SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Piacenza

Regione Emilia-Romagna

SEMINARIO DI STUDIO REGIONALE

Evoluzione dei modelli di gestione dell'infezione da HIV

Bologna, 30 maggio 2019 • Sala 20 maggio 2012
Viale della Fiera 8, Bologna

Strategie di semplificazione e ottimizzazione della terapia antiretrovirale

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Clinica Malattie Infettive,

Policlinico di S.Orsola,

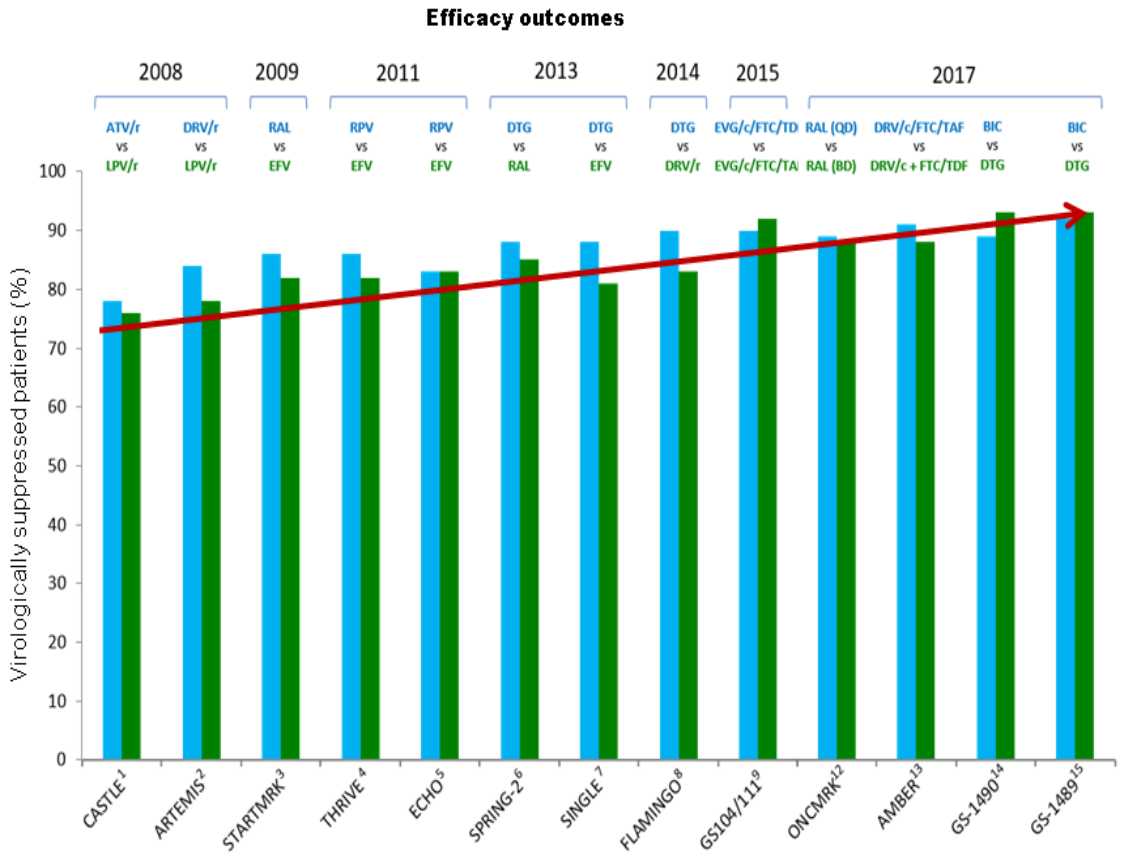
Università degli Studi di Bologna

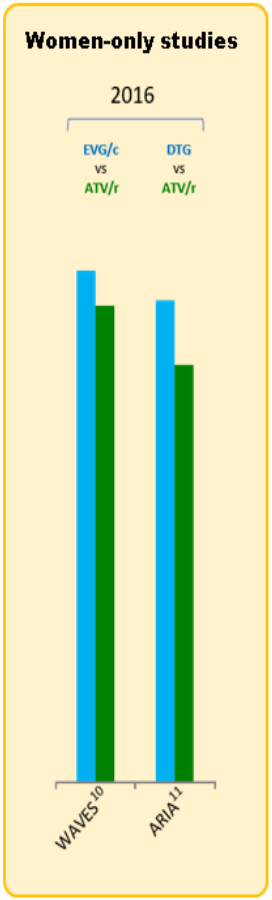
IL SOTTOSCRITTO LEONARDO CALZA

IN QUALITÀ DI RELATORE DELL'EVENTO IN CORSO, AI SENSI DELL'ART. 3.3 SUL CONFLITTO DI INTERESSI, PAG. 17 DEL REG. APPLICATIVO DELL'ACCORDO STATO-REGIONI DEL 5/11/09, PER CONTO DEL PROVIDER DICHIARA CHE NEGLI ULTIMI DUE ANNI HA AVUTO I SEGUENTI RAPPORTI ANCHE DI FINANZIAMENTO CON SOGGETTI PORTATORI DI INTERESSI COMMERCIALI IN CAMPO SANITARIO:

JANSSEN, MSD, VIIV, GILEAD

Overall efficacy outcomes at Week 48





ATV, atazanavir; BD, twice daily; BIC, bictegravir; c, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; LPV, lopinavir; QD, once daily; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

1. Molina JM, *et al. Lancet* 2008;372:646–55; 2. Ortiz R, *et al. AIDS* 2008;22:1389–97; 3. Lennox JL, *et al. Lancet* 2009;374:796–806; 4. Cohen CJ, *et al. Lancet* 2011;378:229–37; 5. Molina JM, *et al. Lancet* 2011;378:238–46; 6. Raffi F, *et al. Lancet* 2013;381:735–43; 7. Walmsley SL, *et al. N Engl J Med* 2013;369:1807–18; 8. Clotet B, *et al. Lancet* 2014;383:2222–31; 9. Sax PE, *et al. Lancet* 2015;385:2606–15; 10. Squires K, *et al. Lancet HIV* 2016;3:e410–20; 11. Orrell C, *et al. Lancet HIV* 2017;4:e536–46; 12. Cahn P, *et al. Lancet HIV* 2017;4:e486–94; 13. TBA; 14. Sax PE, *et al. Lancet* 2017;390:2073–82; 15. Gallant J, *et al. Lancet* 2017;390:2063–72.

HIV continuum of care in Europe and Central Asia

RS Drew,[1] B Rice,[2] K Rüütel,[3] V Delpech,[4] KA Attawell,[5] DK Hales,[6] C Velasco,[7] AJ Amato-Gauci,[8] A Pharris,[8] L Tavoschi[8] and T Noori[8]

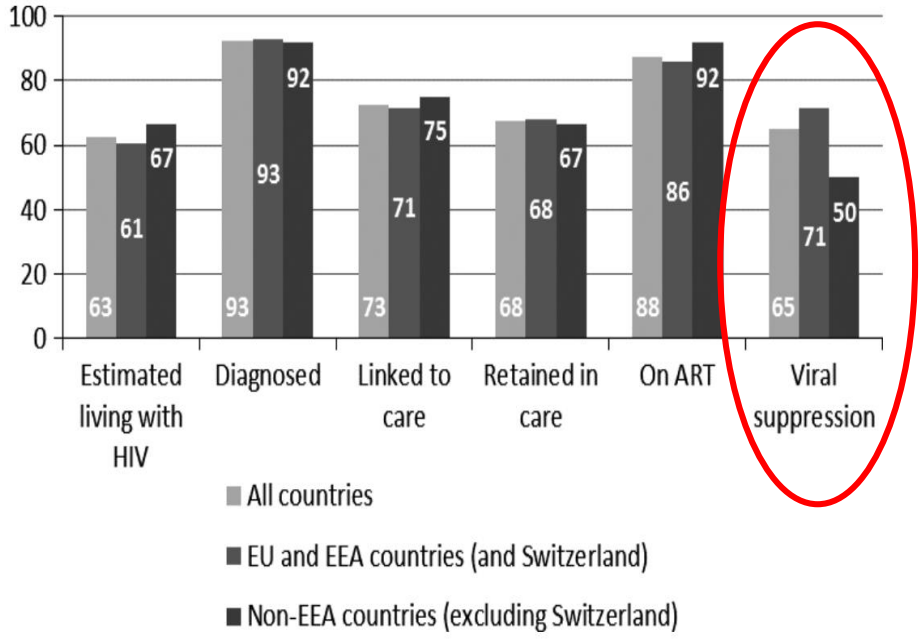
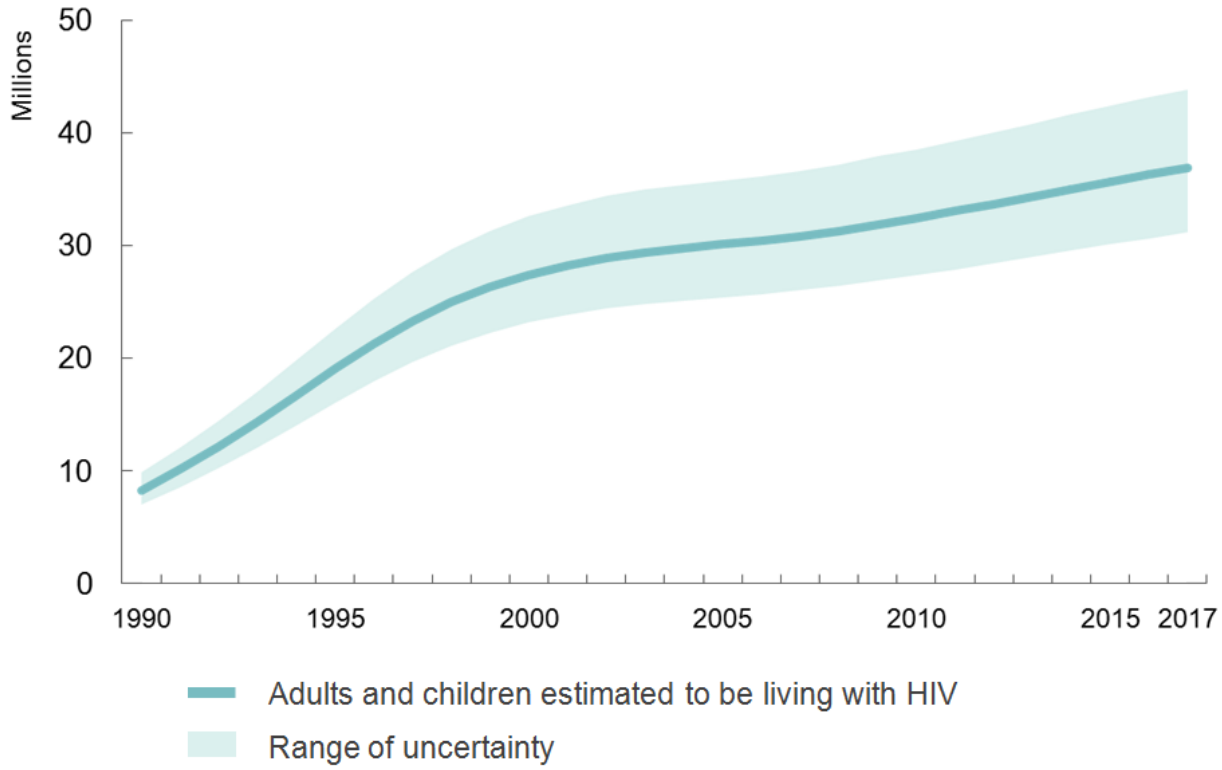


Fig. 1 Percentage of European and Central Asian countries reporting quantitative data for different elements of the HIV continuum of care (n = 40). ART, antiretroviral therapy; EEA, European Economic Area; EU, European Union.

HIV Medicine (2017), 18, 490–499

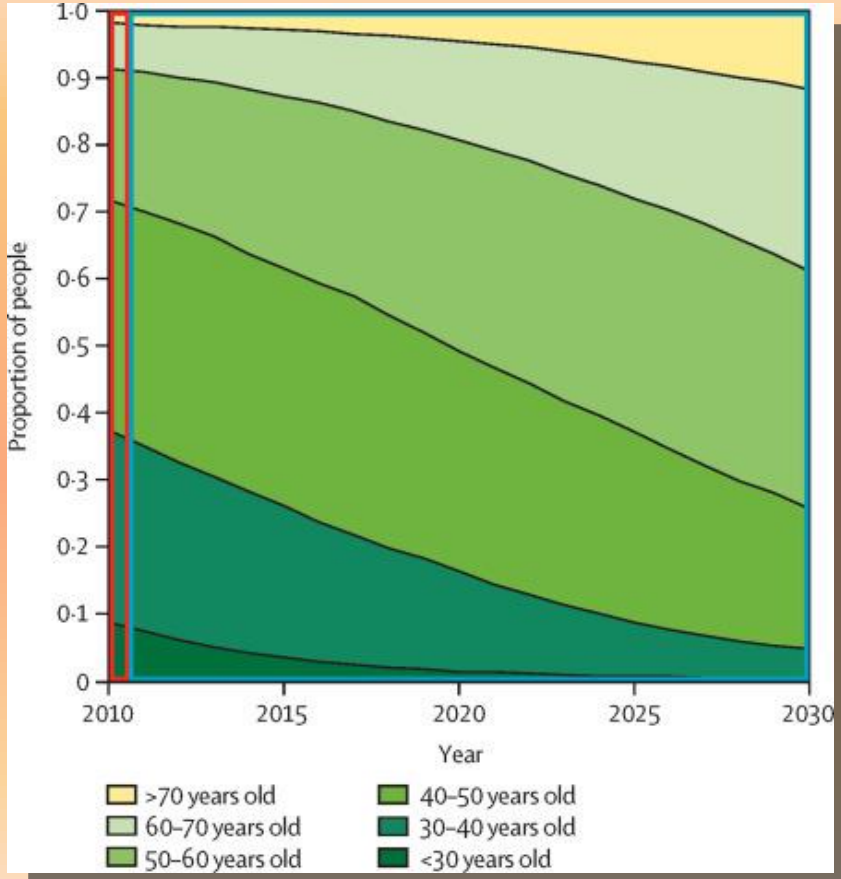
Adults and children estimated to be living with HIV | 1990–2017

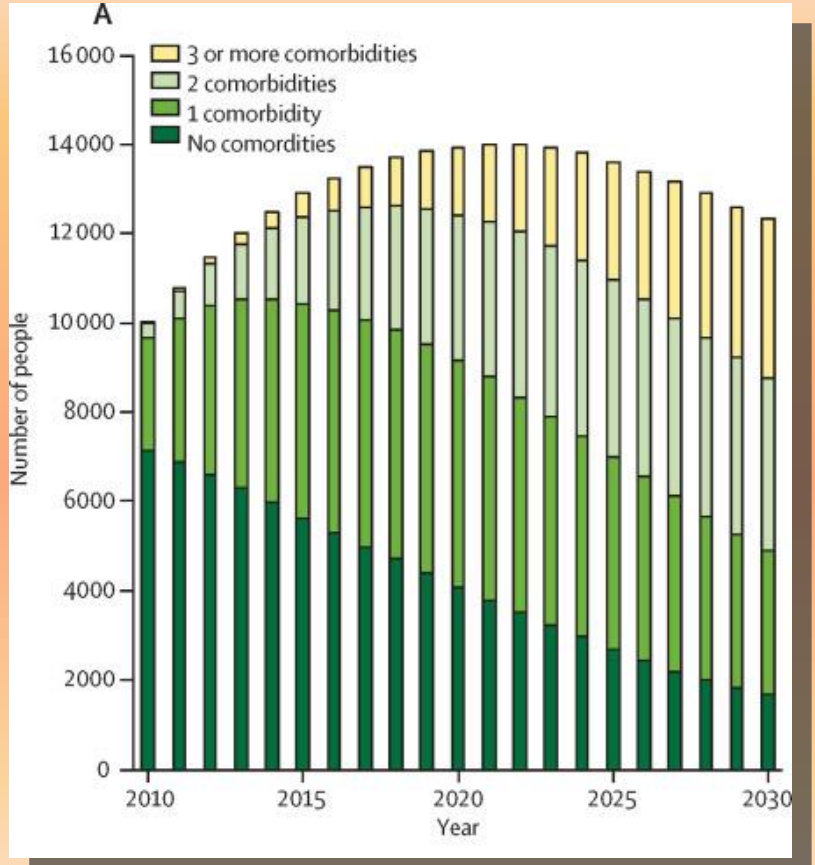


UNAIDS

Future challenges for clinical care of an ageing population infected with HIV: a modelling study

Mikaela Smit, Kees Brinkman, Suzanne Geerlings, Colette Smit, Kalyani Thyagarajan, Ard van Sighem, Frank de Wolf, Timothy B Hallett, on behalf of the ATHENA observational cohort





(Lancet Infect Dis 2015)

OTTIMIZZAZIONE

Il limite delle terapie antiretrovirali di combinazione (ART) attualmente disponibili consiste nell'impossibilità di ottenere l'eradicazione dell'infezione: il trattamento deve quindi essere continuato a tempo indefinito ed è probabile che, per motivi differenti (tossicità, invecchiamento, comorbilità, prevenzione di danni d'organo, interazioni farmacologiche, ridotta aderenza), nel corso degli anni si rendano opportune modifiche al regime in atto, anche in assenza di fallimento virologico.

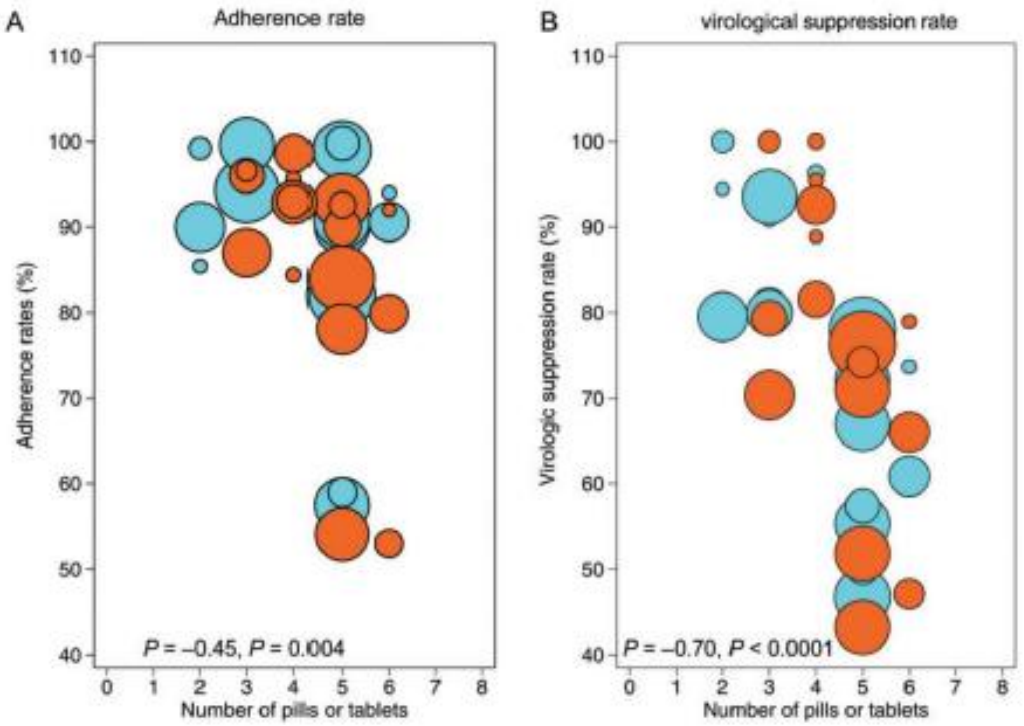
Il termine *ottimizzazione della ART* è utilizzato in queste linee guida per indicare strategie finalizzate alla miglior salute psico-fisica del paziente, attraverso modifiche al regime terapeutico in atto, con finalità differenti, ma sempre in condizioni di soppressione virologica (HIV-RNA <50 copie/mL).

(Linee Guida Italiane 2017)

Reasons to switch an effective cART

- Simplification (adherence improvement)
- Prevention of treatment-emergent toxicities
- Prevention of drug-drug interactions
- Preserve future options
- Increase in the genetic barrier of ARV drugs
- Cost reduction

Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials



Meta-analysis of randomized controlled trials.

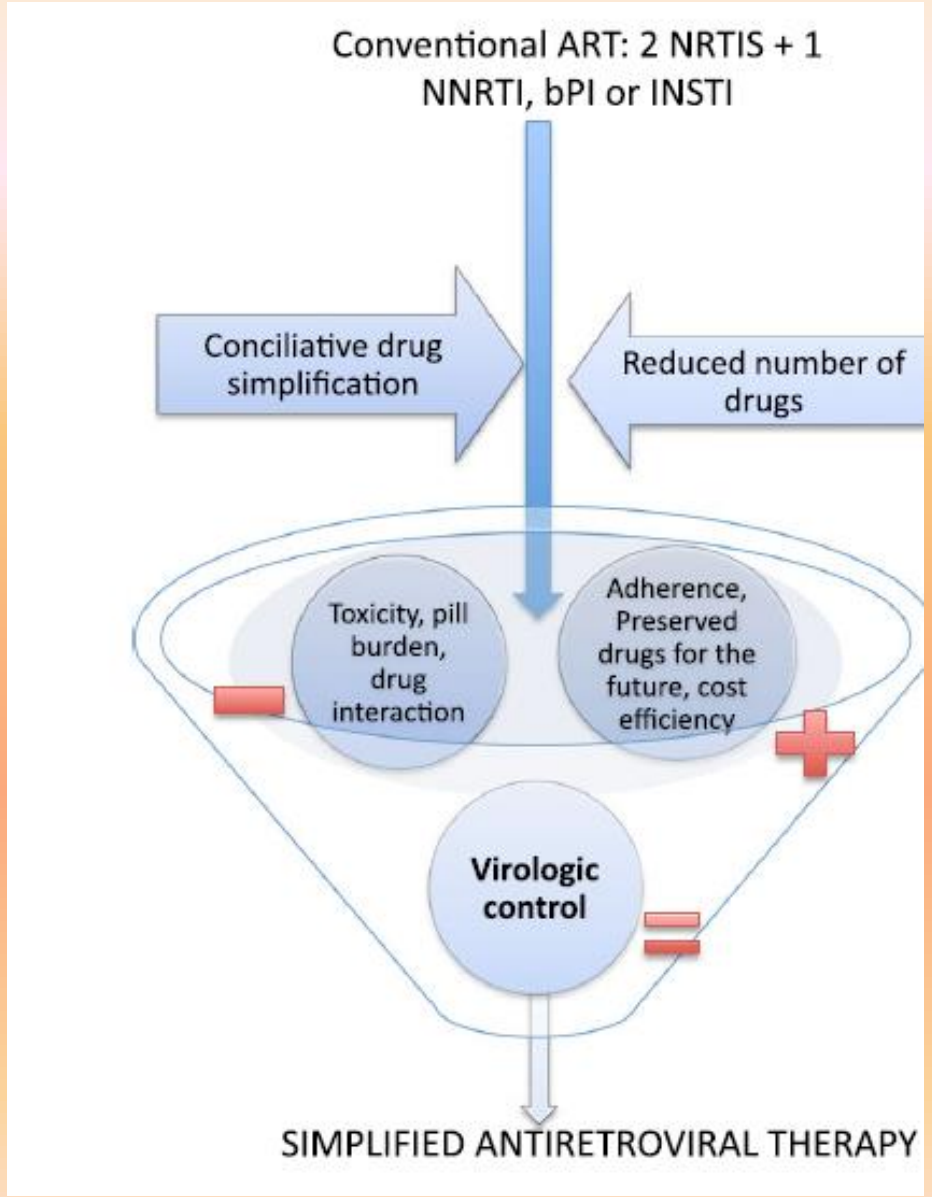
RCTs comparing once daily vs twice-daily ART regimens that also reported on adherence and virological suppression were included. Study quality was rated using the Cochrane risk-of-bias tool.

Nineteen studies met inclusion criteria (N = 6312 adult patients).

Antiretroviral therapy adherence rate, virological response, and pill burden.

Area of circle is proportional to the sample size. Blue, once-daily regimens; orange, twice-daily regimens.

Nachega JB, et al. Clin Infect Dis, 2014



Simplification strategies

- Reduction in pill burden and dosing frequency
- Reduction in the number of drugs

(de Miguel Buckley R et al., Curr HIV/AIDS Reports 2018)

Less Drug Regimens

Monotherapies:

-PI/r or PI/cobi

-DTG

Dual therapies:

-PI/r + 3TC

-DRV/r + RPV

-PI/r + RAL

-DTG + RPV

-DTG + 3TC

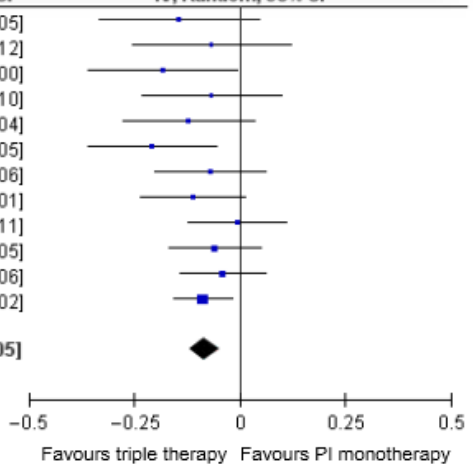
-long-acting CAB + RPV

Efficacy of protease inhibitor monotherapy *vs.* triple therapy: meta-analysis of data from 2303 patients in 13 randomized trials

A

Study or Subgroup	PI/r monotherapy Events	Total	Triple therapy Events	Total	Weight	Risk Difference IV, Random, 95% CI
OK Pilot	17	21	20	21	3.4%	−0.14 [−0.33, 0.05]
KalMo	24	30	26	30	3.6%	−0.07 [−0.25, 0.12]
KRETA	29	44	37	44	4.0%	−0.18 [−0.36, −0.00]
Monarch	14	15	15	15	4.5%	−0.07 [−0.23, 0.10]
MODAT	37	51	44	52	5.1%	−0.12 [−0.28, 0.04]
MOST	23	29	31	31	5.3%	−0.21 [−0.36, −0.05]
DREAM	63	98	69	97	7.3%	−0.07 [−0.20, 0.06]
MONOI	66	112	79	113	8.1%	−0.11 [−0.23, 0.01]
OK-04	77	100	76	98	9.2%	−0.01 [−0.12, 0.11]
MONET	88	127	97	129	10.5%	−0.06 [−0.17, 0.05]
KALESOLO	73	87	87	99	12.4%	−0.04 [−0.14, 0.06]
PROTEA	118	137	129	136	26.5%	−0.09 [−0.16, −0.02]
Total (95% CI)		**851**		**865**	**100.0%**	**−0.08 [−0.12, −0.05]**
Total events	629		710			

Heterogeneity: tau² = 0.00; χ = 7.19, df = 11 (P = 0.78); I^2 = 0%
Test for overall effect: Z = 4.62 (P < 0.00001)



B

Study or Subgroup	PI/r monotherapy Events	Total	Triple therapy Events	Total	Weight	Risk Difference IV, Random, 95% CI
KalMo	25	30	26	30	2.9%	−0.03 [−0.21, 0.15]
KRETA	33	44	37	44	3.3%	−0.09 [−0.26, 0.08]
OK Pilot	20	21	20	21	5.6%	0.00 [−0.13, 0.13]
DREAM	72	98	69	97	5.9%	0.02 [−0.10, 0.15]
MODAT	47	51	44	52	6.2%	0.08 [−0.05, 0.20]
Monarch	15	15	15	15	6.4%	0.00 [−0.12, 0.12]
MONOI	91	112	87	113	8.3%	0.04 [−0.06, 0.15]
OK-04	87	100	76	98	8.3%	0.09 [−0.01, 0.20]
MONET	106	127	106	129	10.9%	0.01 [−0.08, 0.11]
KALESOLO	79	87	87	99	11.9%	0.03 [−0.06, 0.12]
PROTEA	126	137	131	136	30.3%	−0.04 [−0.10, 0.01]
Total (95% CI)		**822**		**834**	**100.0%**	**0.01 [−0.03, 0.04]**
Total events	701		698			

Heterogeneity: tau² = 0.00; χ = 9.29, df = 10 (P = 0.50); I^2 = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

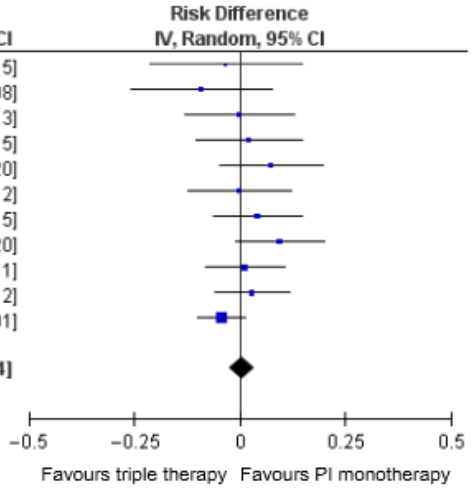
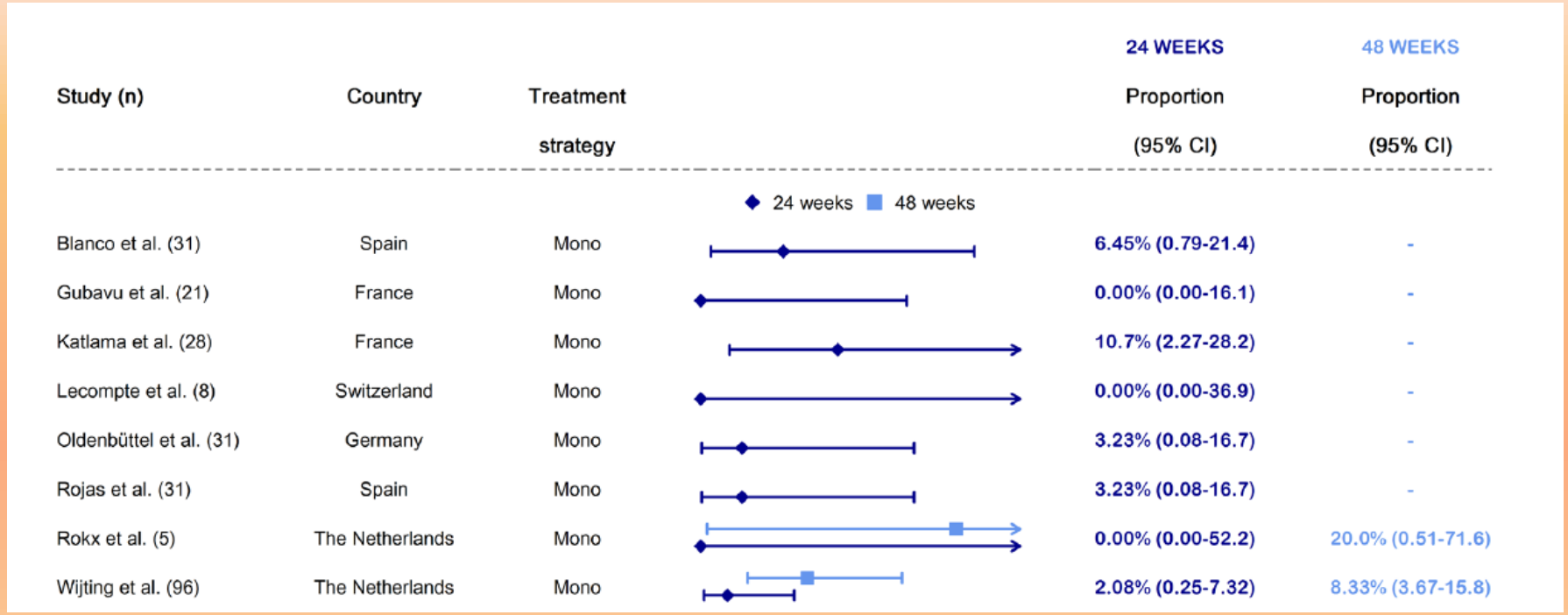


Fig. 1 Rates of HIV-1 RNA suppression for (a) the switch-equals-failure endpoint and (b) the switch-included endpoint. CI, confidence interval; PI/r, ritonavir-boosted protease inhibitor.

(Arribas J et al., HIV Med 2015)

RESEARCH ARTICLE

REVISED Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: Systematic review and meta-analysis [version 2; peer review: 3 approved]



(Wandeler G et al., F1000Res 2018)

Less Drug Regimens

Monotherapies:

-PI/r or PI/cobi

-DTG

Dual therapies:

-PI/r + 3TC

-DRV/r + RPV

-PI/r + RAL

-DTG + RPV

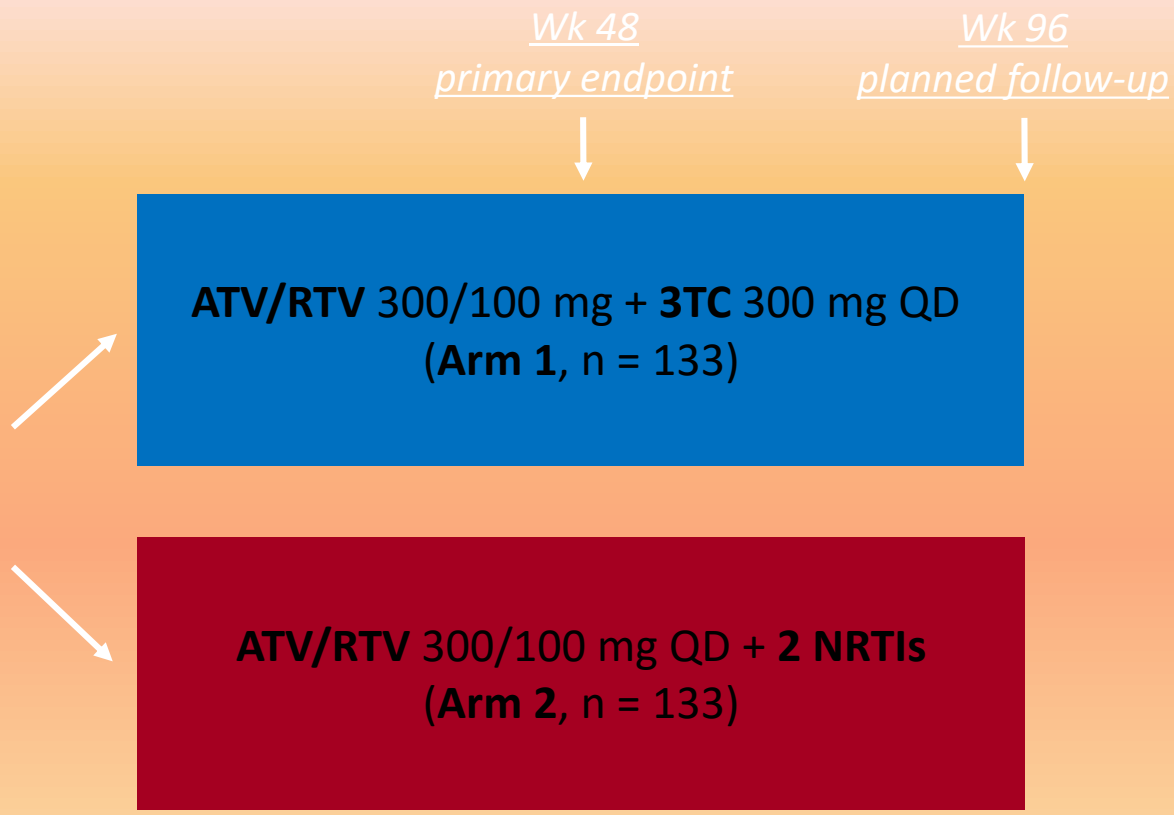
-DTG + 3TC

-long-acting CAB + RPV

PI/r + 3TC

ATLAS-M: study design

Multicenter (23 sites), randomized, open label, non-inferiority trial



Inclusion criteria:

- HIV+ patients treated with ATV/RTV + 2 NRTIs from at least 3 months
- HIV-1 RNA < 50 c/mL from at least 6 months
- CD4 >200 cell/µL from at least 6 months

Exclusion criteria: active or recent (<12 months) OI , previous mono/dual therapies, previous virological failure, Resistance to ATV or 3TC, treatment with proton pump inhibitors, HBsAg+, pregnancy.

(Di Giambenedetto S et al., J Antimicrob Chemother 2017)

Causes of treatment failure, week 48

48 weeks free of treatment failure:
Dual treatment (DT) 89.5% (95% CI 84.3-94.7)
Triple treatment (TT) 79.7% (95% CI 72.9-86.5)

i. Resistance:

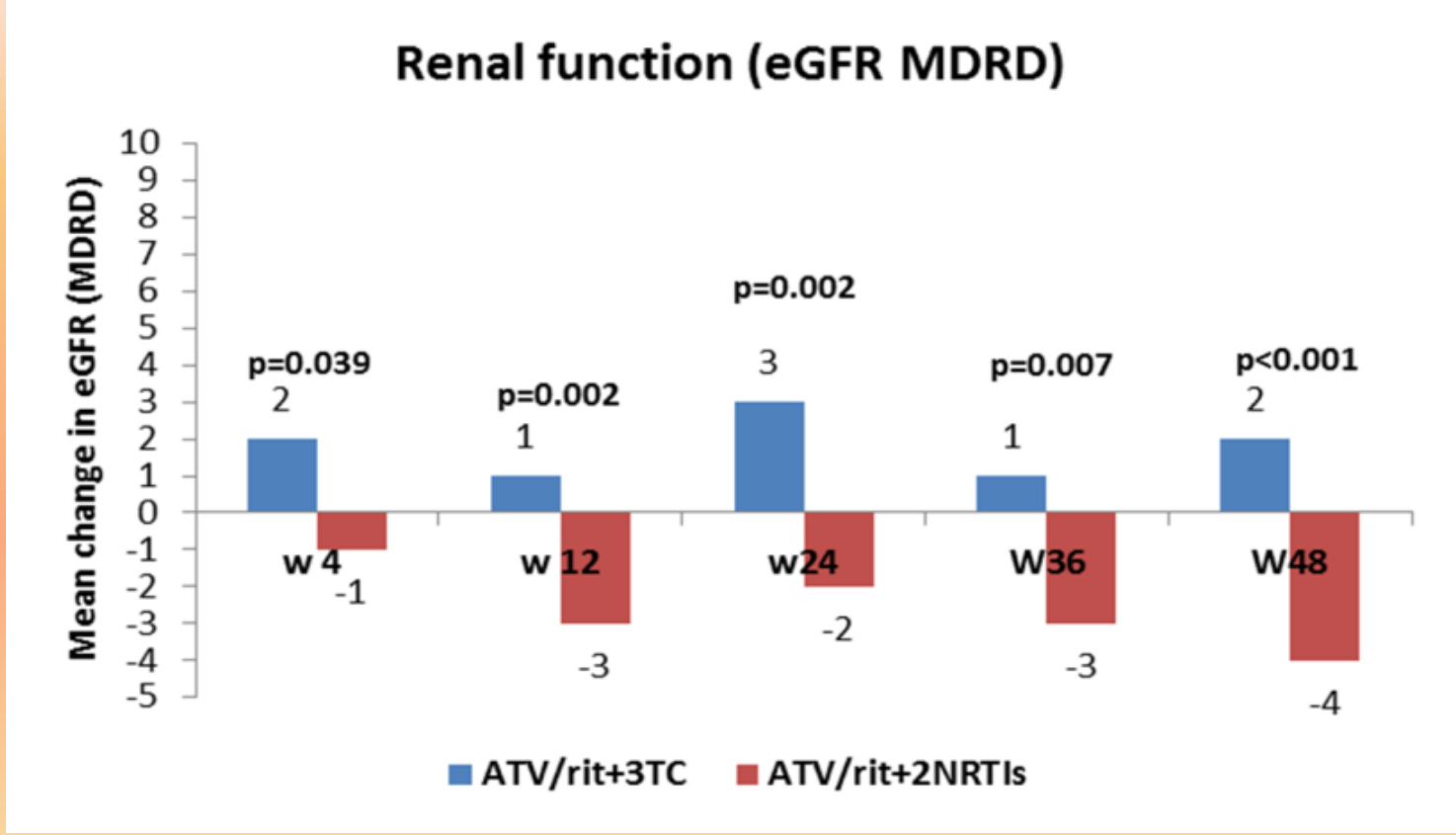
- ✓ dual treatment: no resistance in 2/2
- ✓ triple treatment: 1/4 successfully genotyped carried L10V, G16E, D60E in PR, no mutations in RT

ii. Adverse events (AE) potentially treatment-related:

- ✓ dual treatment: skin rash (week 4) and renal colic (week 26)
- ✓ triple treatment: creatinine increase (week 3 and week 7), osteopenia (week 16), renal colic (week 24), drug nephropathy (week 43)

(Di Giambenedetto S et al., J Antimicrob Chemother 2017)

Evolution of estimeted glomerular filtration rate (eGFR)



(Di Giambenedetto S et al., J Antimicrob Chemother 2017)

Fig.1 Mean change from baseline in BMD and bone biomarkers

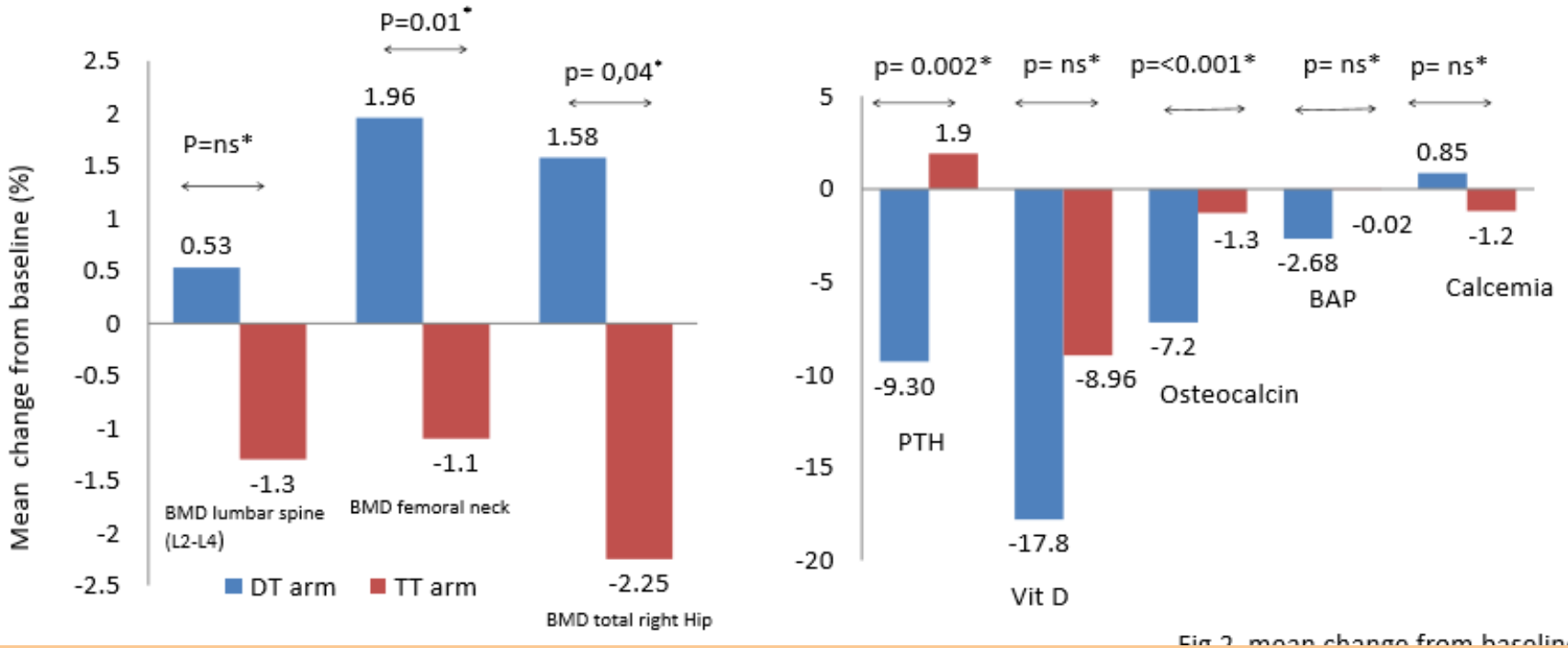


Fig.2 mean change from baseline in

(Di Giambenedetto S et al., J Antimicrob Chemother 2017)

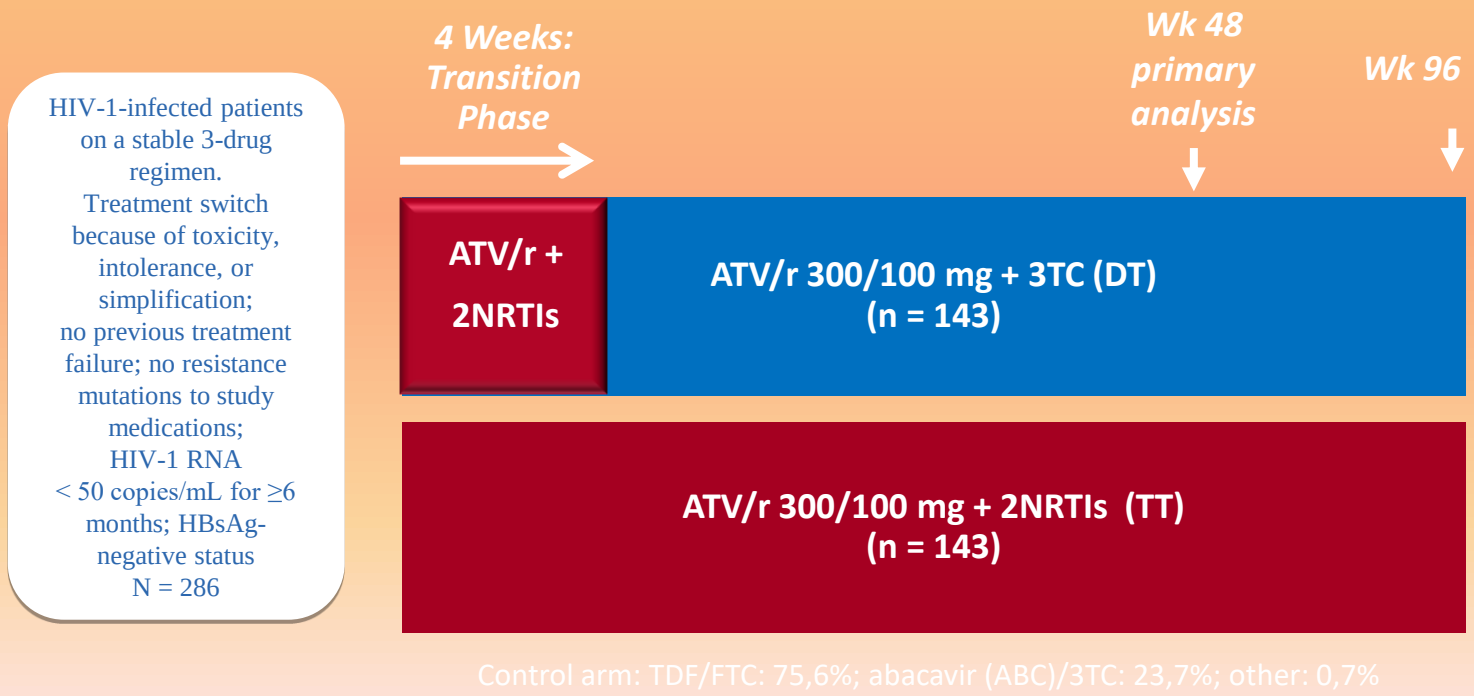
Cerebrospinal fluid drug concentrations and viral suppression in HIV-1-infected patients receiving ritonavir-boosted atazanavir plus lamivudine dual antiretroviral therapy (Spanish HIV/AIDS Research Network, PreEC/RIS 39)

This study aimed to assess cerebrospinal fluid (CSF) drug concentrations and viral suppression in HIV-1-infected patients on ritonavir-boosted atazanavir (ATV/r) plus lamivudine (3TC) dual therapy. HIV-1-infected adults with suppressed plasma HIV-1 RNA who switched to ATV/r plus 3TC were studied. Total ATV and 3TC concentrations at the end of the dosing interval (C_{24h}), using a validated LC-MS/MS method, and HIV-1 RNA were measured in paired CSF and plasma samples 12 weeks after switching. Ten individuals were included. Median (range) age was 42.5 (33–70) years, time on ART was 39.5 (11–197) months, and time with plasma HIV-1 RNA < 40 copies/mL was 15.5 (6–46) months. At baseline, CSF HIV-1 RNA was < 40 copies/mL in all patients. Twelve weeks after switching to ATV/r plus 3TC, HIV-1 RNA remained at < 40 copies/mL in both plasma and CSF in 9/10 patients. One patient with suboptimal adherence to ART had HIV-1 RNA rebound in both plasma and CSF. The median CSF-to-plasma concentration ratios of ATV and 3TC were 0.013 and 0.417, respectively. Median ATV C_{24h} in CSF was 10.4 (3.7–33.4) ng/mL (in vitro ATV IC_{50} range, 1–11 ng/mL). Median 3TC C_{24h} in CSF was 43.4 (16.2–99.3) ng/mL (in vitro 3TC IC_{50} range, 0.68–20.6 ng/mL). Most patients maintained HIV-1 RNA in CSF < 40 copies/mL despite CSF ATV C_{24h} close to or within the IC_{50} range in the majority. ATV PK data in CSF should be considered and rigorous patient selection is advisable to assure effective CSF viral suppression with this two-drug simplification regimen.

(Imaz A et al., J Neurovirol 2018)

SALT: study design

- **Design**: a 96-week multicenter, randomized, open-label, phase IV clinical trial
- **Inclusion criteria:** age >18 years; treatment switch because of toxicity, intolerance, or simplification; no previous treatment failure; no resistance mutations to the study medications; HIV-RNA <50 copies/ml for ≥6 months; HBsAg-negative status



Control arm: TDF/FTC: 75,6%; abacavir (ABC)/3TC: 23,7%; other: 0,7%

(JA Perez-Molina et al., J Antimicrob Chemother 2017)

SALT study: virological failure, CD4 count and renal function at 96 weeks

- At week 96 there were 14 virological failures (confirmed as HIV-1 RNA >50 copies/ml):
  - ✓ 9 in the ATV/r+3TC arm vs. 5 in the ATV/r+2NRTIs arm
  - ✓ 9 samples could not be amplified because of low viral load, 4 of them did not show resistance mutations and only 1 patient (ATV/r+2NRTIs arm) developed resistance mutations (M184V)
  - ✓ No NRTI or protease inhibitor (PI) resistance mutations were documented in the ATV/r+3TC arm
- Average change in CD4 count from baseline was +19.2 cells/µl for ATV/r+3TC and 18.4 cells/µl for ATV/r+2NRTIs (difference 1 cell/µl; 95% CI. –49.3 to 50.7)
- **Changes in renal function, bone density, and fat gain/distribution between groups were similar**

(JA Perez-Molina et al., J Antimicrob Chemother 2017)

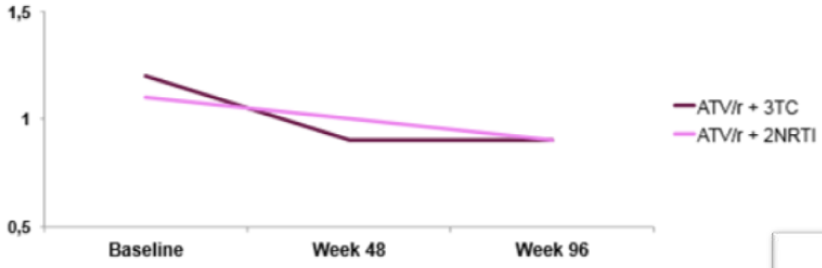
Neurocognitive Safety After 96-Weeks on ATV/r + 3TC: Results of the Randomized SALT Trial

Pérez Valero I[1], Pasquau J[2], Rubio R[3], Ribero A[4], Santos J[5], Sanz J[6], Mariño A[7], Esteban H[3], Pérez-Molina JA[8], for the SALT Study Group

1.Hospital Universitario La Paz, Madrid, Spain; 2. Hospital Virgen de las Nieves, Internal Medicine, Granada, Spain: 3. Hospital Universitario 12 de Octubre, Madrid, Spain; 4. Hospital Reina Sofía, Internal Medicine, Cordoba, Spain. 5. Hospital Virgen de la Victoria, Internal Medicine, Malaga, Spain; 6. Hospital de Alcalá de Henares, Internal Medicine, Alcalá de Henares, Spain; 7. Hospital Arquitecto Marcide, Internal Medicine, Ferrol, Spain; 8. Fundación SEIMC-GESIDA, Madrid, Spain; 9. Hospital Ramón y Cajal, Infectious Diseases, Madrid, Spain

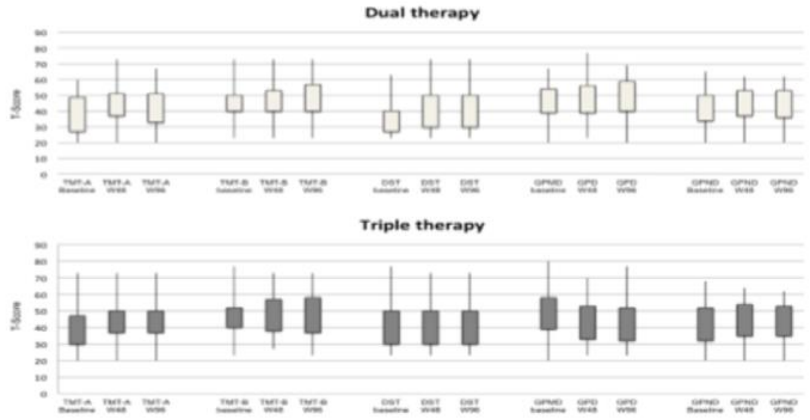
CHANGES IN NEUROCOGNITIVE PERFORMANCE BY GDS

Similar GDS evolution was observed in patients receiving dual therapy (ATV/r + 3TC) or triple therapy (ATV/r + 2NRTI).



DISTRIBUTION BY NEUROCOGNITIVE TASKS

Similar performance changes were observed in all the neurocognitive tasks



(Valero P et al., CROI 2016, Abstract 424LB)

Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial

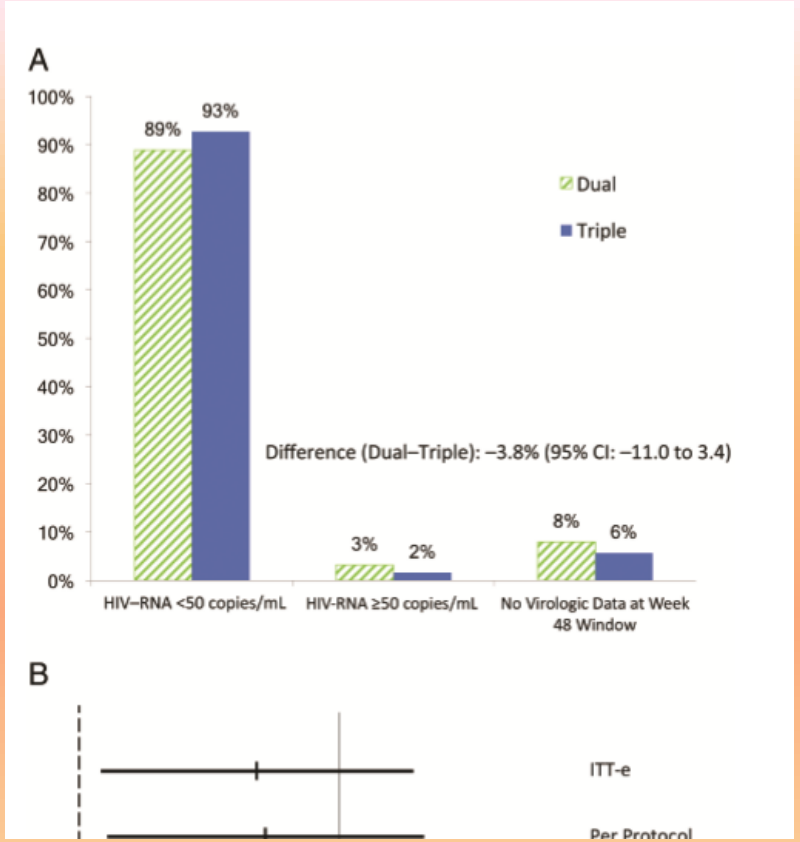
- Open-label, multicenter, randomized study
- 249 experienced patients on triple cART (ABC/3TC or TDF/FTC + DRV/r) with HIV RNA <50 cp/mL for >6 months
- Switch to DRV/r + 3TC or continue triple cART
- 48-week follow-up

Table 1. Demographic and Baseline Characteristics for the 2 Study Arms

Characteristic	Dual Therapy (n = 126)	Triple Therapy (n = 123)	Total (n = 249)
Age, y	44 (36–52)	43 (37–49)	43 (36–50)
Gender			
Male	107 (85)	100 (81)	207 (83)
Mode of transmission			
Intravenous drug use	19 (15.1)	15 (12.2)	34 (13.7)
Men who have sex with men	65 (51.6)	72 (58.5)	137 (55)
Heterosexual	34 (27)	32 (26)	66 (26.5)
Hepatitis C	32 (25.4)	28 (22.8)	60 (24.1)
Baseline CD4 count (cells/μL)	596 (433–810)	568 (451–739)	589 (443–762)
Nadir CD4 count (cells/μL)	253 (122–367)	240 (117–328)	246 (120–327)
Weeks since undetectable viral load (<50 copies/mL)	79.5 (38–157)	113 (57–184)	100 (45–166)
Previous nucleos(t)ide			
Tenofovir	93 (74)	93 (76)	186 (75)
Abacavir	33 (26)	30 (24)	63 (25)

Dual therapy = switching to darunavir/r + lamivudine. Triple therapy = maintain triple therapy with darunavir/r + 2 nucleos(t)ide reverse transcriptase inhibitor. Data are expressed as median (interquartile range) or n (%).

(Pulido F et al., Clin Infect Dis 2017)



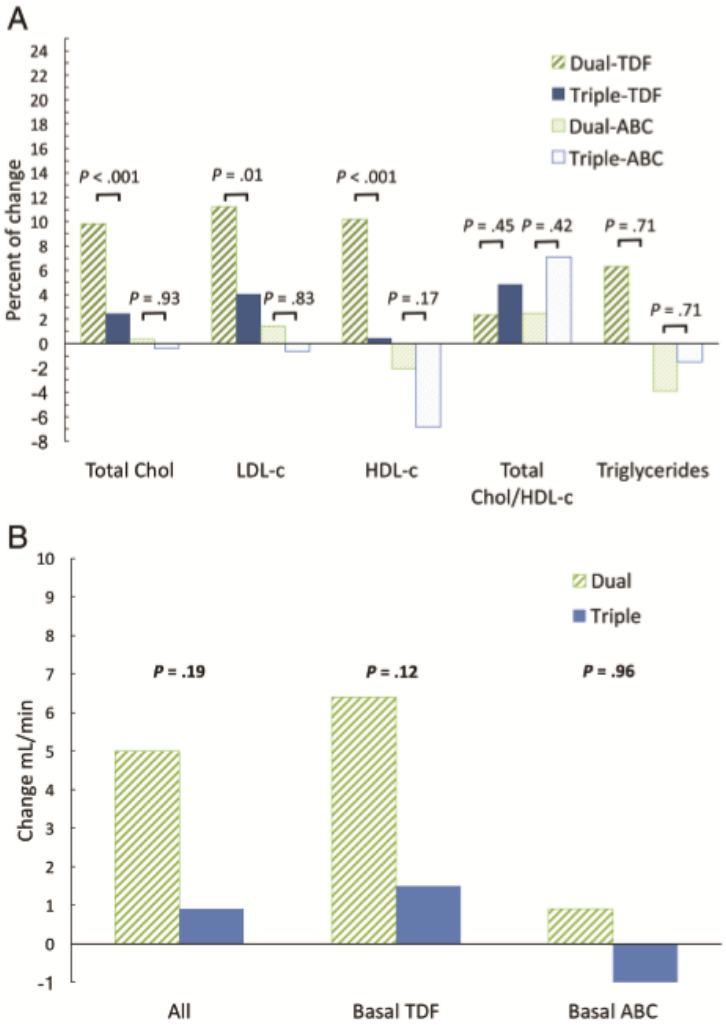


Figure 3. Changes at 48 weeks. *A,* Percent change (mean) in total cholesterol, cholesterol fractions, and triglycerides by nucleos(t)ide at baseline. *B,* Change in estimated creatinine clearance (mean) (mL/min; Cockroft–Gault equation) according to the nucleos(t)ides at baseline. Abbreviations: ABC, Abacavir; Chol, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TDF, tenofovir disoproxil fumarate.

(Pulido F et al., Clin Infect Dis 2017)

Individual patient data meta-analysis of randomized controlled trials of dual therapy with a boosted protease inhibitor plus lamivudine for maintenance of virological suppression
Gesida study 9717

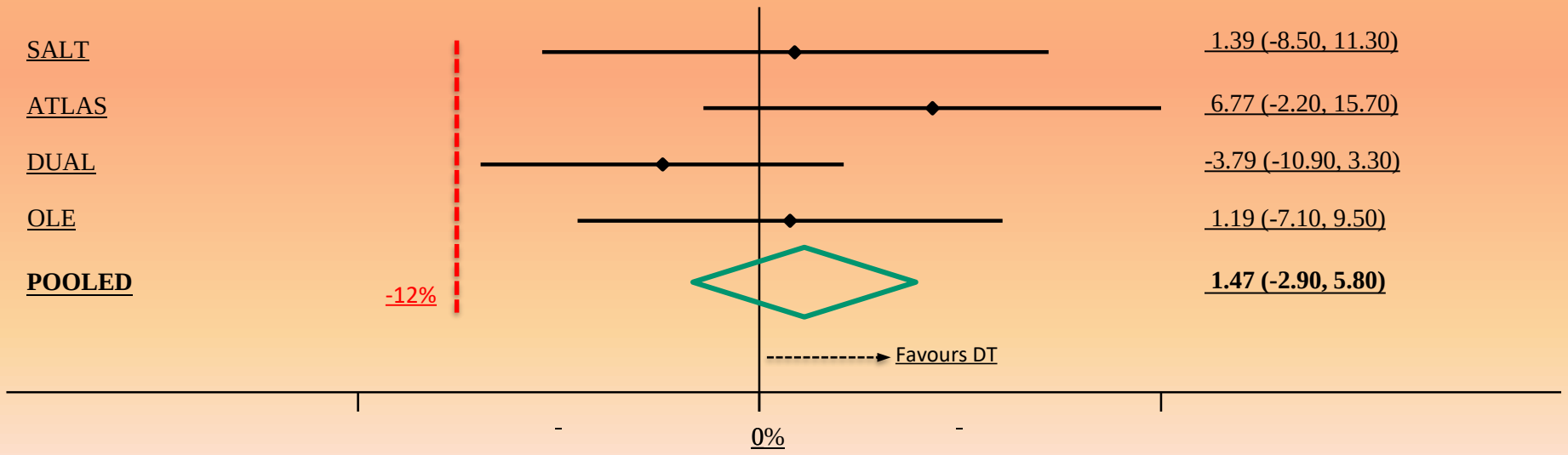
Study (n)	DT group	TT group
ATLAS-M[1] (266)	ATV/r+3TC	ATV/r+2N(t)RTIs
SALT[2] (286)	ATV/r+3TC	ATV/r+2N(t)RTIs
OLE[3] (250)	LPV/r+3TC	LPV/r+2N(t)RTIs
DUAL[4] (249)	DRV/r+3TC	DRV/r+2N(t)RTIs

1. Di Giambenedetto S. et al. Journal of Antimicrobial Chemotherapy. 2017;72:1163-1171
2. Perez-Molina JA. et al. The Lancet Infectious Diseases. 2015;15:775–84
3. Arribas JR. et al. The Lancet Infectious Diseases. 2015;15:785–92
4. Pulido F. et al. Clinical Infectious Diseases 2017; Aug 17. doi: 10.1093/cid/cix734

Virological efficacy

At 48w, 84.7% of patients on DT vs. 83.2% on TT had HIV-RNA< 50 cop/mL

Difference 1.47% (95%CI, -2.9% to 5.8%)



GESIDA Study 9717

Change from baseline to week 48 in CD4 cell count, blood lipid levels and renal function

VARIABLE	DT group	TT group	Difference DT vs. TT (95% CI)
CD4 cell µ/L	29.6	13.8	15.8 (-12.7; 44.3)
Total cholesterol mg/dL	11.03	-1.66	**12.6 (8.7; 16.5)**
LDL mg/dL	6.9	-1.01	**7.88 (4.47; 11.31)**
HDL mg/dL	2.48	1.21	1.30 (-1.08; 3.69)
Triglycerides mg/dL	8.77	-4.75	**13.54 (2.05; 25.02)**
Total cholesterol/HDL	0.017	-0.06	0.08 (-0.04; 0.20)
GFR mL/min	3.32	-1.89	**5.24 (2.90; 7.58)**

GESIDA Study 9717

Resistance mutations

Only 3 patients developed resistance mutations:

- 1 in DT group (0.19%)
- 2 in TT group (0.38%)

Patient	Clinical Trial	Treatment	Mutation
1	SALT	TT	M184V, L63P
2	DUAL	TT	L10I, A71T, L76W
3	OLE	DT	K103N, M184V

GESIDA Study 9717

Impact of previous M184V on virological outcome of switch to 3TC-based dual therapies

- Retrospective study (ARCA Database)
- 436 HIV+ suppressed patients switching to a dual therapy with 3TC + PI or INSTI
- At least one previous genotype

Figure 2: estimated probability of remaining free from VF according to previous M184V detection

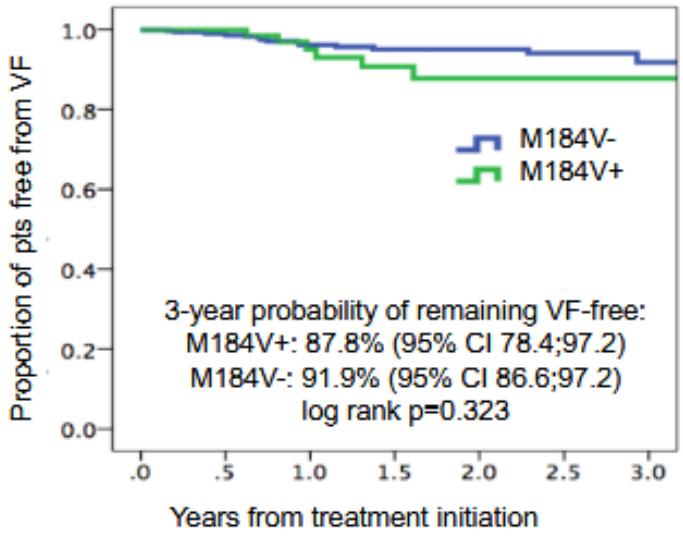
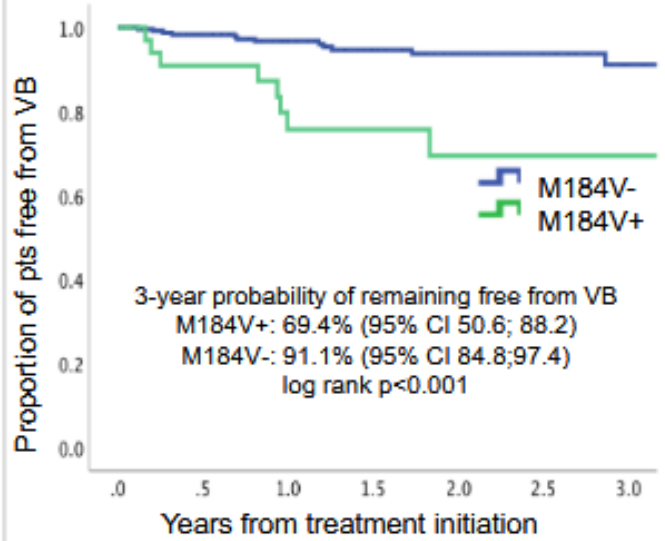


Figure 5: estimated probability of remaining free from VB in patients with viral suppression ≤6.6 years



(Gagliardini R et al., Abstract 498, CROI 2018)

DRV/r + RPV

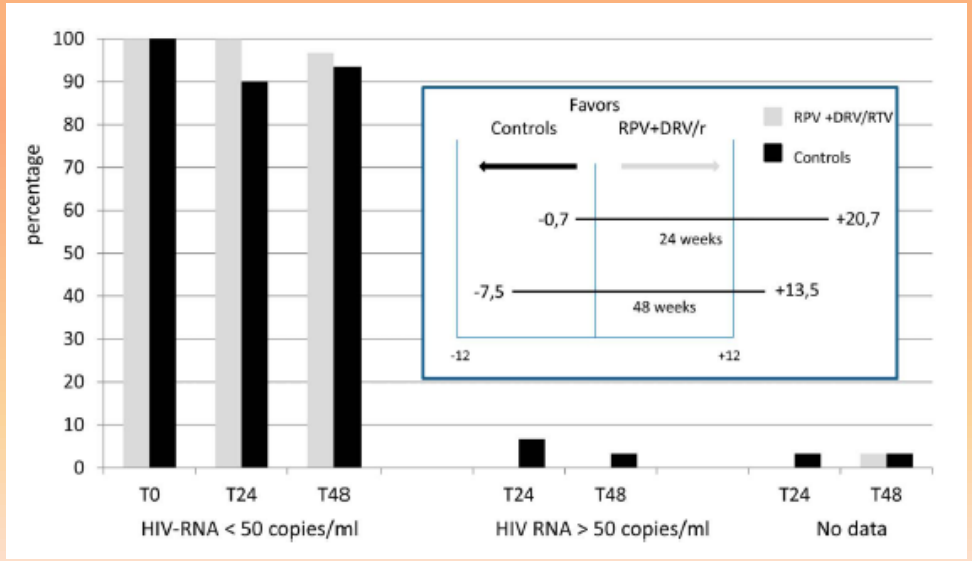
NRTI Sparing Therapy in Virologically Controlled HIV-1 Infected Subjects: Results of a Controlled, Randomized Trial (Probe)

TABLE 1. Demographic and Baseline Characteristics (Mean and SD Unless Differently Specified)

Variable	RPV + DRV/RTV	Controls
Subjects, number	30	30
Male/female, number	21/9	27/3
Risk factor for HIV, %		
Heterosexual contacts	64	60
MSM	13	17
IDU	20	23
Other	3	0
Ongoing cART, %		
TDF + FTC		90
Abacavir + lamivudine		10
DRV/RTV		43
ATV/RTV		57
Age, yrs	49 (10)	48 (8)
Time on cART, mo	93 (71)	98 (79)
Time on current cART, mo	49 (30)	38 (21)
Last HIV-RNA >50 copies/mL, mo	57 (35)	59 (50)
Pre-cART CD4, cells/μL	233 (163)	263 (196)
Pre-cART HIV-RNA, copies/mL	272K (503K)	215K (365K)
Baseline CD4, cells/μL	615 (271)	631 (339)
Baseline CD8, cells/μL	839 (387)	948 (506)
Baseline $CD8^+38^+HLA^*DR+$, % (SD)	13.4 (10.7)	14.2 (6.5)
Baseline HIV-DNA, copies/10^6 cells, median (interquartile range)	15.2K (31K)	10.9K (19K)

MSM, men who have sex with men; IDU, intravenous drug users.

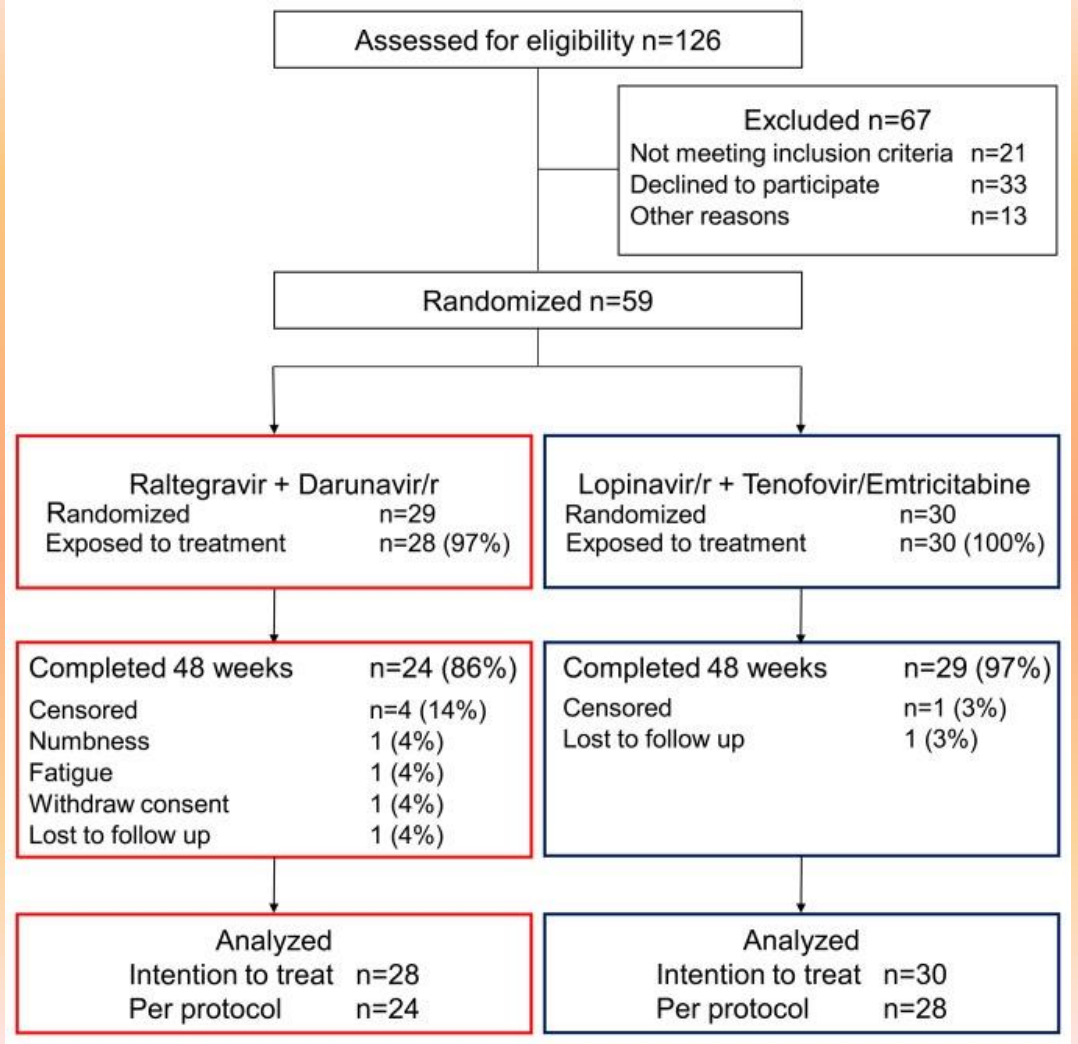
- Open-label, proof-of-concept, randomized trial
- 60 HIV+ patients on suppressive cART (2 NRTIs + PI/r)
- Switch to DRV/r + RPV or continue triple cART
- 48-week follow-up
- Virological efficacy at week 48: 96.7% (DT) vs 93.4% (TT)
- Similar changes in lipids and renal function parameters
- Greater reduction in bone stiffness in TT arm



(Maggiolo F et al., J Acquir Immune Defic Syndr 2016)

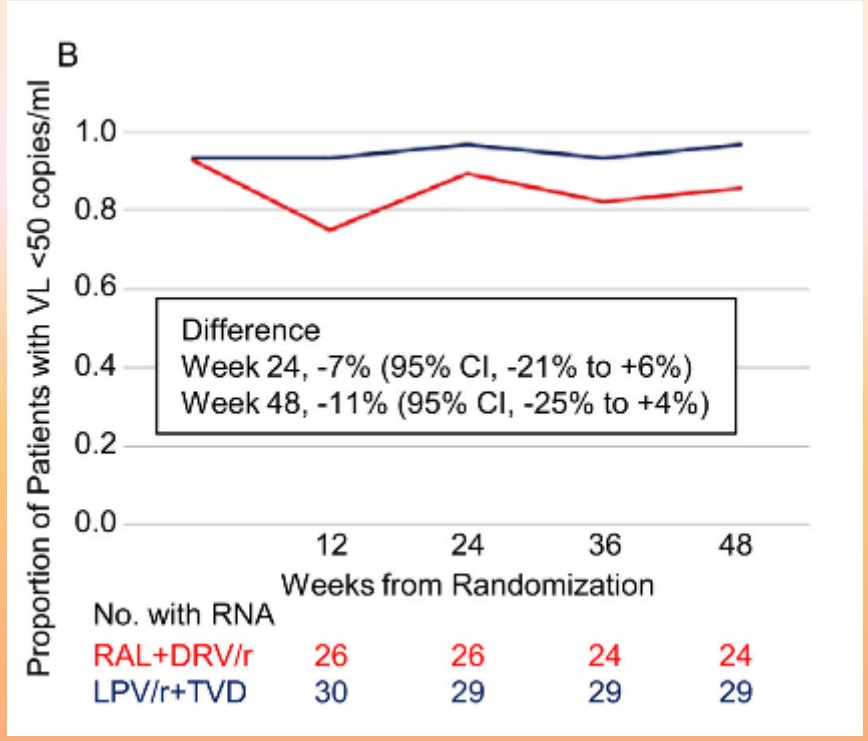
PI/r + RAL

Switching Tenofovir/Emtricitabine plus Lopinavir/r to Raltegravir plus Darunavir/r in Patients with Suppressed Viral Load Did Not Result in Improvement of Renal Function but Could Sustain Viral Suppression: A Randomized Multicenter Trial

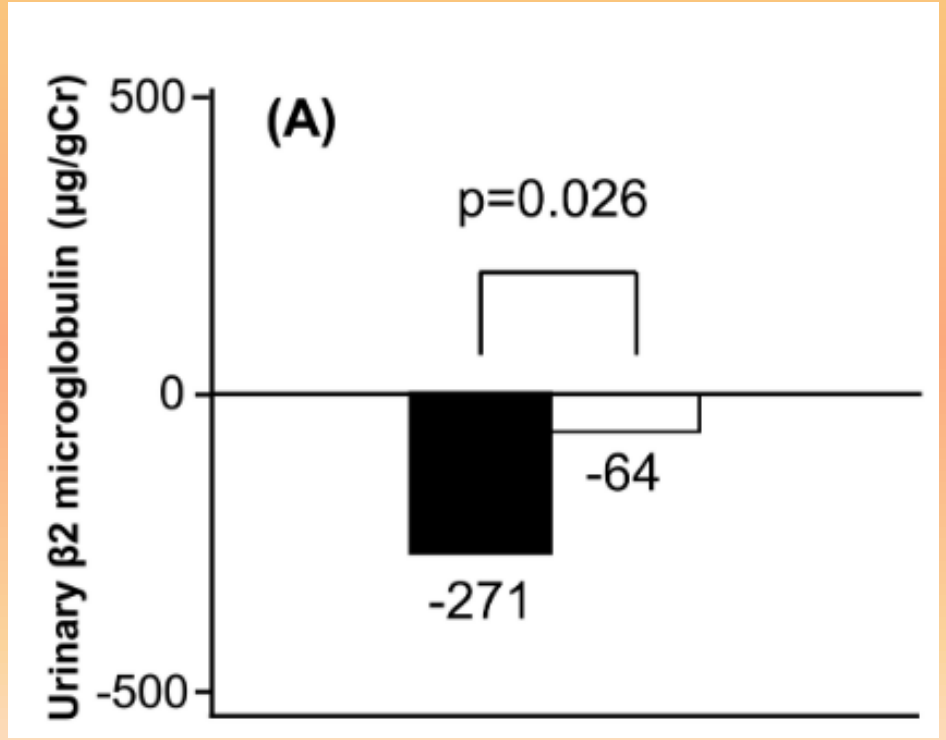


- SPARE multicenter, randomized trial
- 58 patients on TDF/FTC + LPV/r with HIV RNA <50 cp/mL;
- switch to DRV/r + RAL or continue triple cART
- Primary endpoint: % of patients with>10% improvement in eGFR

(Nishijma T et al., PLoS One 2013)



>10% improvement in eGFR:
RAL + DRV/r: 25%
TDF/FTC + LPV/r: 11%
(p=0.272)



(Nishijima T et al., PLoS One 2013)

Efficacy and tolerability of switching to a dual therapy with darunavir/ritonavir plus raltegravir in HIV-infected patients with HIV-1 RNA ≤50 cp/mL

(ICONA Prospective Cohort Study; 72 HIV-positive patients with HIV RNA <50 cp/mL and switched to DRV/rtv + RAL)

Table 2 Number of patients experiencing virological failure (VF) and treatment failure (TF) and the Kaplan–Meier estimates by 12 and 24 months

Endpoint	12 months			24 months		
	No. events	Point estimate (%)	95% CI (%)	No. events	Point estimate (%)	95% CI (%)
Pure virological failure (VF)						
Confirmed[a] VL >50 copies/mL	5	7	1–13	6	9	2–16
Treatment failure (TF)						
Single VL >200 copies/mL or stop/intensification	9	13	1–17	13	22	11–33

[a] First of two consecutive VL values

Higher risk of virological failure associated with:
- male gender
- younger age
- previous PI failure

(Madeddu G et al., Infection 2017)

Switch to Ritonavir-Boosted Atazanavir Plus Raltegravir in Virologically Suppressed Patients With HIV-1 Infection: A Randomized Pilot Study

(HARNESS Open-label, randomized, pilot study: 109 patients with HIV RNA <40 cp/mL; switch to ATV/r + TDF/FTC or ATV/r + RAL)

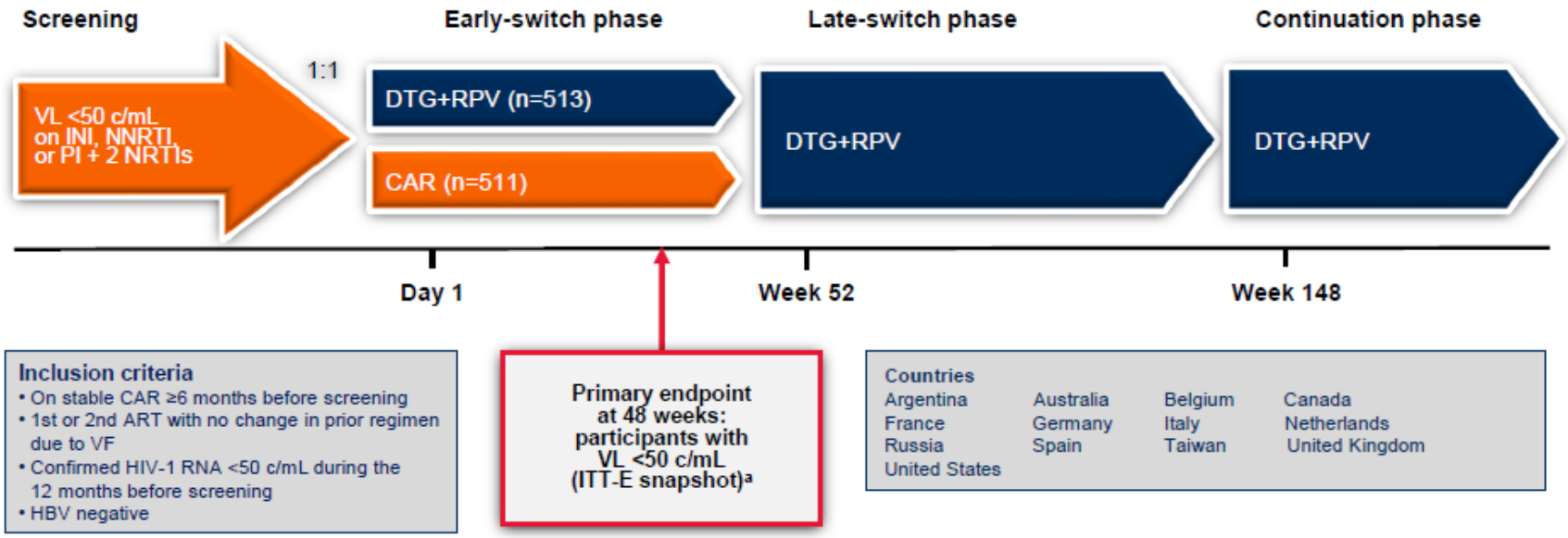
TABLE 2. Results at Weeks 24 and 48

	Week 24		Week 48	
	ATV/r+RAL (N = 72)	ATV/r+TDF/FTC (N = 37)	ATV/r+RAL (N = 72)	ATV/r+TDF/FTC (N = 37)
Virological suppression*				
ITT results, n (%) [95% CI of proportion]	58/72 (80.6) [69.5 to 88.9]	35/37 (94.6) [81.8 to 99.3]	50/72 (69.4) [57.5 to 79.8]	32/37 (86.5) [71.2 to 95.9]
Observed, n (%) [95% CI of proportion]	58/64 (90.6) [80.7 to 96.5]	35/35 (100) [90.0 to 100.0]	50/56 (89.3) [78.1 to 96.0]	32/32 (100) [89.1 to 100.0]
Virological rebound, n (%)	7 (9.7)	1 (2.7)	9 (12.5)	1 (2.7)
No. patients with tested isolates	4	0	5	0
No. PI genotypic resistance mutations	1	0	1†	0
No. INSTI genotypic resistance mutations	2	0	2†	0
Adverse events, n (%)				
All AEs	47 (65.3)	27 (73.0)	51 (70.8)	28 (75.7)
Treatment-related AEs	23 (31.9)	16 (43.2)	26 (36.1)	16 (43.2)
Serious AEs	2 (2.8)	1 (2.7)	4 (5.6)	1 (2.7)
Discontinuation due to AEs	3 (4.2)	1 (2.7)	4 (5.6)	1 (2.7)
Grade 3–4 AEs	11 (15.3)	5 (13.5)	13 (18.1)	5 (13.5)
Grade 2–4 treatment-related AEs	11 (15.3)	8 (21.6)	12 (16.7)	8 (21.6)
Grade 3–4 hyperbilirubinemia	4 (5.6)	3 (8.1)	5 (6.9)‡	3 (8.1)§
Renal and urinary disorders (all grades)‖	1 (1.4)	4 (10.8)	1 (1.4)	6 (16.2)

(van Lunzen J et al., J Acquir Immune Defic Syndr 2016)

DTG + RPV

Safety and Efficacy of DTG+RPV in the Phase III SWORD-1 and SWORD-2 Studies: 48 Week Subgroup Analysis by Baseline Third Agent Class and Geographic Location

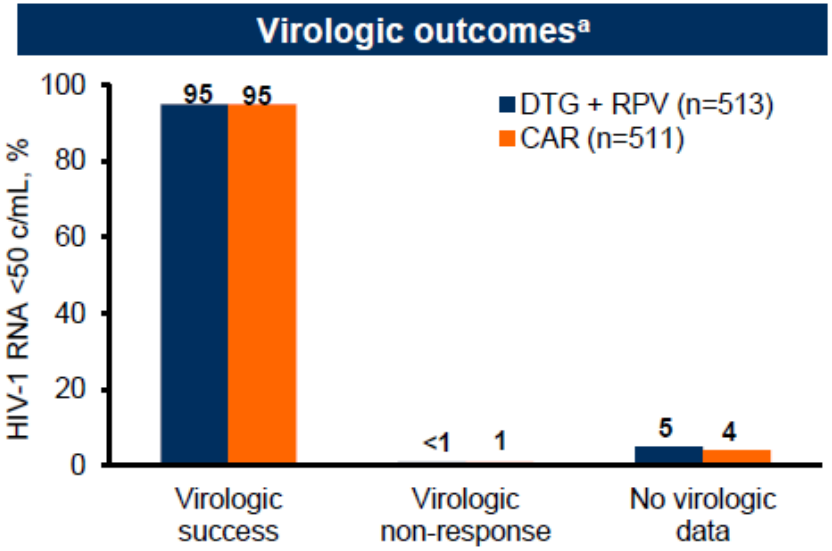


- [a]Noninferiority margin of −8% for pooled data. Noninferiority margin of −10% for individual studies.
- Orkin et al. EACS 2017; Milan, Italy. Poster BPD1/5.

(Orkin et al., EACS 2017)

Virologic Efficacy at Week 48 (Pooled)

- DTG + RPV is non-inferior to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48
  - Adjusted treatment difference, −0.2% [95% CI, −3.0, 2.5])



	Early switch phase[a]	
	DTG + RPV n=513 n (%)	CAR n=511 n (%)
Virologic success	486 (95)	485 (95)
Virologic non-response	3 (<1)	6 (1)
Data in window not <50 c/mL	0	2 (<1)
Discontinued for lack of efficacy	2 (<1)	2 (<1)
Discontinued while VL not <50 c/mL	1 (<1)	1 (<1)
Change in ART	0	1 (<1)
No virologic data	24 (5)	20 (4)
Discontinued due to AE or death[1]	17 (3)	3 (<1)
Discontinued for other reasons	7 (1)	16 (3)
Missing data during window but on study	0	1 (<1)

(Orkin et al., EACS 2017)

Renal Biomarkers: Change From Baseline to Week 48 (Pooled SWORD Data)

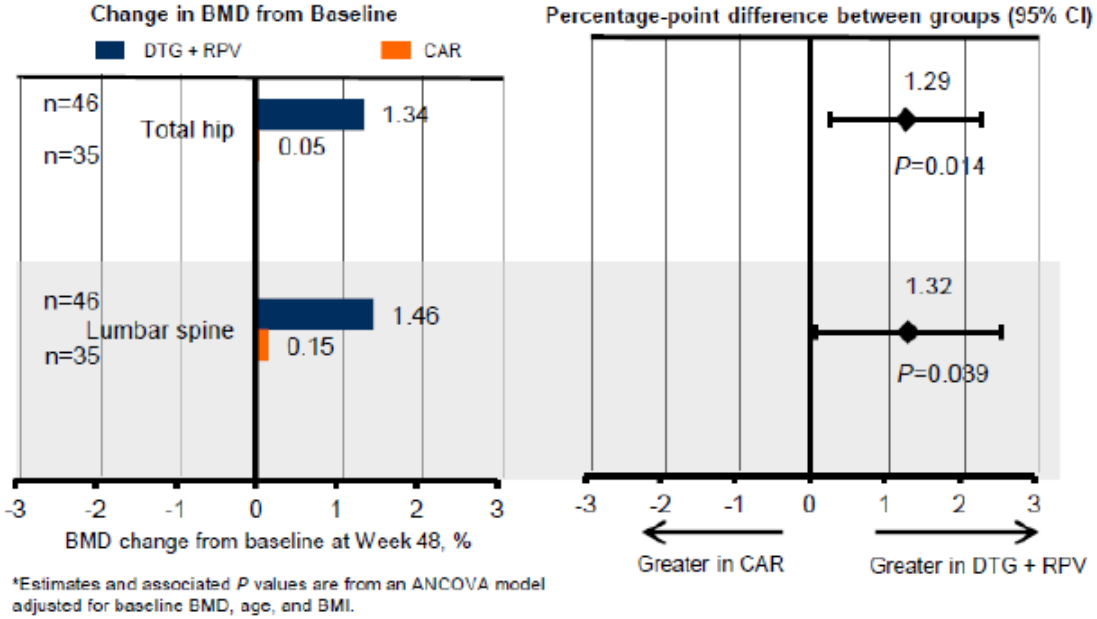
- **Renal biomarkers: greater decreases were observed in the tubular biomarkers** urine retinol binding protein, urine beta-2 macroglobulin, and urine phosphate in the 2DR vs CAR group

	DTG + RPV		CAR	
Renal biomarker	**n**	**Median (min, max)**	**n**	**Median (Min, Max)**
Cystatin C, mg/L				
Baseline	511	0.70 (0.3, 1.3)	505	0.70 (0.4, 1.3)
Week 48	483	0.00 (−0.4, 0.5)	482	0.00 (−0.4, 0.4)
Retinol binding protein (urine), nmol/L				
Baseline	487	5.61 (0.37, 190.50)	484	5.13 (0.37, 190.50)
Week 48	453	**−1.87 (−189.98, 17.92)**	455	**−0.76 (−169.06, 186.72)**
Beta-2 microglobulin (urine), nmol/L				
Baseline	319	14.41 (6.78, 11,271.22)	325	14.41 (6.78, 4830.52)
Week 48	161	**−3.39 (−11,129.70, 125.42)**	174	**0.00 (−333.05, 3411.03)**
Urine phosphate, mmol/L				
Baseline	486	19.70 (3.22, 81.40)	480	19.54 (3.22, 64.60)
Week 48	453	−0.65 (−66.86, 66.21)	453	−0.97 (−43.93, 59.76)

(Orkin et al., EACS 2017)

Primary and Key Secondary Endpoints: Week 48*

- DTG + RPV patients had an increase from Baseline to Week 48 in hip (1.34%) and spine (1.46%) BMD, which differed statistically significantly (*P*=0.014, *P*=0.039, respectively) from CAR patients



*Estimates and associated *P* values are from an ANCOVA model adjusted for baseline BMD, age, and BMI.

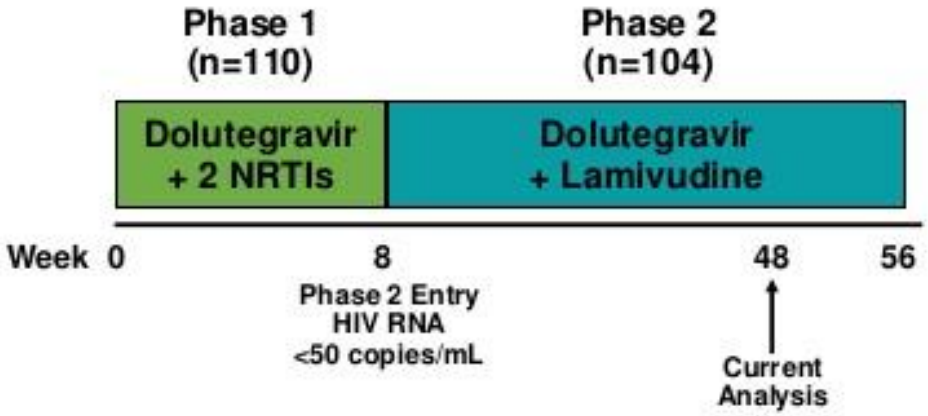
- The primary endpoint result was supported by the significantly greater percentage change from Baseline to Week 48 in the DTG + RPV group compared with the CAR group for BMD in both total hip and lumbar spine when expressed as T-scores or as Z-scores (data not shown)

(McComsey GA et al., AIDS 2018)

DTG + 3TC

LAMIDOL Trial: Dolutegravir + Lamivudine as Maintenance Therapy

Open-Label
(2 phases, 56 weeks)
Treatment-experienced
Stable ART
(HIV RNA <50 copies/mL for ≥2 years)
Nadir CD4 >200 cells/mm^3
No major resistance mutations
No HBV

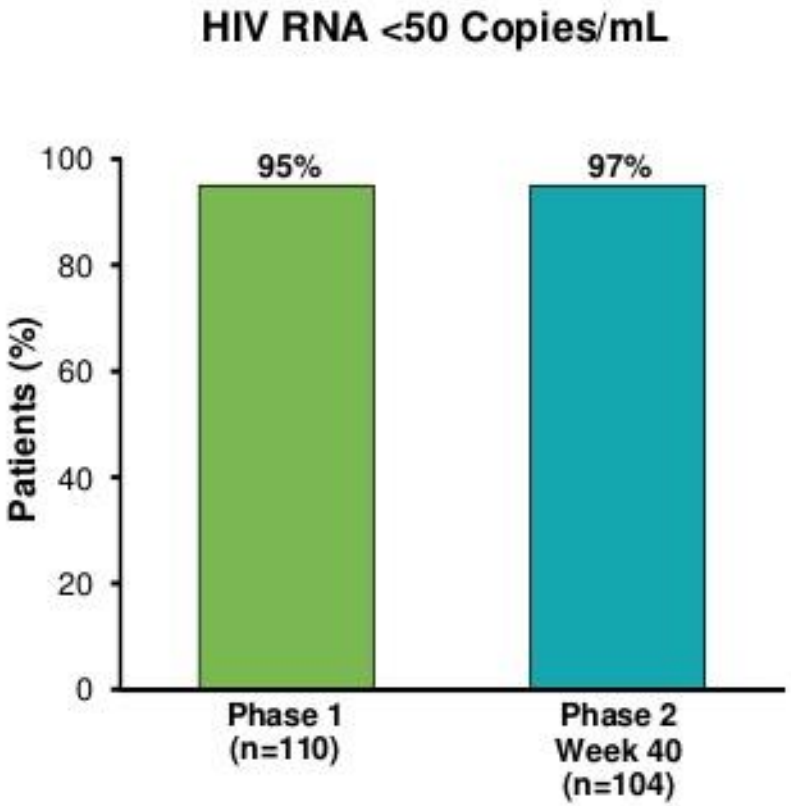


*2 NRTIs: lamivudine or emtricitabine plus another NRTI.
Primary endpoint: proportion of patients with HIV RNA <50 copies/mL at week 56 (ie, 48 weeks on dual therapy).
Baseline characteristics:
- Male: 86%.
- Age: 45 years.
- MSM: 70%.
- Time on current ART: 4 years.
- CD count: 743 cells/mm^3.
- Stable ART (3rd agent):
  - NNRTI: 56%.
  - PI: 23%.
  - INSTI (not dolutegravir): 21%.

Joly V, et al. 24th CROI. Seattle, 2017. Abstract 458.

LAMIDOL Trial: Treatment Outcomes With Dolutegravir + Lamivudine as Maintenance Therapy

- Similar proportion of patients achieved HIV RNA <50 copies/mL before and after switching to dolutegravir + lamivudine
  - Maintenance failure (n=3; virologic failure, lost to follow-up, and treatment modification)
- Blips, but not virologic failure, during phase 2 that did not require ART modification (n=2 with ≥1 value of HIV RNA >50 copies/mL)
- Maintenance therapy was generally safe and well tolerated



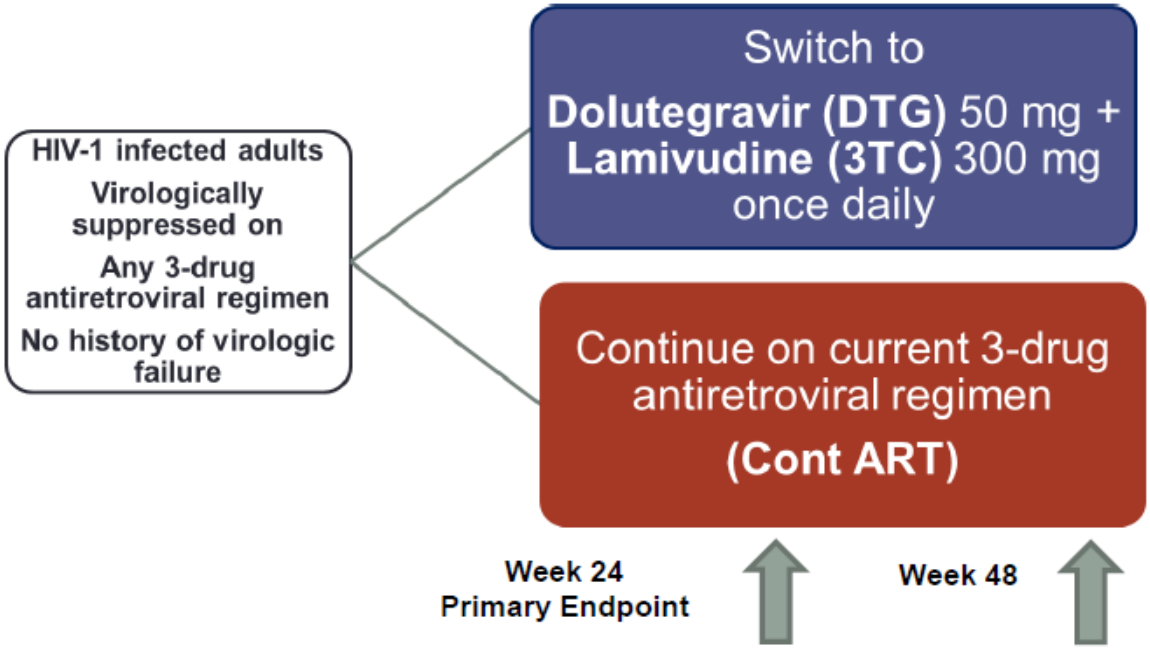
Joly V, et al. 24th CROI. Seattle, 2017. Abstract 458.

PE8/5 DTG + 3TC Maintains HIV-1 Suppression Through Week 48 in a Pilot Randomized Trial (ASPIRE)

- Babafemi O Taiwo,et al

Results of a pilot randomized trial of DTG + 3TC versus continuation of standard 3-active drug maintenance therapy

Open-label, randomized, multicenter investigator-initiated clinical trial



Primary analysis: Compare virologic failure rate by week 24 (loss to follow up; or discontinuation/modification of randomized treatment also counted as failure)

- A secondary analysis censored participants at the time of loss to follow-up or discontinuation/modification of study treatment

Other Secondary analyses: Virologic outcomes using the FDA snapshot algorithm
Incidence of viral blips and drug resistance
Changes in CD4 counts, lipid profile and creatinine clearance
Incidence of Grade 3/4 AEs or treatment discontinuation

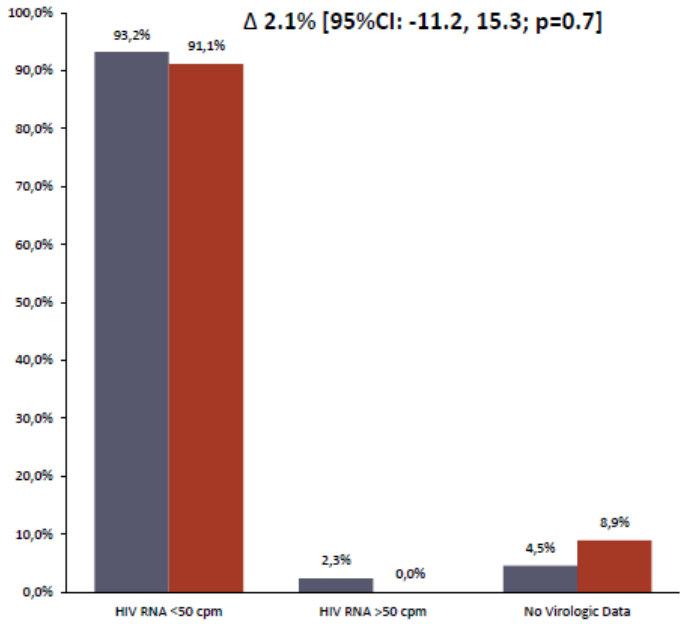
Virologic failure = confirmed HIV-1 RNA > 50cpm

Viral blip = HIV-1 RNA > 50cpm that was preceded or followed by ≤ 50 cpm

		DTG + 3TC (N=44)	Cont. ART (N=45)	TOTAL (N=89)
Age (years)	Median (Q1, Q3)	46 (37, 55)	50 (41, 53)	47 (38, 54)
Sex	Male	89%	87%	88%
Race	White	52%	64%	60%
	Black	43%	33%	38%
Ethnicity	Hispanic	18%	11%	15%
CD4 Count	Cells/mm³	694 (533, 1034)	646 (380, 819)	680 (498, 927) p=0.047
Nadir	Median (Q1, Q3)	333 (184, 408)	228 (91, 341)	278 (109, 387) p=0.027
Time on ART	Years, Median	5.28 (3.81, 7.49)	6.03 (3.72, 7.44)	5.70 (3.72, 7.48)
Current ART	EFV, RPV, NVP	12 (27%)	15 (33%)	27 (30%)
	DRV/r, ATV/r	14 (32%)	15 (33%)	29 (33%)
	DTG, RAL, ELV/c	18 (41%)	15 (33%)	33 (37%)
Current NRTI	**TDF/FTC**	**35 (80%)**	**41 (91%)**	**76 (86%)**
	ABC/3TC	8 (18%)	4 (9%)	12 (14%)

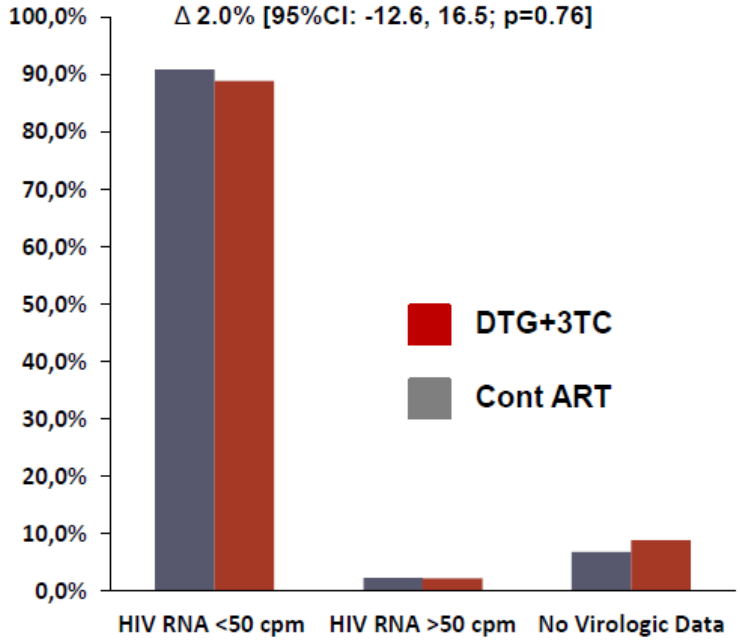
Taiwo et al. EACS 2017; Milan, Italy. Poster PE8/5.

Virologic Outcomes at Wk 24 (FDA Snapshot)



N	41	41	1	0	2	4
On Study	44	45	44	45	44	45

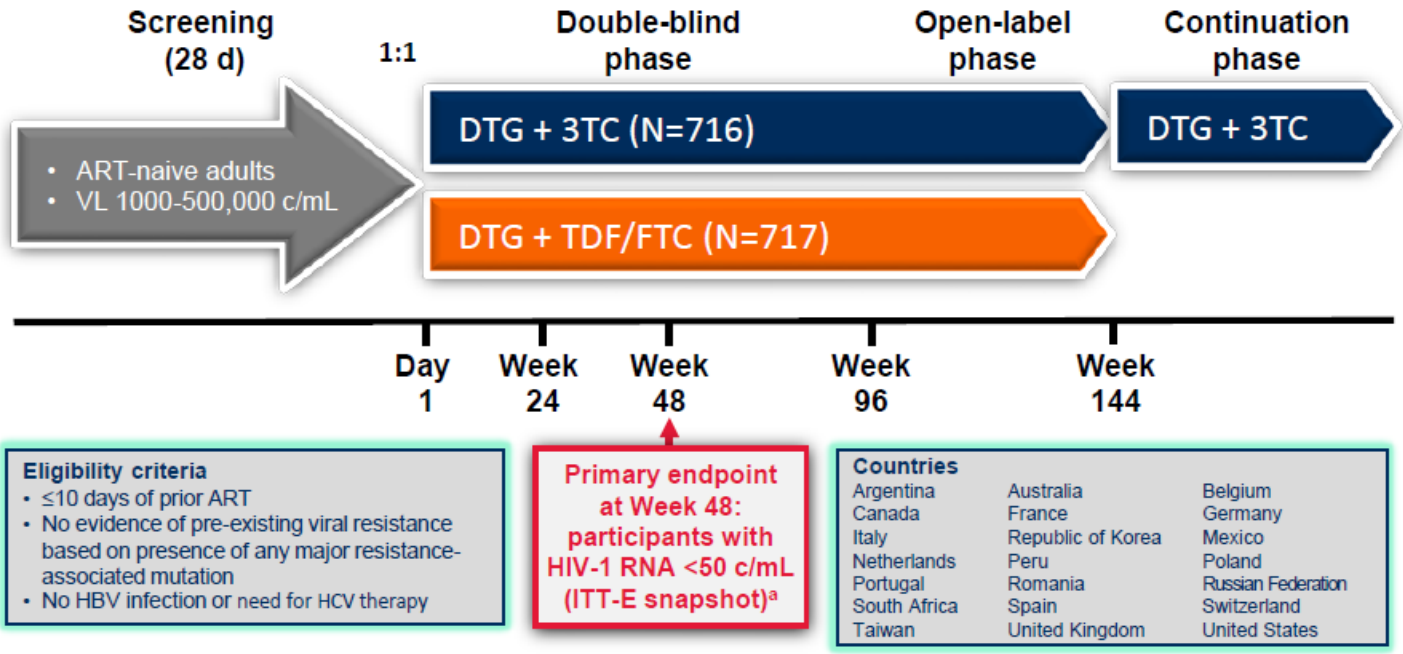
Virologic Outcomes at Wk 48 (FDA Snapshot)



N	40	40	1	1	3	4
On Study	44	45	44	45	44	45

Taiwo et al. EACS 2017; Milan, Italy. Poster PE8/5.

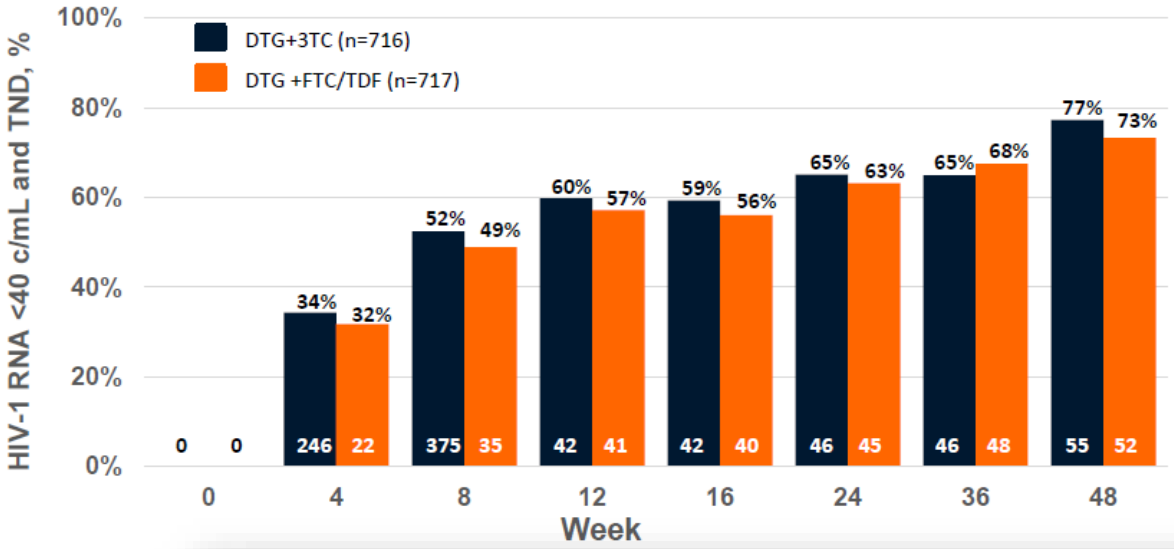
GEMINI-1 and -2 Phase III Study Design



Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm³ vs >200 cells/mm³).

[a]10% noninferiority margin for individual studies.

Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and TND Status by Visit - Snapshot Analysis



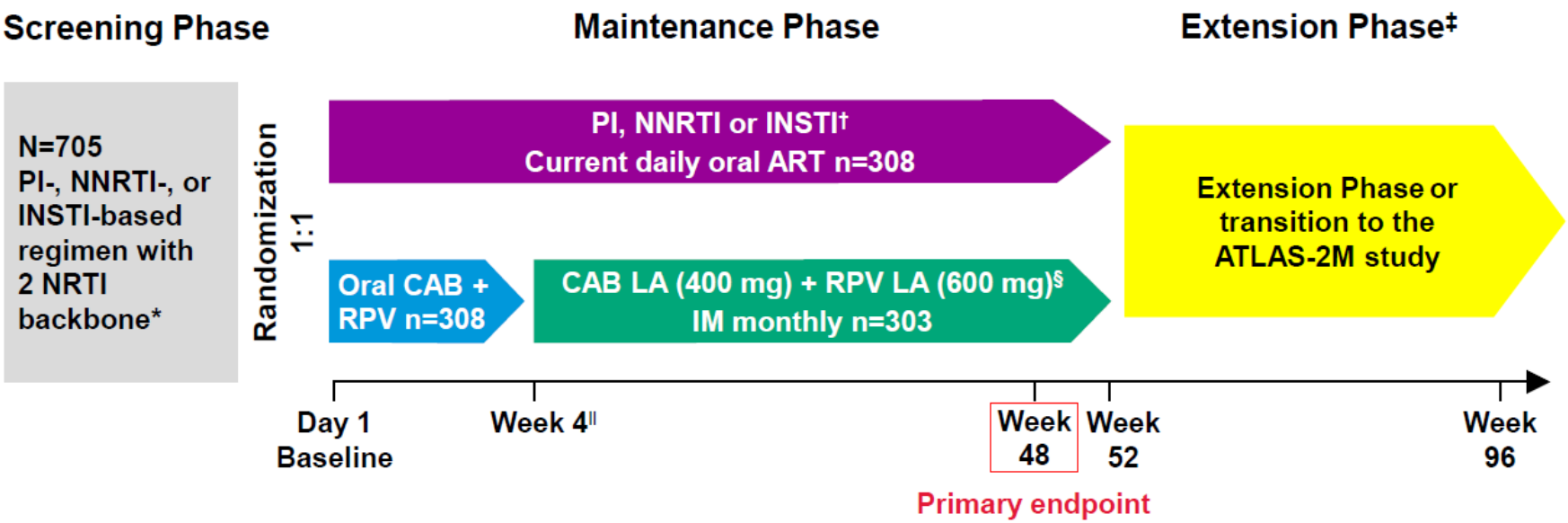
Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL and TND at Week 48 (Snapshot Analysis) by Baseline VL

Baseline VL strata (c/mL)	Subgroups[a]	DTG + 3TC n/N(%)[b]	DTG + TDF/FTC n/N(%)[b]	Treatment difference[c]
≤100,000	Pooled	463/576 (80)	446/564 (79)	1.3 (–3.4 to 6.0)
>100,000	Pooled	90/140 (64)	79/153 (52)	12.7 (1.4 to 23.9)
	>250,000 c/mL Pooled	25/51 (49)	20/46 (43)	5.5 (–14.3 to 25.4)
	>400,000 c/mL Pooled	5/18 (28)	6/24 (25)	2.8 (–24.2 to 29.8)

a - Key subgroups included for pooled baseline VL strata >100,00 c/mL include pooled data for >250,000c/mL and >400,000c/mL. b - Number Responded/Number Assessed (%); c - Unadjusted proportion of DTG+3TC - proportion of DTG+TDF/FTC (95% CI). .

Long-acting CAB + RPV

ATLAS Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in Adults with Virologic Suppression (Ongoing)

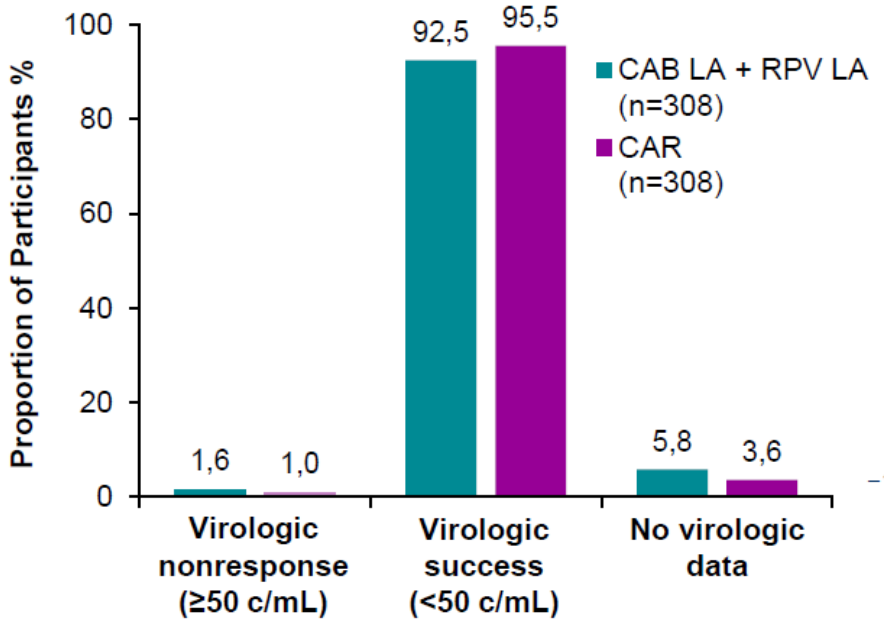


ART, antiretroviral therapy; CAB, cabotegravir; CAR, current ART; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside RTI; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; VL, viral load.
*Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrolment; Triumeq excluded from study; ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB LA + RPV LA must complete 52 weeks of follow-up; ‖Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks.

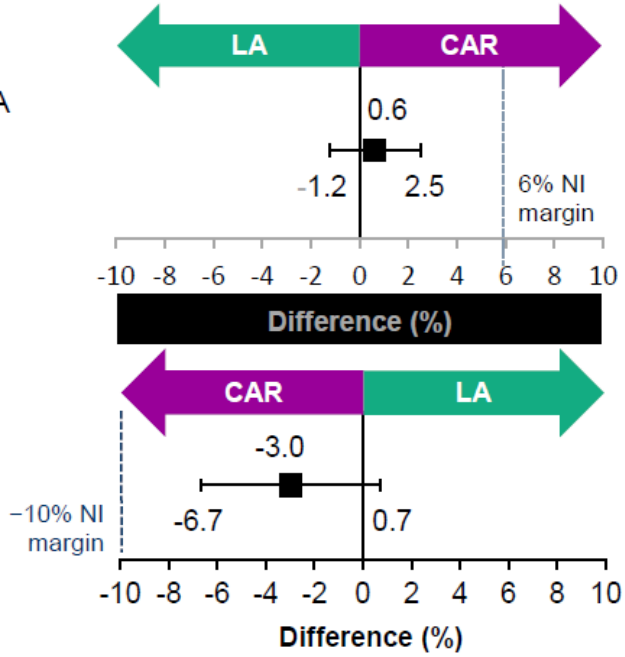
Swindells S, et al. *CROI 2019*; Seattle, WA. Abstract 1475.

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

Virologic outcomes



Adjusted treatment difference (95% CI)*



Primary endpoint:

LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

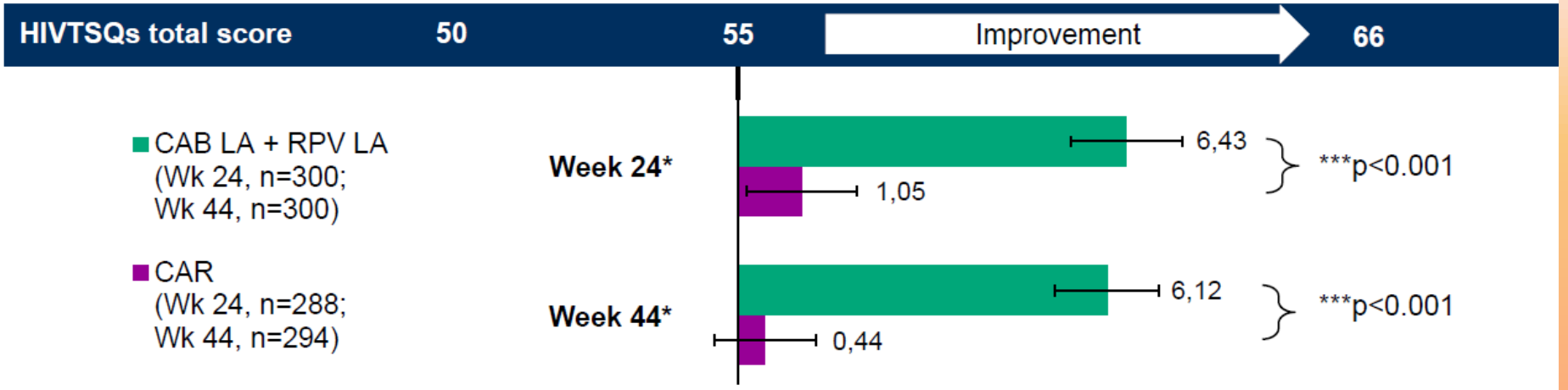
Key secondary endpoint:

LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

CAB, cabotegravir; CAR, current ART; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline third agent class.

Swindells S, et al. *CROI 2019*; Seattle, WA. Abstract 1475.

ATLAS: High Participant Satisfaction (HIVTSQs) and Preference For Injectable Therapy



Patient Preference Survey (LA arm)

Single-item question on participants' preference at Week 48

- ITT-E population: 86% (266/308) preferred LA; 2% (7/308) preferred daily oral therapy
  - Responding participants: 97% (266/273) preferred the LA regimen over previous oral therapy

CAB, cabotegravir; CAR, current ART; HIVTSQs, HIV Treatment Satisfaction Questionnaire Status; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.
*Adjusted mean change from baseline; adjusted for baseline score, sex, age, race, and baseline third agent class. Error bars show 95% confidence interval.

Swindells S, et al. *CROI 2019*; Seattle, WA. Abstract 1475.

ART simplification by LDRs: conclusions

- Despite the availability of very effective and well-tolerated triple regimens, there is still a role for simplification strategies
- Some LDRs are valuable switching strategies in selected patients with virological efficacy usually comparable to triple regimens
- The leading advantages include prevention of long-term toxicites, prevention of DDIs and cost reduction
- The current paradigm of triple regimens as the standard of care should be reconsidered in some patients