50 c/mL	NA: Unplanned change in ART	NA	≥50[a,b]
10	VL ≥50 c/mL	PV: randomized in error[c]	15	102
12	VL ≥50 c/mL	Lost to follow-up	356	64366
5	No virologic data	AE: pulmonary TB	206	<50
6	No virologic data	AE: cerebral chagoma	164	507,564[d]
7	No virologic data	Treatment for HCV infection	165	<50
8	No virologic data	Withdrew consent	115	<50
11	No virologic data	PV: randomized in error[e]	28	1,848,435[f]
13	No virologic data	Lost to follow-up	100	<50
DTG + TDF/FTC				
14	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
16	VL ≥50 c/mL	Investigator discretion: incarceration	76	384
15	No virologic data	Withdrew consent	342	<50
17	No virologic data	Lost to follow-up	175	<50

DC, discontinuation; NA, not applicable; PV, protocol violation, [a]VL results from Week 60 shown for participants who continued the study beyond Week 48. [b]Value not provided due to potential for unblinding. [c]Enrolled with HBV coinfection. [d]Participant had discontinued study treatment prior to study DC. [e]Enrolled with Screening VL of >500,000 c/mL. [f]VL result available from Day 1 only.

Orkin et al. HIV Glasgow 2018; Glasgow, UK. Poster P021.

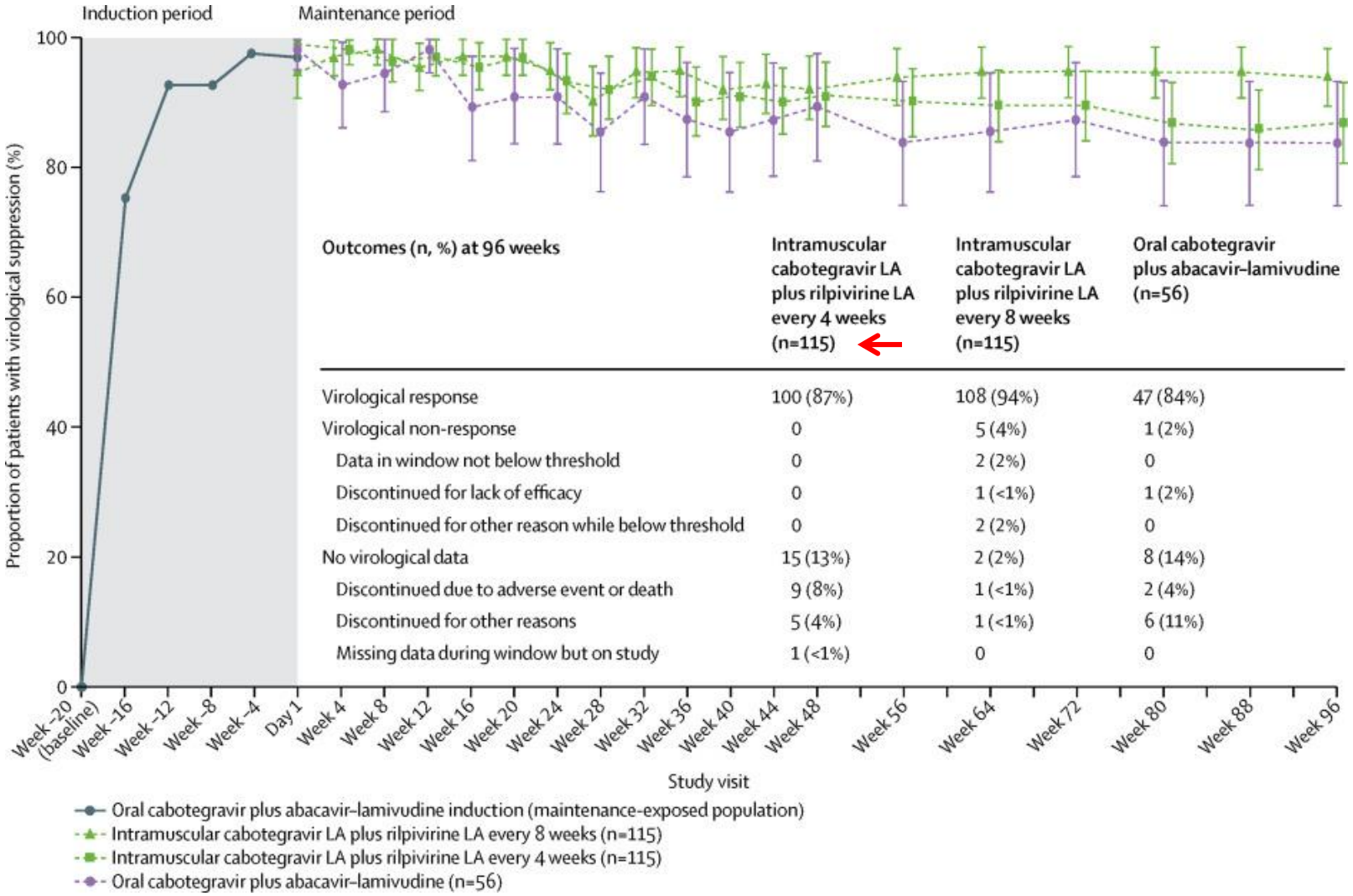
Future options in dual therapy?

Future dual options in switch strategy?

Experimental arm	Switch studies *versus* triple regimns
DRV/c + RPV_{25mg}	Studio PROBE-2 (160 pts)
DRV/r + $DTG_{50\ mg}$	Studio DUALIS (320 pts)
$DTG_{50\ mg}$ + $3TC_{300\ mg}$	Studio TANGO (440 pts on TAF)

Cabotegravir *plus* **RPV** (long acting formulation)

Long-acting intramuscular **cabotegravir and rilpivirine** in adults (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial



Outcomes (n, %) at 96 weeks	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

Margolis DA et al. Lancet HIV 2017; sept

Changing a paradigm

- ✓ Do we need a benefit to switch to a dual regimen?
- ✓ What do we neede to change a paradigm?
  a) How many patients?
  b) How many trials?
  c) How long follow up?
  d) Other markers?

Is a «triple regimen» more protective to control HIV replication in tissues/sanctuaries?

Triple or dual regimens to control HIV infection?

Thanks for the attention