Inibitori dell'integrasi e flessibilità terapeutica: focus sulle varie tipologie di pazienti

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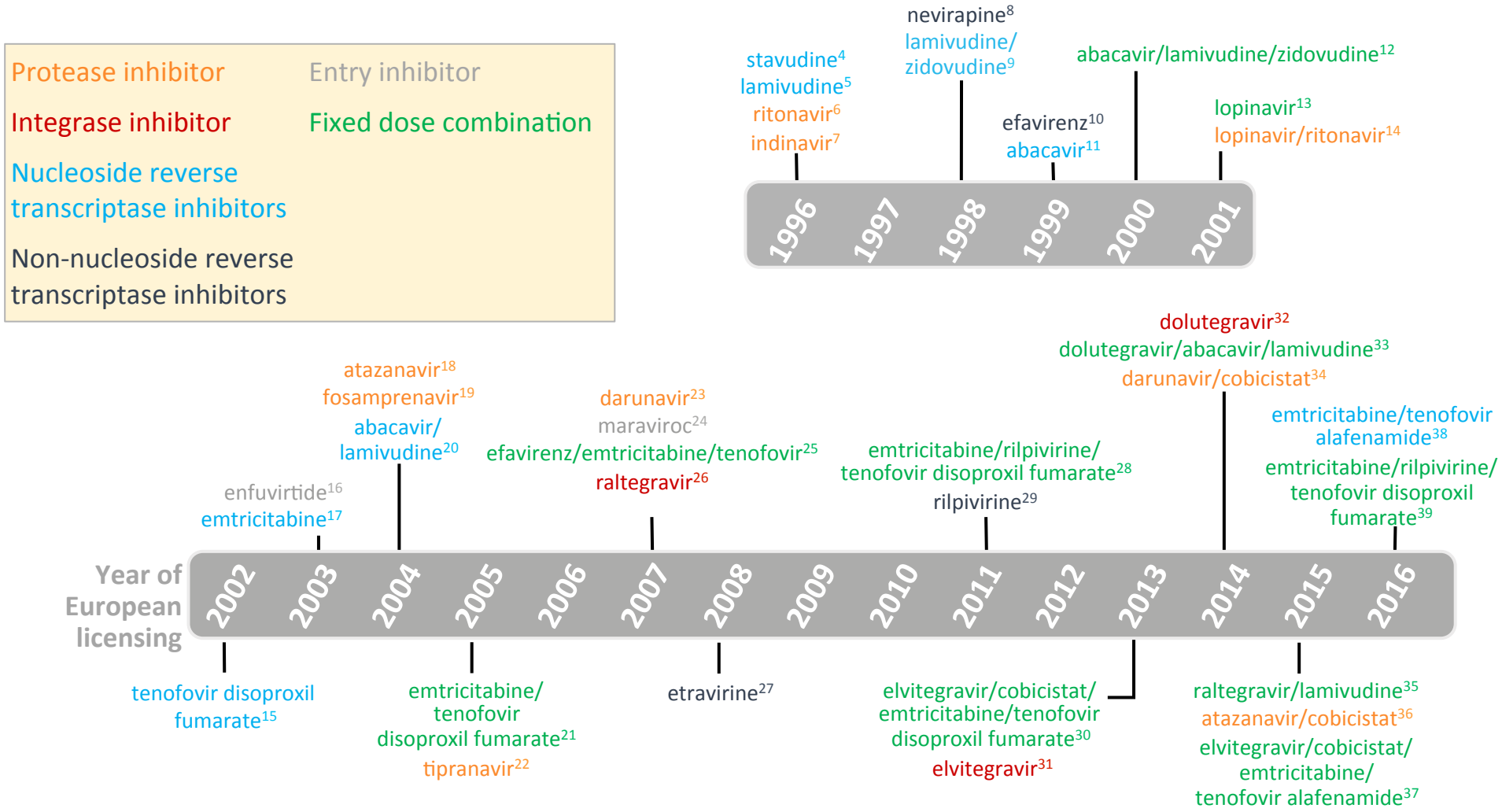
Disclosure statement

- Personal fees for consultancy and lectures from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck, ViiV.
- Travel grants from Abbvie, Bristol Myers Squibb, Gilead, ViiV.
- Research grants from Bristol Myers Squibb, Gilead, Janssen, ViiV.

Approved medications for HIV infection[1-3]: 1996–2016



IHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_37.pdf (accessed August 2016); 2. EACS. elines October 2015: http://www.eacsociety.org/files/guidelines_8_0-english_web.pdf (accessed August 2016); 3. WHO. HIV/AIDS: http://www.who.int/hiv/en/ (Accessed August 2016); 4–12. European cines Agency. Summary of Product Characteristics: http://www.ema.europa.eu/ema/ (Accessed August 2016); 13. Proj Inf Perspect. 1999 Sep;(28):4-8; 14-39. European Medicines Agency. Summary of uct Characteristics: http://www.ema.europa.eu/ema/ (Accessed August 2016)

What to Start 2016

Regimen	WHO 2016	DHHS 2016	IAS-USA 2016	EACS 2016	BHIVA 2016	GESIDA 2016	SIMIT 2016
EFV/TDF/FTC	Preferred	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
EFV/TAF/FTC		Alternative			Alternative		Alternative
RPV/TDF/FTC		Alternative#	Alternative	Recommended*	Preferred*	Alternative*	Recommended#
RPV/TAF/FTC		Alternative#	Alternative	Recommended*	Preferred*		Recommended#
ATV/r + TDF/FTC		Alternative		Alternative	Preferred	Alternative	Recommended**
ATV/r + TAF/FTC		Alternative		Alternative	Preferred		Recommended**
ATV/c + TDF/FTC		Alternative		Alternative		Alternative	Recommended**
ATV/c + TAF/FTC		Alternative		Alternative			Recommended**
DRV/r + TDF/FTC		Recommended	Alternative	Recommended	Preferred	Alternative	Recommended**
DRV/r + TAF/FTC		Recommended	Alternative	Recommended	Preferred		Recommended**
DRV/c + TDF/FTC		Alternative	Alternative	Recommended		Alternative	Recommended**
DRV/c + TAF/FTC		Alternative	Alternative	Recommended			Recommended**
RAL + TDF/FTC		Recommended	Alternative	Recommended	Preferred	Preferred	Recommended
RAL + TAF/FTC		Recommended	Recommended	Recommended	Preferred		Recommended
EVG/COBI/TDF/FTC		Recommended	Alternative	Recommended	Preferred	Alternative	Recommended
EVG/COBI/TAF/FTC		Recommended	Recommended	Recommended	Preferred	Preferred	Recommended
DTG + TDF/FTC	Alternative	Recommended	Alternative	Recommended	Preferred	Preferred	Recommended
DTG + TAF/FTC		Recommended	Recommended	Recommended	Preferred		Recommended
DTG + ABC/3TC		Recommended	Recommended	Recommended	Preferred	Preferred	Recommended

** Only if HIV-RNA <100.000 c/mL; # Only if HIV-RNA <100.000 c/mL and CD4 >200 cell/mm3; ** Only for specific conditions*

Available Single-Tablet Regimens in EU

Agent	Trade name	Type	Yr of EMA Approval
Efavirenz/tenofovir DF/ emtricitabine (EFV/TDF/FTC)	ATRIPLA®	NNRTI + dual NRTI	2007
Rilpivirine/tenofovir DF/ emtricitabine (RPV/TDF/FTC)	EVIPLERA®	NNRTI + dual NRTI	2011
Elvitegravir/cobicistat/ tenofovir DF/emtricitabine (EVG/COBI/TDF/FTC)	STRIBILD®	INSTI + booster + dual NRTI	2013
Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)	TRIUMEQ®	INSTI + dual NRTI	2014
Elvitegravir/cobicistat/ tenofovir alafenamide/emtricitabine (EVG/COBI/TAF/FTC)	GENVOYA®	INSTI + booster + dual NRTI	2015
Rilpivirine/tenofovir alafenamide/emtricitabine (RPV/TAF/FTC)	ODEFSEY®	NNRTI + dual NRTI	2016
Darunavir/cobicistat/tenofovir alafenamide/ emtricitabine (DRV/COBI/TAF/FTC)	SYMTUZA®	PI + booster + dual NRTI	2018
Bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC)	-	INSTI + dual NRTI	2018 (?)
Dolutegravir/rilpivirine (DTG/RPV)	-	INSTI + NNRTI	2018 (?)
Dolutegravir/lamivudine (DTG/3TC)	-	INSTI + mono NRTI	2019 (?)

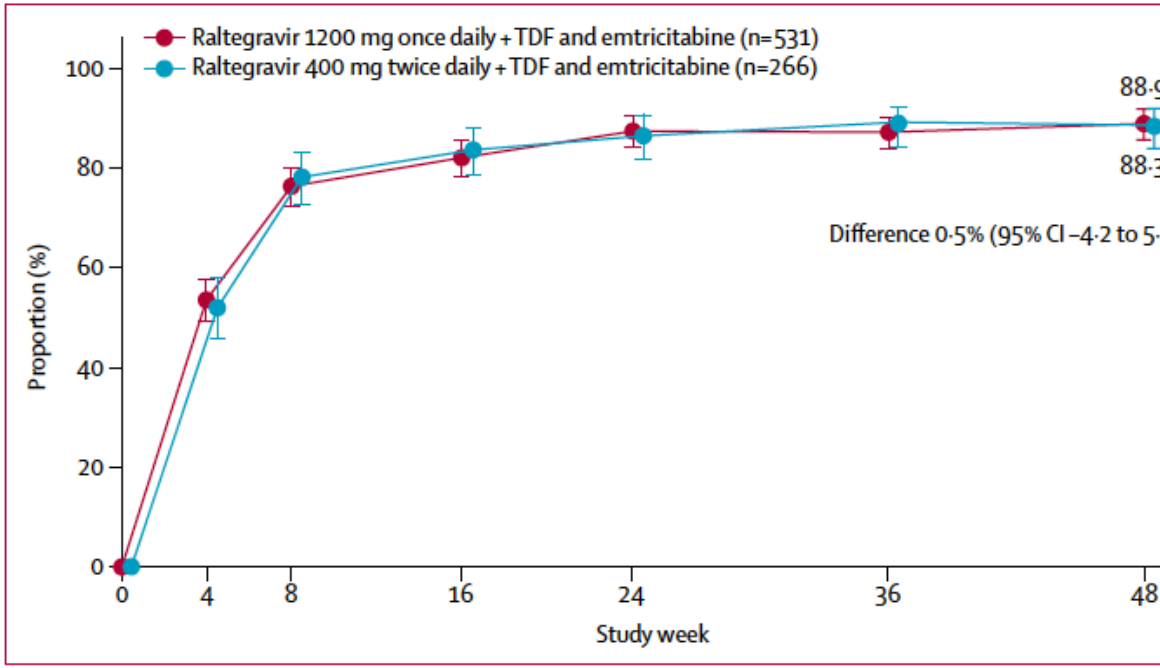
ONCEMRK

Once daily raltegravir 1200 mg was non-inferior compared with raltegravir 400 mg twice daily for initial treatment of HIV-1 infection

	Raltegravir 1200 mg once daily (n=531)	Raltegravir 400 mg twice daily (n=266)
HIV-1 RNA <40 copies per mL	472 (89%)	235 (88%)
HIV-1 RNA ≥40 copies per mL		
≥40 and <200 copies per mL	12 (2%)	8 (3%)
≥200 copies per mL	6 (1%)	2 (1%)
Discontinued for lack of efficacy*	11 (2%)	6 (2%)
Total	29 (5%)	16 (6%)
No virological data at week 48 window		
Discontinued study because of adverse event or death†	6 (1%)	6 (2%)
Discontinued study for other reasons‡	20 (4%)	7 (3%)
On study but missing data in window	4 (1%)	2 (1%)
Total	30 (6%)	15 (6%)

Data are n (%). Raltegravir 1200 mg once per day and raltegravir 400 mg twice per day were administered with tenofovir disoproxil fumarate and emtricitabine.*Includes participants who discontinued for other reasons and had HIV-1 RNA ≥40 copies per mL. †Includes participants who discontinued because of adverse event or death after day 1 if this resulted in no virological data during the specified window. ‡Other reasons: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, and withdrawal by participant.

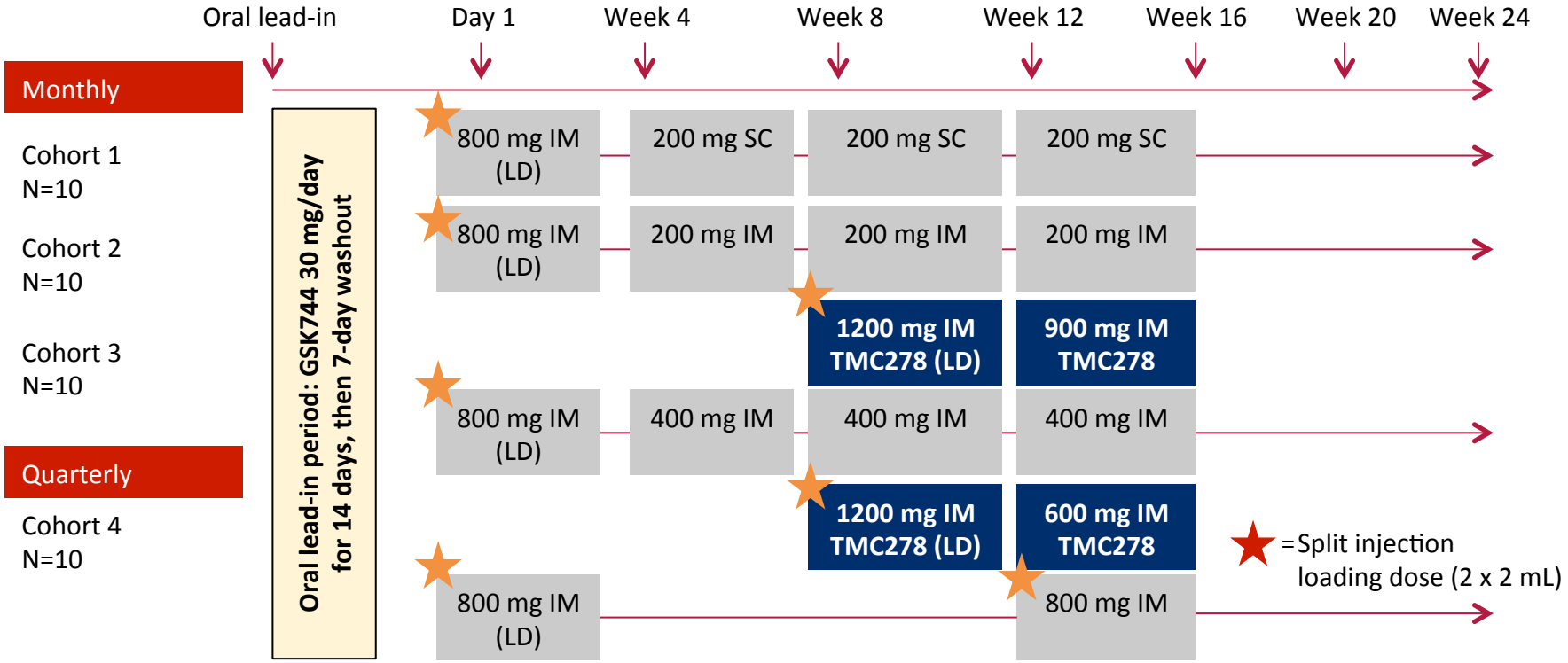
Table 2: **Virological outcomes at week 48, US Food and Drug Administration snapshot approach**



Cahn P, et al. Lancet HIV, 2017

LAI115428 Study
Repeat dose co-administration of GSK1265744 and TMC278 long-acting parenteral nanosuspensions

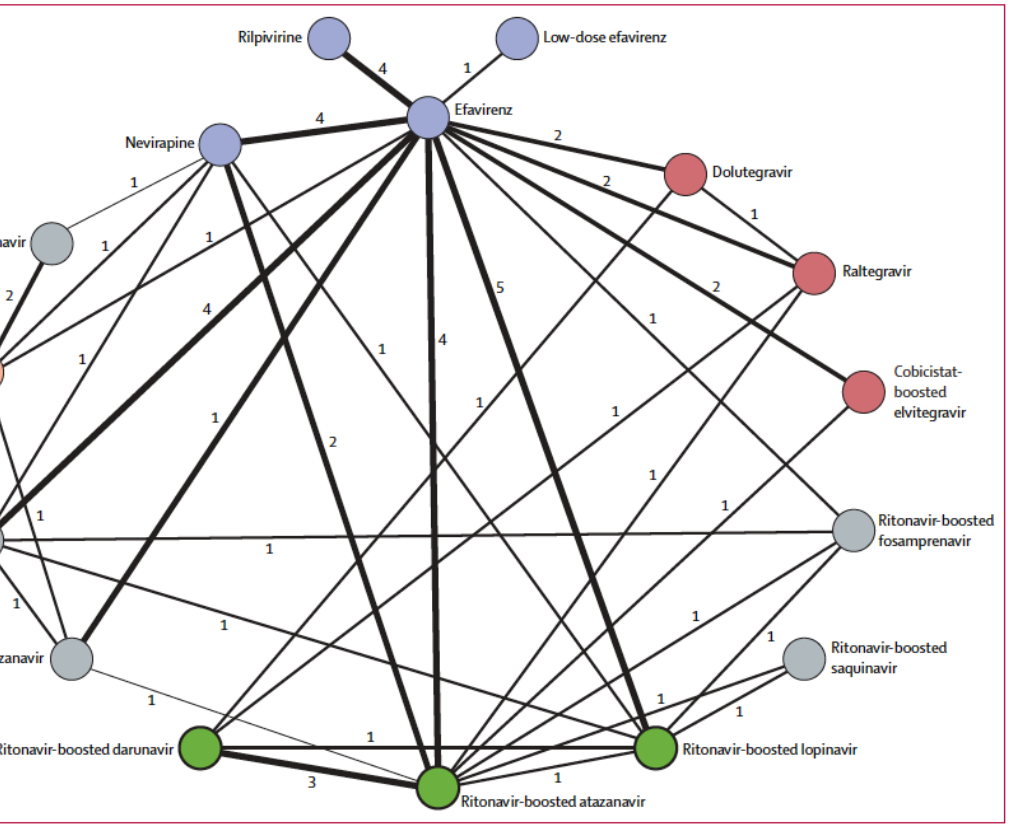
- Two-center, Phase I, randomized, open-label, repeat-dose study in healthy adults
- GSK744 200 mg/mL given as IM (gluteal) or SC (abdominal) injection; TMC278 given as IM (gluteal) injection
- Subjects followed 52 weeks after last injection (ongoing)



Spreen W, et al. J Acquir Immune Defic Syndr, 2014

letwork of eligible comparisons between ARV treatments

all, the network included 34,032 patients randomly
ned to 161 treatment groups across 71 trials.



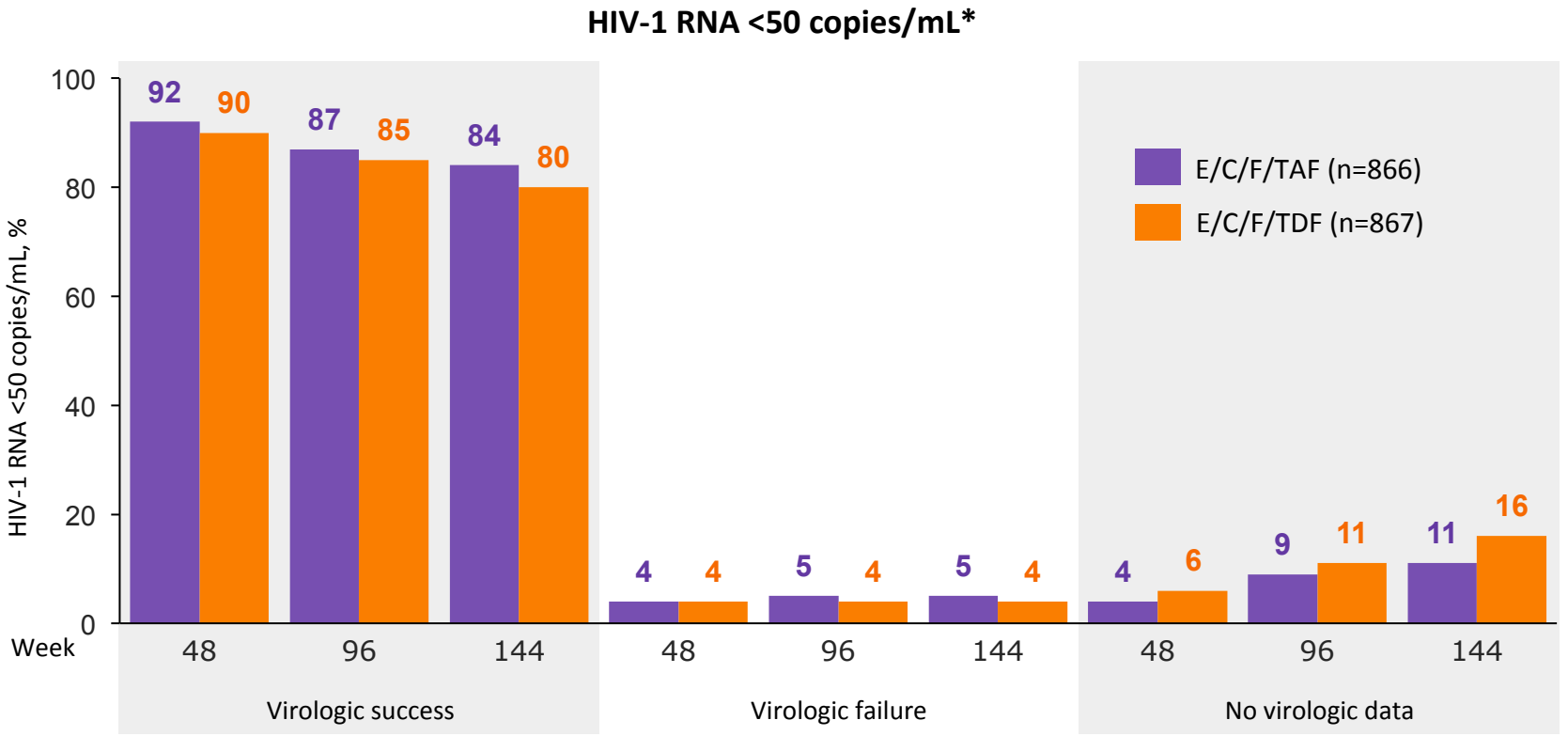
Random-effects network meta-analyses of the relative efficacy of antiretrovirals for viralsuppressio

EFV	**1·90 (1·40–2·59)**	**1·45 (1·07–1·95)**	1·10 (0·77–1·59)	0·69 (0·48–1·03)	0·93 (0·74–1·18)	0·99 (0·71–1·40)	**0·49 (0·30–0·82)**	1·19 (0·73–1·95)	(0·
1·87 (1·34–2·64)	DTG	0·76 (0·56–1·03)	**0·58 (0·37–0·92)**	**0·36 (0·24–0·56)**	**0·49 (0·35–0·69)**	**0·52 (0·37–0·74)**	**0·26 (0·14–0·47)**	0·63 (0·35–1·11)	(0·
1·40 (1·02–2·59)	0·75 (0·53–1·05)	RAL	0·76 (0·49–1·18)	**0·48 (0·32–0·73)**	**0·64 (0·47–0·88)**	**0·68 (0·48–0·97)**	**0·34 (0·19–0·61)**	0·82 (0·46–1·44)	(0·
1·28 (0·87–1·89)	0·68 (0·41–1·14)	0·91 (0·56–1·50)	EVG/c	0·63 (0·39–1·03)	0·84 (0·59–1·22)	0·90 (0·57–1·44)	**0·45 (0·24–0·83)**	1·09 (0·58–1·98)	(0·
0·76 (0·59–0·98)	**0·40 (0·27–0·60)**	**0·54 (0·37–0·78)**	**0·59 (0·38–0·92)**	LPV/r	1·34 (0·96–1·85)	1·43 (1·00–2·00)	0·72 (0·39–1·27)	1·73 (0·91–3·11)	**(1·**
0·90 (0·74–1·10)	**0·48 (0·33–0·69)**	**0·64 (0·46–0·89)**	0·70 (0·48–1·04)	1·18 (0·92–1·54)	ATV/r	1·07 (0·78–1·48)	**0·54 (0·31–0·92)**	1·28 (0·73–2·20)	(0·
0·91 (0·66–1·28)	**0·49 (0·33–0·72)**	**0·65 (0·45–0·94)**	0·71 (0·44–1·16)	1·21 (0·87–1·69)	1·02 (0·74–1·40)	DRV/r	**0·50 (0·27–0·90)**	1·20 (0·65–2·17)	(0·
0·87 (0·70–1·07)	**0·46 (0·32–0·68)**	**0·62 (0·43–0·89)**	0·68 (0·44–1·04)	1·15 (0·85–1·54)	0·97 (0·76–1·23)	0·95 (0·65–1·37)	NVP	**2·42 (1·18–4·88)**	**(1·**
1·16 (0·67–2·02)	0·62 (0·33–1·17)	0·82 (0·44–1·55)	0·90 (0·46–1·77)	1·52 (0·83–2·59)	1·29 (0·72–2·31)	1·26 (0·67–2·39)	1·33 (0·74–2·40)	low EFV	(0·
1·18 (0·90–1·55)	**0·63 (0·41–0·98)**	0·85 (0·55–1·28)	0·92 (0·57–1·48)	**1·57 (1·07–2·25)**	1·32 (0·93–1·83)	1·29 (0·83–1·98)	1·36 (0·96–1·92)	1·02 (0·56–1·87)	

Treatment 48 week network results, OR (95% CI) 96 week network results, OR (95% CI)

ters S, et al. Lancet HIV, 2016

udies 104 & 111: ART-naïve adults, week 144 combined analysis
rologic outcomes at weeks 48[1], 96[2], and 144[3]



- At week 144, E/C/F/TAF was superior to E/C/F/TDF in efficacy difference at both
  - <50 copies/mL: 4.2% (95% CI 0.6%, 7.8%; p=0.02)
  - <20 copies/mL: 5.4% (95% CI 1.5%, 9.2%; p=0.01)

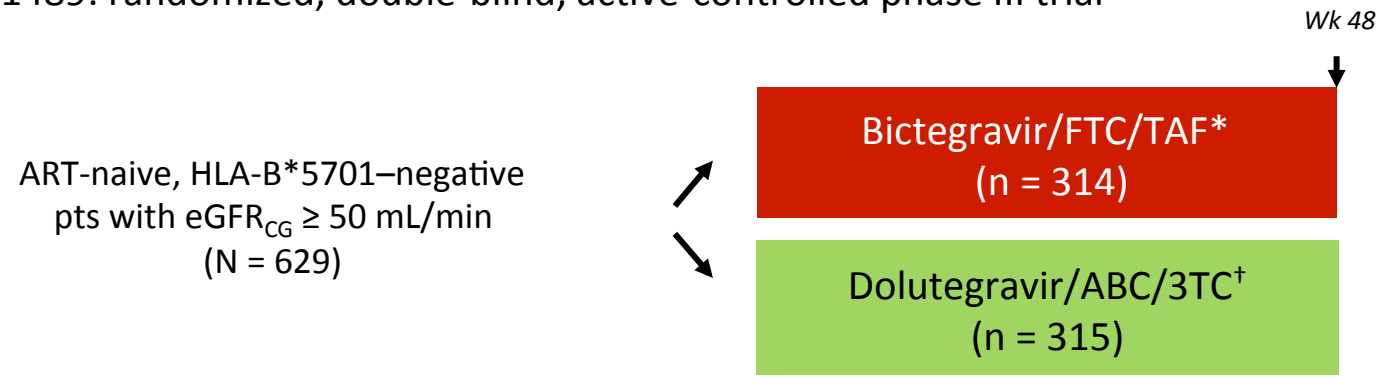
*By FDA snapshot analysis (12% non-inferiority margin of TAF to TDF). CI, confidence interval.

1. Sax P, et al. J Acquir Immune Defic Syndr 2014;67:52–8; 2. Sax P, et al. Lancet 2015;385:2606–15; 3. Arribas J, et al. CROI 2017. Seattle, WA. Poster #453

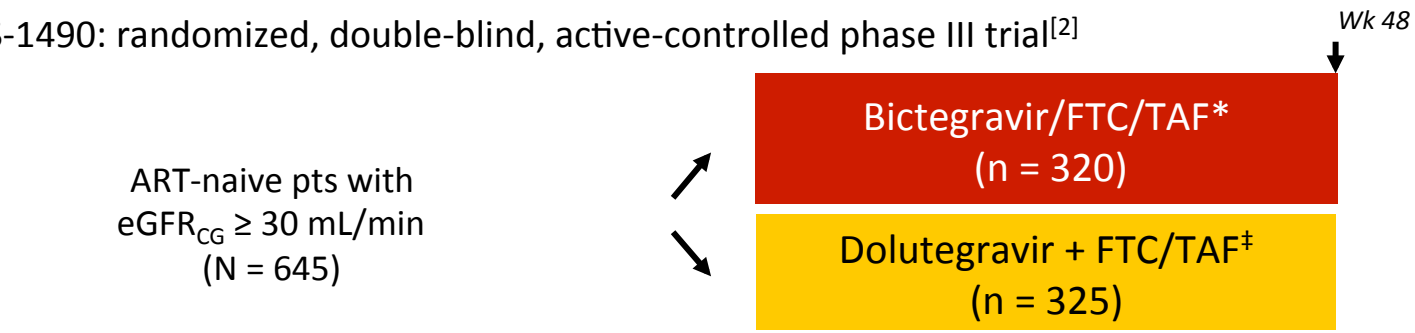
Bictegravir/FTC/TAF vs Dolutegravir-Containing Regimens for Treatment-Naive Pts

Bictegravir: novel QD unboosted INSTI coformulated with FTC/TAF

- GS-1489: randomized, double-blind, active-controlled phase III trial[1]



- GS-1490: randomized, double-blind, active-controlled phase III trial[2]

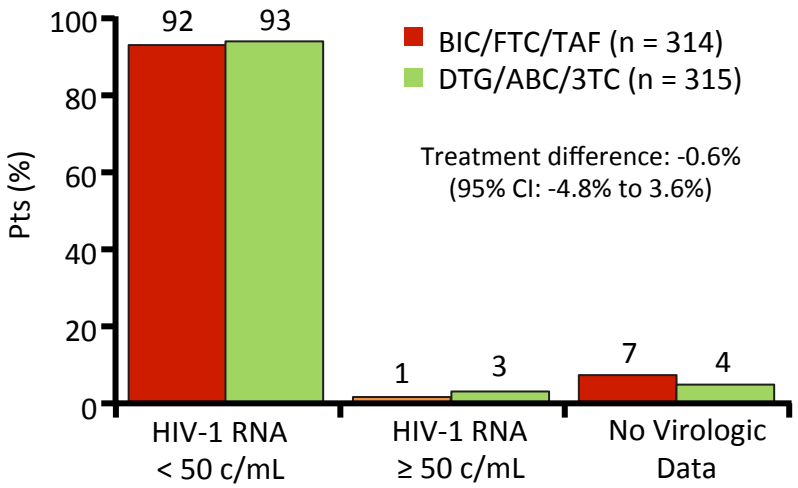


All pts also received placebo tablets for comparator regimen (eg, pts in GS-148 who received BIC/FTC/TAF also receive DTG/ABC/3TC placebo). *BIC/FTC/TAF, 50/200/25 mg PO QD. †DTG/ABC/3TC, 50/600/300 mg PO QD. ‡DTG + FTC/TA 50 + 200/25 mg PO QD

llant J, et al. IAS 2017. Abstract MOAB0105LB; Gallant J, et al. Lancet 31 Aug, 2017 [Epub ahead of print]
x PE, et al. IAS 2017. Abstract TUPDB0201LB; Sax P, et al. Lancet 31 Aug, 2017 [Epib ahead of print]

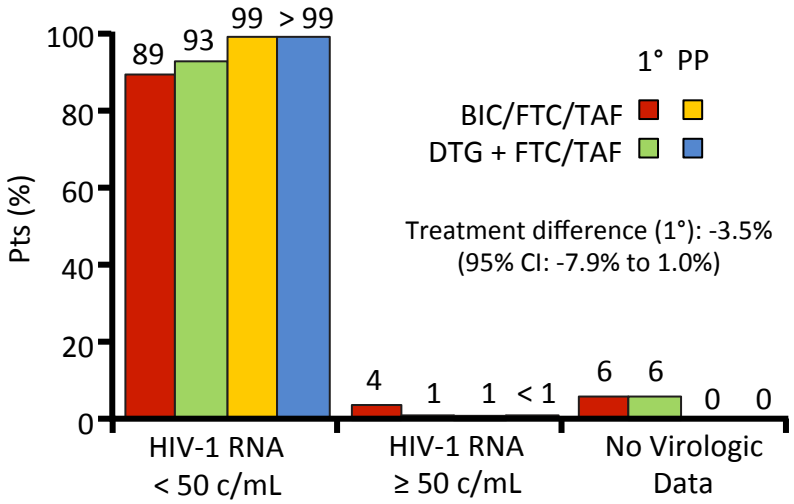
BIC/FTC/TAF vs DTG-Containing Regimens: Key Efficacy Findings

GS-1489: Wk 48 Virologic Efficacy[1]



- No resistance for any regimen components detected for either group

GS-1490: Wk 48 Virologic Efficacy[2]



- No resistance for any regimen components detected for either group

llant J, et al. IAS 2017. Abstract MOAB0105LB; Gallant J, et al. Lancet 31 Aug, 2017 [Epub ahead of print]
Sax PE, et al. IAS 2017. Abstract TUPDB0201LB; Sax P, et al. Lancet 31 Aug, 2017 [Epib ahead of print]

Baseline characteristics and efficacy results in PI/r and INSTIs studies in HIV naive pts

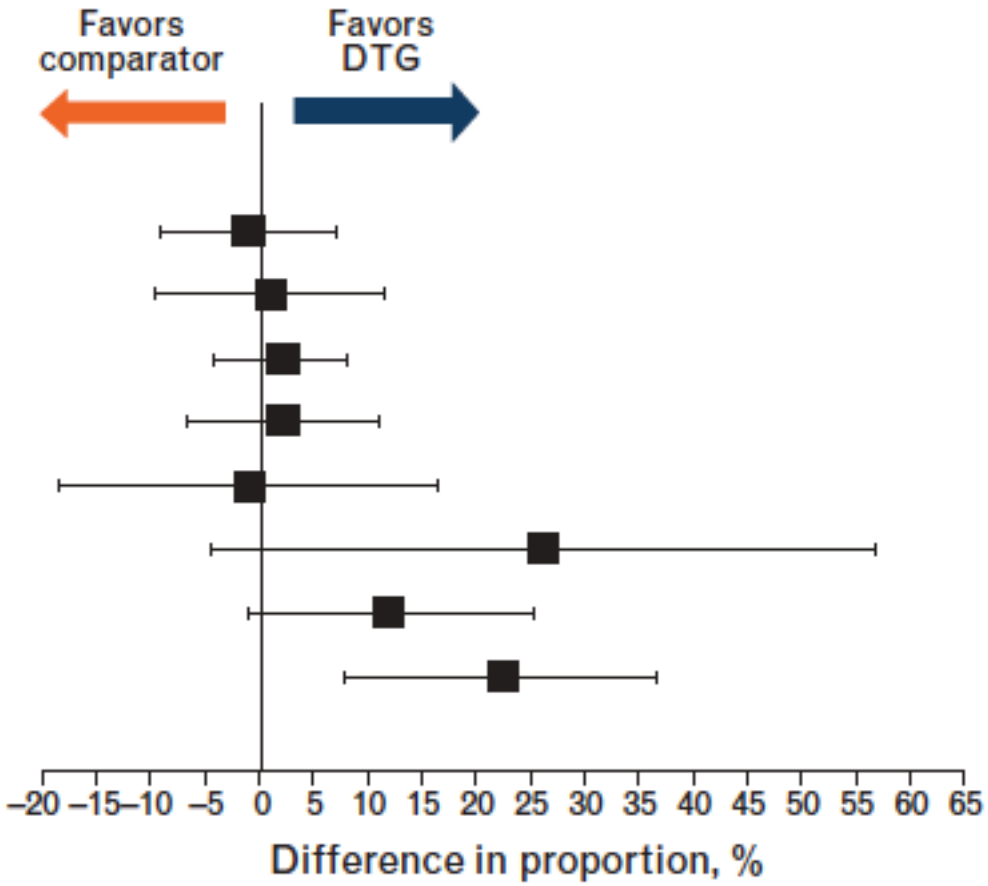
		pVL (median)	VL>5 log	CD4 median	CD4<200	pVL<50c/mL at 48 w
CASTLE	ATV/r	5.01	51%	205	50%	78%
	LPV/r	4.96	47%	204	49%	76%
ARTEMIS	DRV/r	4.86	34%	228	41%	84%
	LPV/r	4.84	35%	218	43%	78%
ACTG5257	RAL	4.7	32%	304	31%	80 %
	ATV/r	4.6	32%	309	29%	63 %
	DRV/r	4.6	28%	310	29%	73 %
STARMRK	RAL	5.1	55%	212	47%	86 %
	EFV	5	51%	204	48%	82 %
102	EVG/c	4.75	34%	391	12%	88 %
	EFV	4.78	33%	382	14%	84 %
103	EVG/c	4.88	43%	364	15%	89 %
	ATV/r	4.86	40%	375	11%	87 %
SINGLE	DTG	4.67	32%	335	14%	88 %
	EFV	4.70	31%	339	14%	81 %
SPRING-2	DTG	4.52	28%	359	13%	88 %
	RAL	4.58	28%	362	12%	85 %
FLAMINGO	DTG	4.49	25%	390	10%	90 %
	DRV/r	4.48	25%	400	10%	83 %

TG Randomized trials

napshot response rates by subgroup in each study: bivariat ummaries by baseline viral load and NRTI backbone

(b)

Parameter	DTG	Comparator	Study
NRTI: ABC/3TC	115/132 (87)	110/125 (88)	Spring-2
VL ≤100,000 c/mL	59/66 (89)	60/68 (88)	Flamingo
NRTI: TDF/FTC	152/165 (92)	154/170 (91)	Spring-2
VL ≤100,000 c/mL	101/115 (88)	97/113 (86)	Flamingo
NRTI: ABC/3TC	30/37 (81)	32/39 (82)	Spring-2
VL>100,000 c/mL	12/13 (92)	8/12 (67)	Flamingo
NRTI: TDF/FTC	64/77 (83)	55/57 (71)	Spring-2
VL>100,000 c/mL	45/48 (94)	35/49 (71)	Flamingo

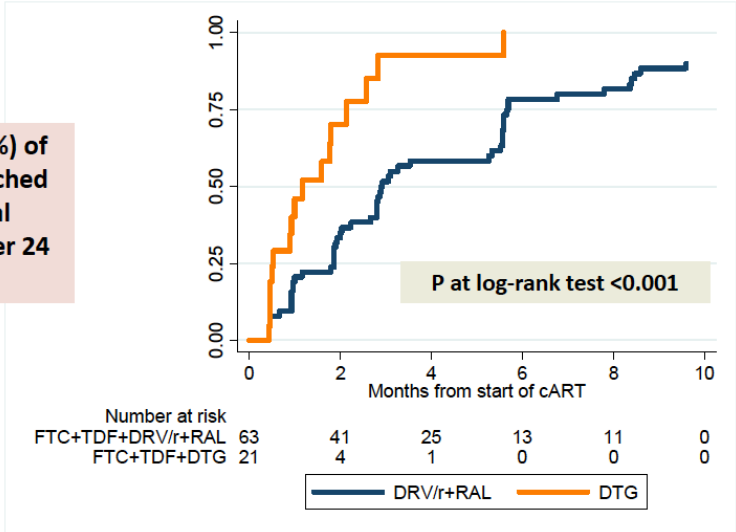


Raffi F, et al. AIDS, 20

Probability of reaching viral suppression in patients with primary HIV infection (PHI)

Probability of HIV RNA detectable <40 cp/ml during the first year of cART estimated by Kaplan Meier curve

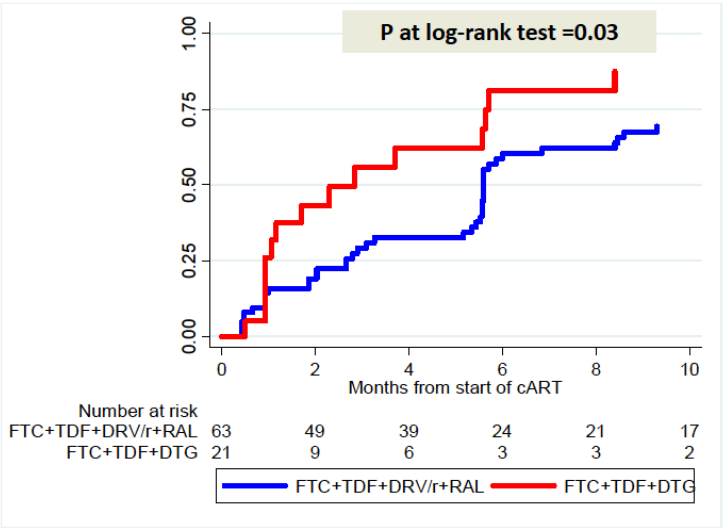
76/84 (90.5%) of patients reached virological response over 24 PYFU



	3-month probability	6-month probability
FTC+TDF+DRV/r+RGV	52% (95%CI 40-64)	78% (95%CI 67-88)
FTC+TDF+DGV	92% (95%CI 72-99)	100%

Probability of HIV RNA not detectable <40 cp/ml during the first year of cART estimated by Kaplan Meier curve

65/84 (77.4%) of patients reached virological response over 37 PYFU



	3-month probability	6-month probability
FTC+TDF+DRV/r+RGV	29% (95%CI 19-42)	58% (95%CI 46-71)
FTC+TDF+DGV	56% (95%CI 35-79)	81% (95%CI 60-95)

Pinnetti C, et al. ICAR 2016

elected Previous Trials of Dual Therapy Regimens for nitial Therapy

Study	N	Regimen	Results
PI-Based Dual Therapy			
NEAT001[1]	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF; poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts
GARDEL[2]	426	LPV/RTV + 3TC	Similar efficacy as LPV/RTV + 2 NRTIs
DTG-Based Dual Therapy			
PADDLE[3]	20	DTG + 3TC	18/20 pts achieved virologic suppression; n = 1 experienced PDVF (BL HIV-1 RNA > 100,000 c/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit

Raffi F, et al. Lancet. 2014;384:1942-1951. 2. Cahn P, et al. EACS 2015.
bstract 961. 3. Cahn P, et al. IAC 2016. Abstract FRAB0104LB.

NEAT001/ANRS143

Which is the weight of CD4/VL strata on virological outcome?

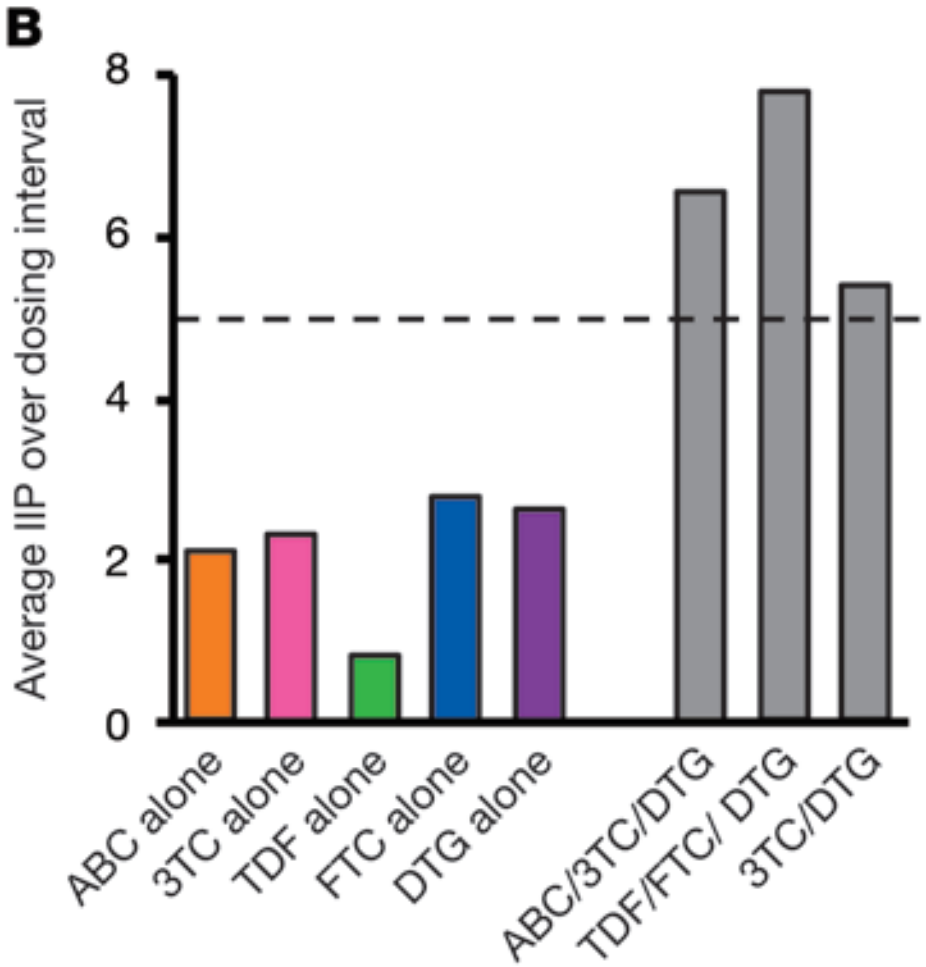
	Baseline CD4 cell count <200 cells per µL and HIV RNA concentration <100 000 copies per mL (n=46)		Baseline CD4 cell count ≥200 cells per µL and HIV RNA concentration <100 000 copies per mL (n=484)		Baseline CD4 cell count <200 cells per µL and HIV RNA concentration ≥100 000 copies per mL (n=77)		Baseline CD4 cell count ≥200 cells per µL and HIV RNA concentration ≥100 000 copies per mL (n=198)	
	RAL+DRV/r	TDF–FTC+DRV/r	RAL+DRV/r	TDF–FTC+DRV/r	RAL+DRV/r	TDF–FTC+DRV/r	RAL+DRV/r	TDF–FTC+DRV/r
Number meeting endpoint	3/23	3/23	19/232	21/252	23/37	12/40	32/109	25/89
Proportion meeting primary endpoint	9·4%	9·0%	7·1%	7·1%	60·1%	29·9%	26·5%	28·4%
Difference (95% CI)	0·4% (–13·7 to 14·6)*	..	0% (–3·9 to 3·9)	..	30·3% (13·8 to 46·8)	..	–1·9% (–13·9 to 10·0)	..

RAL=raltegravir. DRV/r=ritonavir-boosted darunavir. TDF-FTC=tenofovir–emtricitabine. * Difference unadjusted because of very small numbers in this group.

Table 3: Kaplan-Meier estimates of proportions of patients meeting primary endpoint at week 96

Raffi F, et al. Lancet, 2014

Quantitative evaluation of the antiretroviral efficacy of dolutegravir



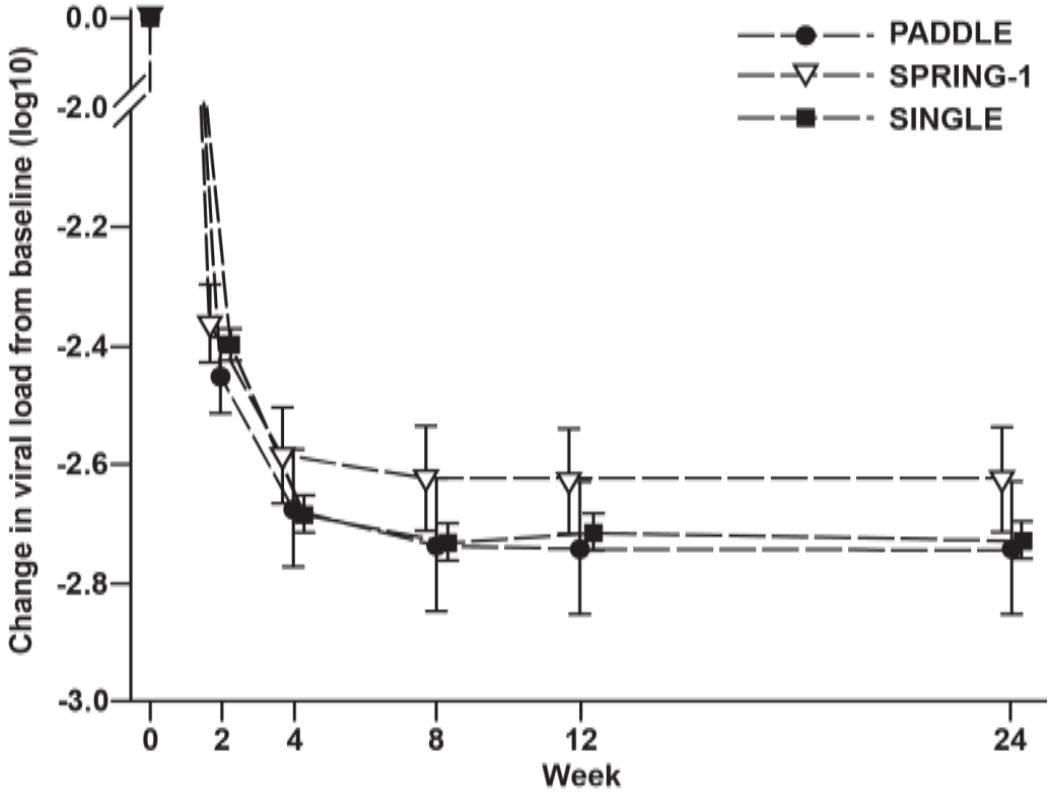
Using an in vitro infectivity assay and quantitative analysis, we evaluated critical DTG pharmacodynamic parameters.

Instantaneous inhibitory potential (IIP) is a metric of combined drug efficacy. IIP correlates with the clinical success of antiretroviral regimens.

Average instantaneous inhibitory potential (IIP) over 24-hour dosing period for individual drugs and their combinations. A dashed line at IIP = 5 shows the minimum IIP for a fully suppressive antiretroviral regimen.

Laskey SB & Siliciano RF. JCI Insight, 2

Comparable Viral Decay in Dual and Triple DTG-Based ARV Therapy



Baseline pVL (Mean+SD) was 4.43 (0.50), 4.30 (0.45) and 4.31 (0.52) for PADDLE, SINGLE and SPRING-1 respectively

Rapid decline in viral load was observed in the three regimens

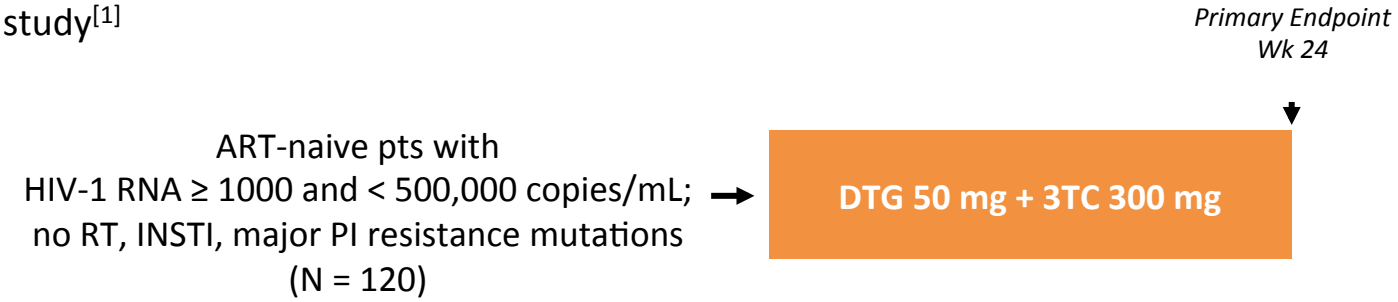
Average effects of treatment in PADDLE, SPRING-1 and SINGLE were -2.75±0.45 (Mean±SD), -2.53±0.49 and -2.61±0.48 log10 respectively

In an attempt to account for the differences observed at baseline in viral load, viral load decay was normalized to such differences

ued et al. CROI 2016; Boston, MA. Poster 947.

ACTG A5353: DTG + 3TC for ART-Naive Pts

- Single-arm phase II study[1]



- Baseline: 31% HIV-1 RNA > 100,000 c/mL

Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, copies/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

*HIV-1 RNA < 50 copies/mL.

- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
  - All 3 pts had DTG levels reflective of suboptimal adherence
- GEMINI 1/2 randomized phase III trials of DTG + 3TC ongoing[2,3]

aiwo BO, et al. IAS 2017. Abstract MOAB0107LB.
linicalTrials.gov. NCT02831673. 3. ClinicalTrials.gov. NCT02831764.

GEMINI 1 and 2: DTG with 3TC vs F/TDF

Study design (identical studies*)

Prospective, randomised, phase 3b, multicentre, open-label, 48 week studies, with two planned interim analyses at 24 weeks

Study purpose: Compare safety, efficacy, and tolerability of DTG plus 3TC QD with DTG plus F/TDF QD in HIV-infected treatment-naive individuals

- **Treatment-naïve HIV-positive individuals**
- **≥18 years of age**
- **HIV-1 RNA between 1,000 to ≤100,000copies/mL****
- **N=700**

1:1

n=350 — **DTG (50mg) + 3TC (300mg) QD**

F/TDF Placebo QD

n=350 — **DTG (50mg) + F/TDF**

3TC Placebo QD

BL — Week 48 (Primary endpoint HIV-1 RNA<50copies/mL) — Week 96

**enrolment opened to subjects with screening plasma HIV 1 RNA of 1000 c/mL to <=500,000 c/mL

ClinicalTrials.gov Identifier: NCT02831673 and NCT02831764

Primary endpoint: Number and percentage of individuals with a viral load of <50copies/mL at Week 48
Secondary endpoints: Include change in fasting lipids, viral load reduction from baseline and change in CD4 cell count

3TC, lamivudine; BL, baseline; DTG, dolutegravir; F, emtricitabine; QD, once daily; TDF, tenofovir disoproxil fumarate
*study design presents N for 1 study

1. Clinicaltrials.gov. Gemini 1: https://clinicaltrials.gov/ct2/show/NCT02831673?term=NCT02831673&rank=1 (accessed April 2017);
2. Clinicaltrials.gov. Gemini 2: https://clinicaltrials.gov/ct2/show/NCT02831764?term=NCT02831764&rank=1 (accessed April 2017)
3. https://www.viivhealthcare.com/media/press-releases/2016/august/viiv-healthcare-launches-phase-iii-programme-evaluating-a-two-drug-regimen-combining-dolutegravir-and-lamivudine-for-hiv-1-treatment.aspx (accessed April 2017)

Dolutegravir trials in treatment-experienced adult subjects with HIV

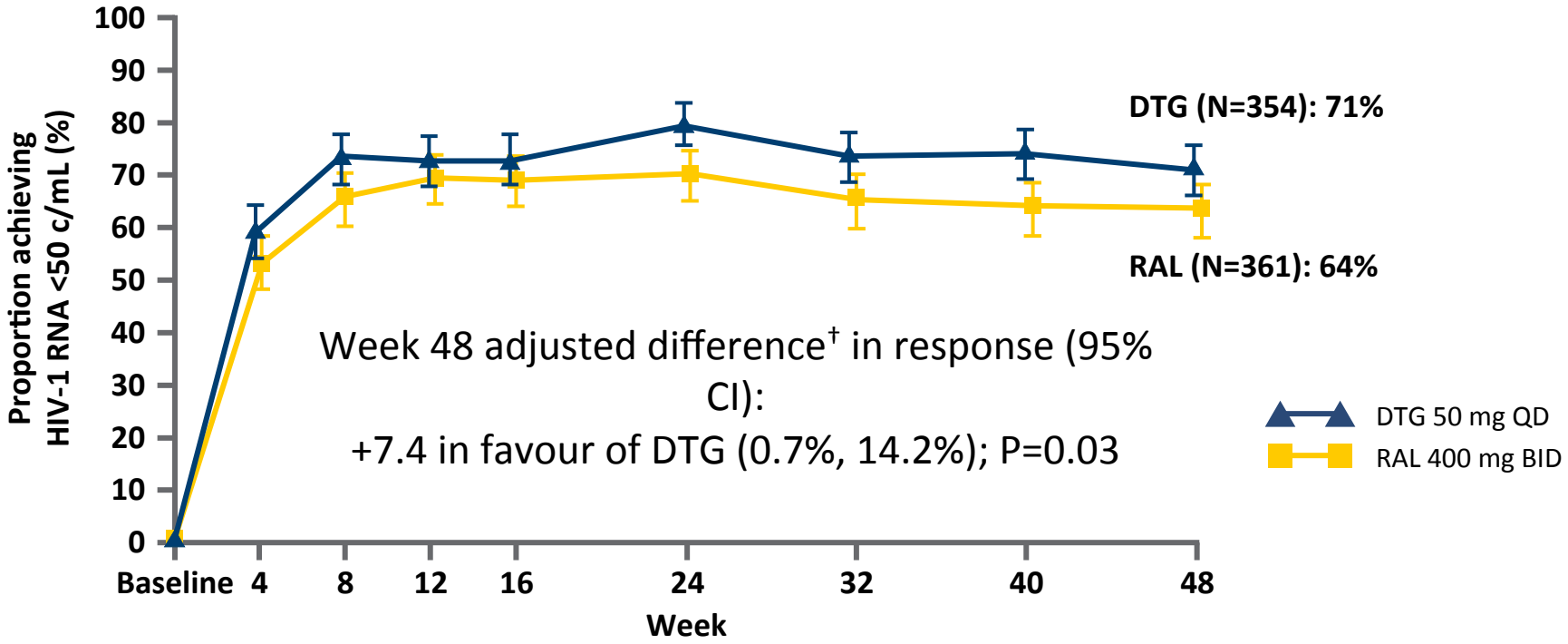
SAILING[1] INI-naïve	N=719	Phase III, randomised, double-blind, active-controlled, parallel group, non-inferiority, multicentre study of: • DTG (50 mg QD) + BR • RAL (400 mg BID) + BR
VIKING[2] (Cohort I) INI-resistant	N=27	Phase IIb open-label, single-arm multicentre study (Cohort I) of: • DTG 50 mg QD + OBR (not incl. RAL)
VIKING[2] (Cohort II) INI-resistant	N=24	Phase IIb open-label, single arm multicentre study (Cohort II) of: • DTG (50 mg BID) + OBR (not incl. RAL) • Subjects required to have ≥1 fully active ARV for Day 11 optimisation (not required for Cohort I)
VIKING-3[3] INI-resistant	N=183	Phase III, open-label, single-arm, multicentre study of: • DTG (50 mg BID) + OBR (not incl. RAL)
VIKING-4[4] INI-resistant	N=30	Phase III, open-label, placebo-controlled, multicentre study of: • DTG 50 mg BID vs placebo (both plus current failing regimen) • At Day 8, all subjects received DTG (50 mg BID) + OBR (containing ≥1 fully active ARV)

BID, twice daily; BR, background regimen
QD, once daily; OBR, optimised background regimen

1. Cahn P, et al. Lancet 2013;382:700–8; 2. Eron JJ, et al. J Infect Dis 2013;207:740–8
3. Castagna A, et al. J Infect Dis 2014. Epub ahead of print
4. Akil B, et al. EACS 2013. Abstract PE7/3

Proportion of subjects with HIV-1 RNA <50 c/ml (snapshot*)

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 48



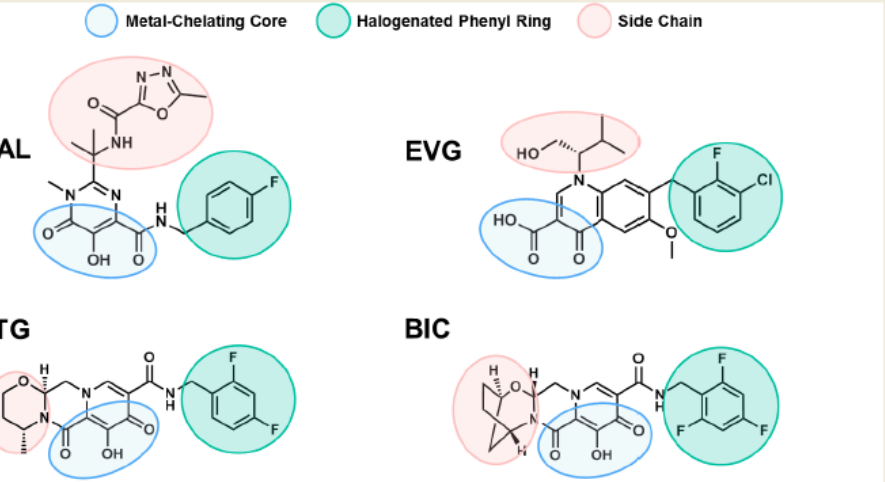
- Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm^3; RAL: +153 (144) cells/mm^3

ysis based on all subjects randomised who received ≥1 dose of study drug, excluding four cts at one site with violations of good clinical practice; SD, standard deviation
sted difference based on stratified analysis adjusting for BL HIV-1 RNA (≤50,000 c/mL vs 00 c/mL), DRV/r use without primary PI mutations and baseline PSS (2 vs <2)

Adapted from Cahn P, et al. Lancet 2013;38

ctegravir has the longest measured dissociation half-life from wild
ype HIV-1 IN-DNA complexes compared to DTG, RAL, and EVG

1. Structure of Bictegravir (BIC) and other INSTIs



ing Core: Oxygen atoms chelate a pair of Mg^{2+} ions and bind the integrase catalytic active site
Phenyl: Interacts with the integrase pocket that is normally occupied by the terminal 3' base of viral DNA

ravir also has ***the longest measured dissociation fe from mutant G140S/Q148H*** HIV-1 IN-DNA exes compared to DTG

K, et al. CROI 2017, Seattle (WA). Poster #497.

- Long residence times of INSTIs on the integrase-DNA complex have been correlated with potent antiretroviral activity and a high barrie to resistance *in vitro*.
- The long plasma half-life and high C_{min} of BIC *in vivo* should also contribute to a high resistance barrier

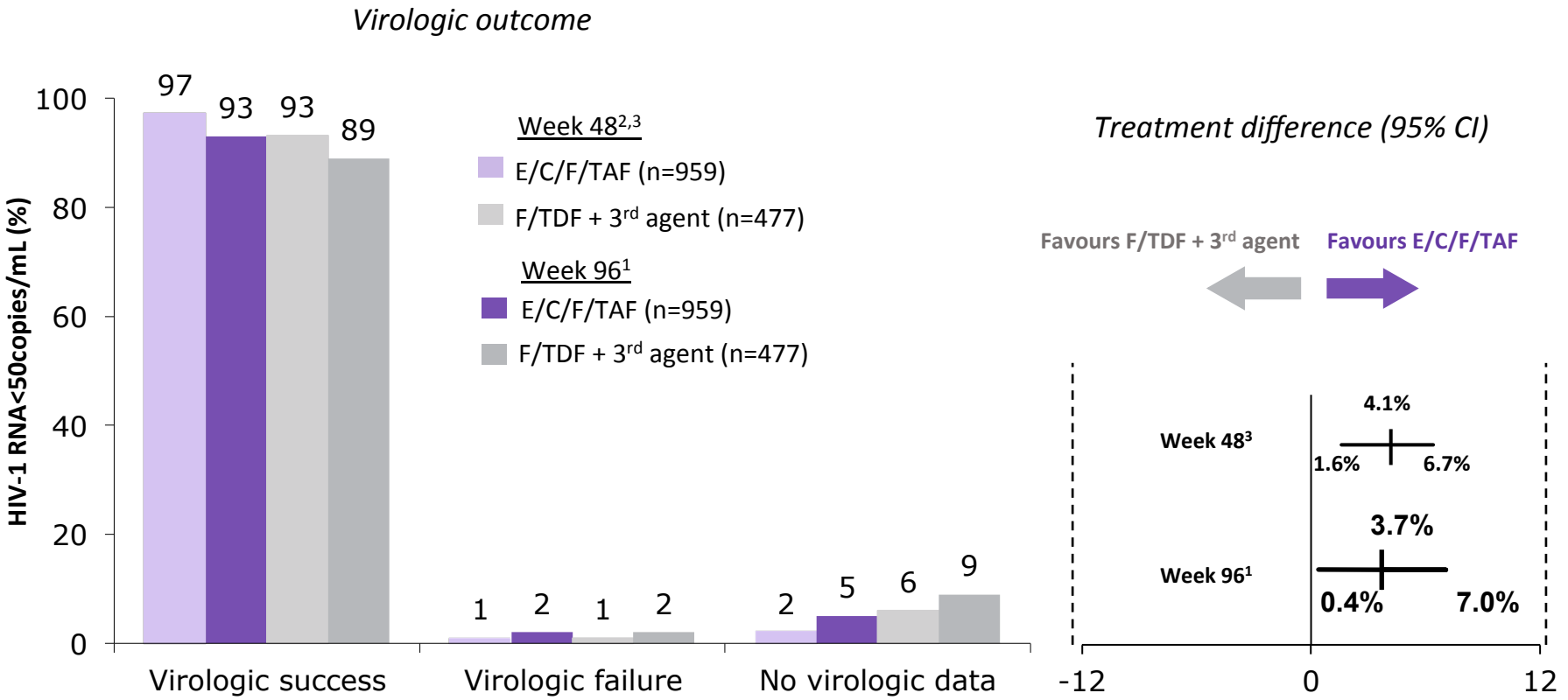
Table 3. Dissociation Half-lives of INSTIs from WT HIV-1 Integrase Complexes

INSTI	Dissociation of INSTI from Wild-type IN-DNA Complexes			
	By Exponential Decay		By Equilibrium Binding M	
	Apparent $t_{1/2}$ (hr) [**]	p-value vs BIC	$t_{1/2}$ (hr)	p-value v
BIC	135 ± 20 [na]	--	38 ± 19	--
DTG	79 ± 13 [71]	< 0.0001	16 ± 9	0.01
RAL	14 ± 3 [8.8]	< 0.0001	5.2 ± 0.6	0.00
EVG	3.6 ± 0.7 [2.7]	< 0.0001	1.5 ± 0.2	0.000

*Average ± standard deviation from 5 to 7 experiments
**Published $t_{1/2}$ values from Hightower et al., Antimicrobial Agents and Chemotherapy. (2011) 55(10):455

Study 109: ART-suppressed adults switched to E/C/F/TAF

Virologic outcomes (HIV-1 RNA<50copies/mL) at Week 96

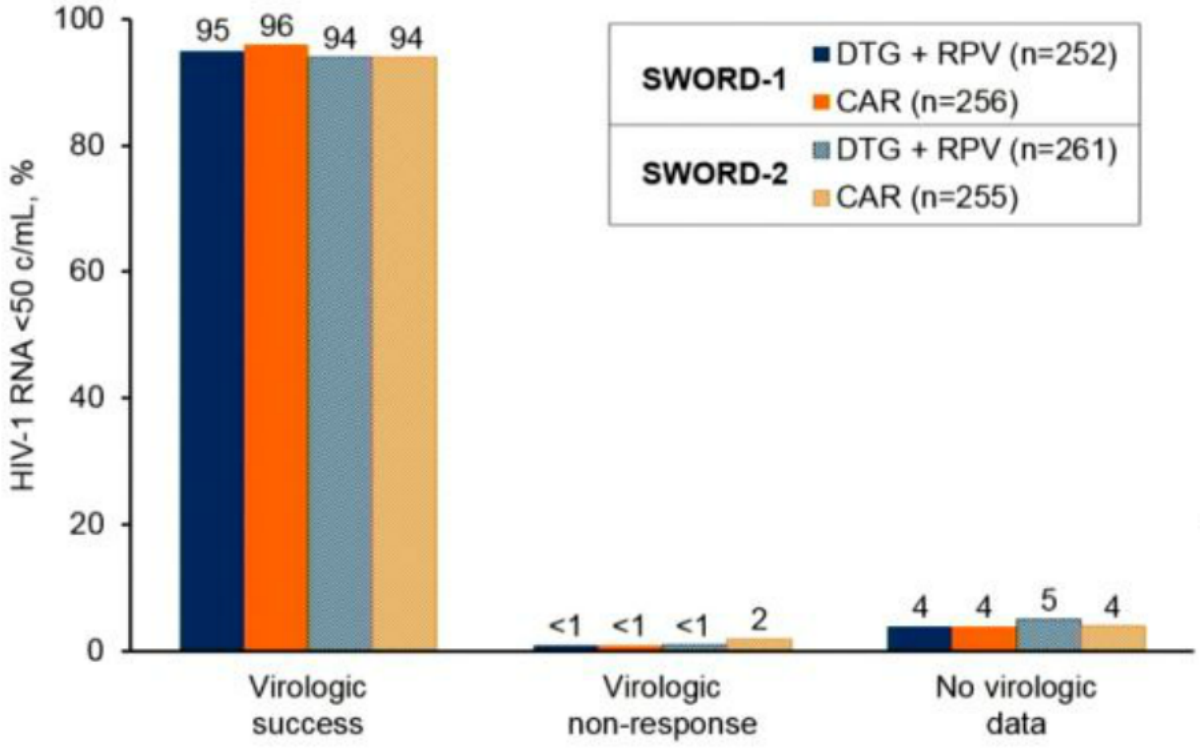


- Patients who switched to E/C/F/TAF were significantly more likely to maintain virologic success compared to continuing F/TDF+3rd agent treatment through Week 96[1]

eJesus E et al. ASM 2016. Boston MA. #087LB; 2. Mills A et al. Lancet Infect Dis 2016;16:43–52;
Mills A et al. IAS 2015. Vancouver, Canada. # TUAB0102

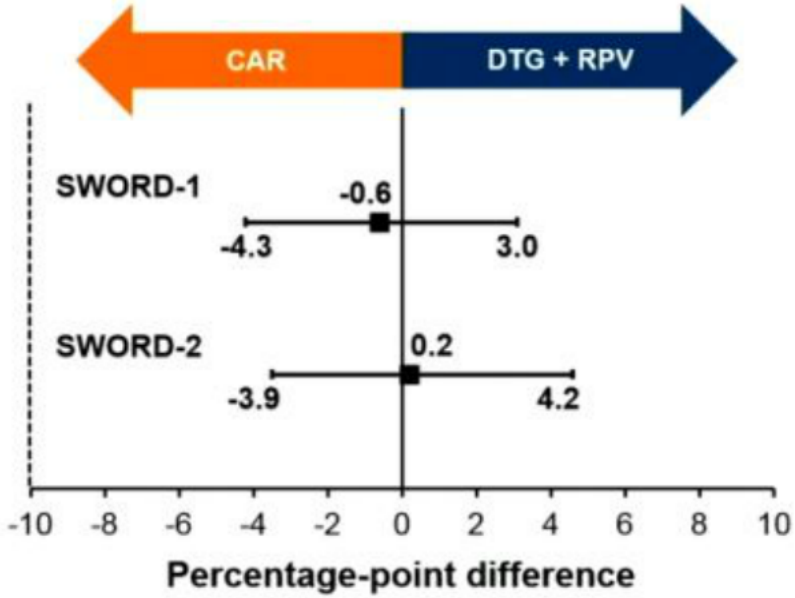
Snapshot Outcomes at Week 48 (SWORD-1&2)

Virologic outcomes



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

Adjusted treatment differences (95% CI)[a]

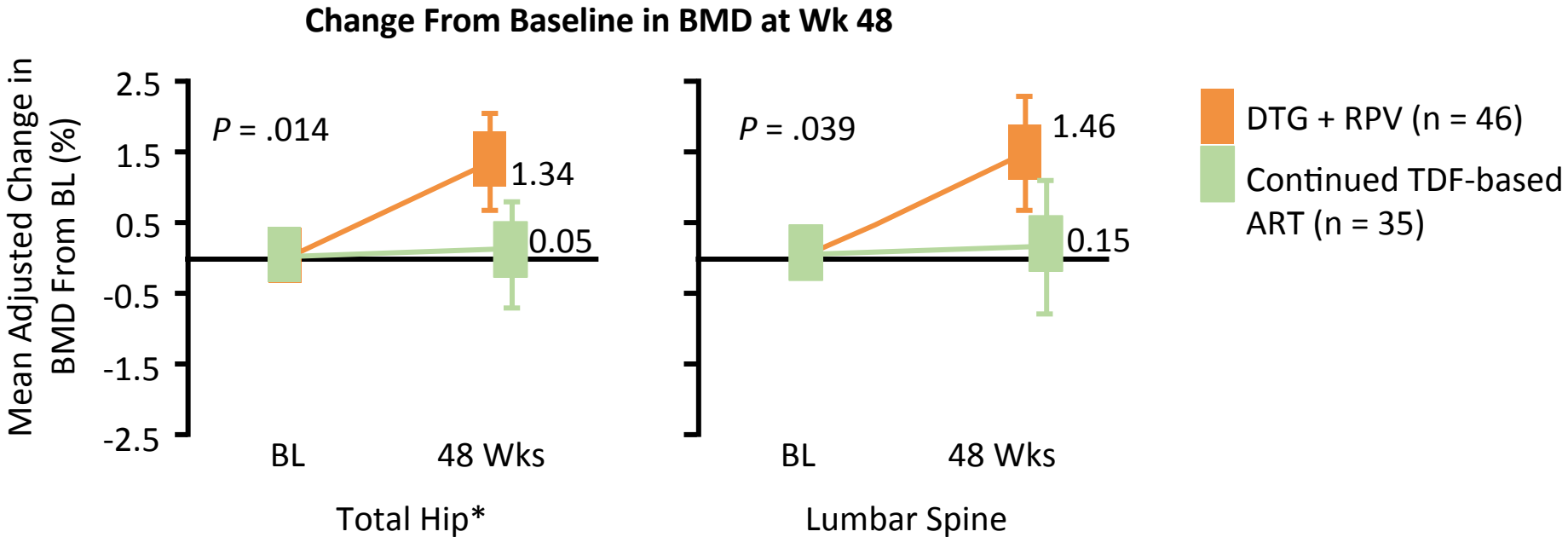


DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48 in both studies

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

SWORD 1 & 2 Substudy: BMD Impact of Switch From TDF-Based ART to DTG + RPV

- Randomized, open-label, multicenter phase III trials demonstrated that switch to DTG + RPV noninferior to remaining on baseline ART at Wk 48 in virologically suppressed pts
- Current analysis assessed BMD in pts who continued on TDF-containing triple ART regimen or switched from TDF-containing triple ART to DTG + RPV (N = 102)



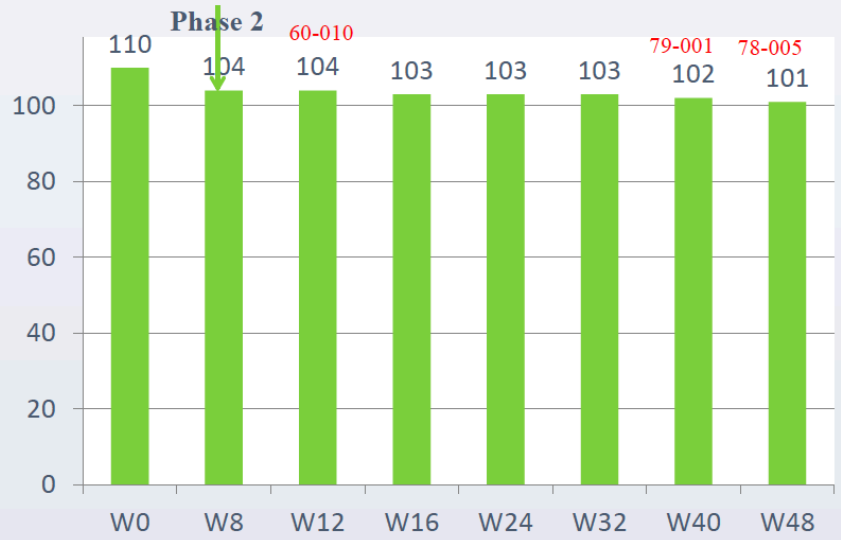
imary endpoint.

Comsey G, et al. IAS 2017. Abstract TUPDB0205LB.

Lamidol – ANRS167

Lamivudine + Dolutegravir Maintenance Therapy

Figure 2: Patients in Therapeutic Success



All patients have reached **W48 of the study, i.e. W40 of dual therapy**. 101/104 = 97%) are in therapeutic success).

At W48, therapeutic strategy has failed in 3 patients:

- Pt 60-010: virologic failure at W12 (W4 dual therapy)
- Pt 79-001: lost to follow-up at W40 (W32 dual therapy)
- Pt 78-005: treatment modification at W48 (W40 dual therapy) decided by the investigator

101 patients are still on study treatment and the last visit of the last patient is planned for 03/27/2017

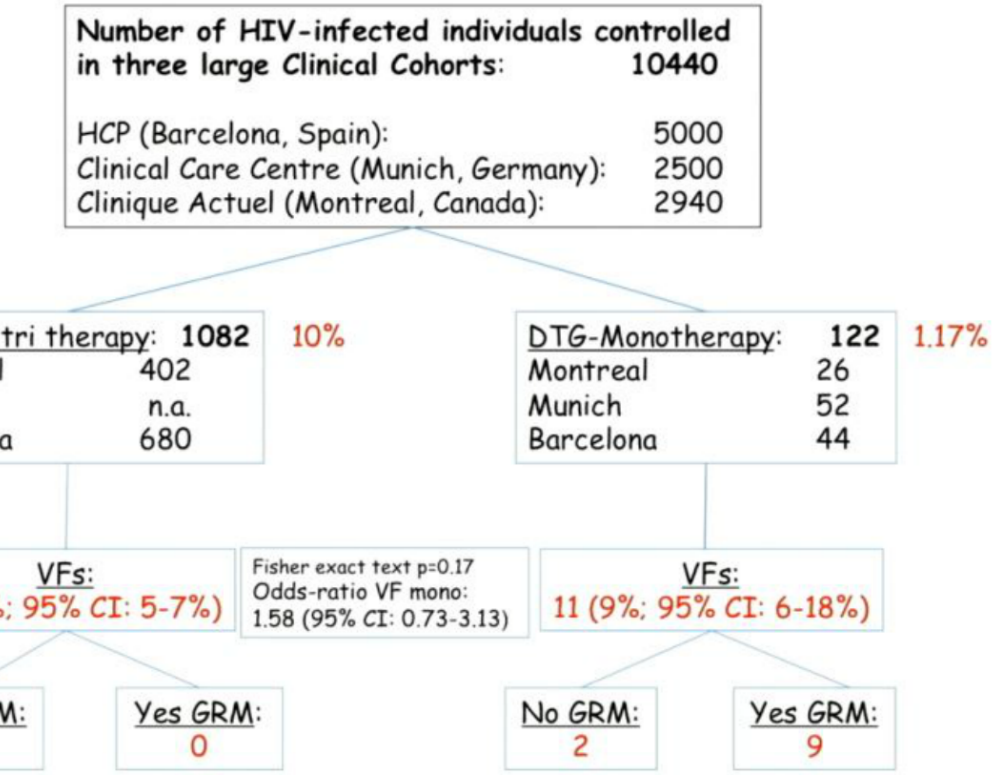
Switching to DTG + 3TC combination maintained virologic suppression at W40, was safe and well tolerated in this population of selected patients without previous virological failure.
Longer follow-up and comparative trials are needed to evaluate more precisely the role of this attractive maintenance strategy in HIV care.

Patient	Baseline		Follow-up					
	Previous ART	INSTI RAM	Visit	pVL	End Point	Plasma drug levels	RAM	Modification of A
60-010	TDF/FTC+RAL then ABC/3TC+RAL	Absence	W12 W16 W24 W32 W40 W48 W56	84 cps/mL 77 cps/mL 38 cps/mL 56 cps/mL 52 cps/mL 100 cps/mL 99 cps/mL	Virological failure at W12	At W12 (at 12h) DTG 2401 ng/mL 3TC 299 ng/mL	Not amplifiable (RNA and DNA)	ABC/3TC+DTG at RAL+ETR at W40
78-005	TDF/FTC+RPV then TDF/FTC+EFV	Absence	W40 W48 W56	59 cps/mL < 50 cps/mL 55 cps/mL	Therapeutic failure at W48	At W40: DTG 908 ng/mL 3TC 130 ng/mL	RNA: L74V/L: resistance to ABC DNA: M230I and V106I	TDF/FTC+DTG at although pVL < 50 c (investigator decisi
60-001	ABC/3TC/fAPV then ABC/.3TC/RAL	Absence	W32 From W36 to W56	51 cps/mL < 50 cps/mL	Blip	NA	NA	No
62-006	TDF/FTC+EFV then TDF/FTC+RPV	NA	W48 W51 W56 W60 (control)	67 cps/mL < 50 cps/mL 130 cps/mL < 50 cps/ml	Blip	At W56 (at 10h): DTG 2616 ng/mL At W60 (at 11,5h): DTG 529 ng/mL	No RAM for RT NA for INSTI	No

TDF: tenofovir, FTC: emtricitabine, RAL: raltegravir, ABC: abacavir, fAPV: fosamprenavir, EFV: efavirenz, RPV: rilpivirine, ETR: etravirine, NA: not available, RAM: resistance associated muta

Joly V, et al. CROI 2017, Seattle (WA). Post

apid and frequent selection of genotypic resistance nutations in individuals failing to DTG monotherapy



Results (II): Virological data

- In 5 of 11 (45%) individuals DTG was their first InSTI
- 8 of 11 (72%) had been virologically supressed for longer than 3 years
- Adherence was less than 95% in 4 of 11
- Weeks (median,IQR) from VF until GRT: 5 (3-14)

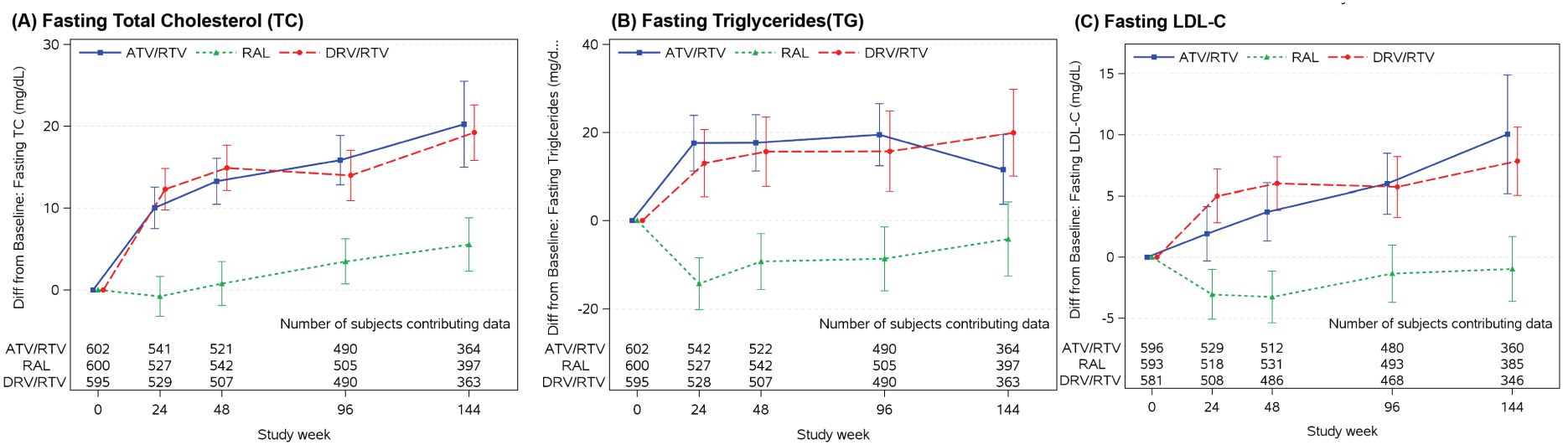
Pt code	Prior IsSTI without VF	Weeks UVL before DTG-M	Baseline VL	VLs on DTG-M	ADH	Weeks to VF	VL at VF	Weeks to GRT	VL at GRT
B001	None	768	<37	330 (8),146(10), 1393(18)	98% (PC)	8	330	8	330
B002	RAL	0 (LLV)	86 (prior 71,51)	80 (16), 171 (18), 122 (32), 3228 (48)	98% (PC)	16	80	32	122
B003	None	312	<37	26180 (20), 6014 (22), 10560 (28)	50% (PC)	20	26180	28	6014
B004	RAL (LLV/GRT:WT)	12	249 (prior <37)	123 (12), 1350 (24) 22170 (25)	82% (PC)	0	123	32	22170
B007	EGV	240	<37	57 (52), 51 (64), <37 (88)	100% (PC)	52	57	64	57
B008	None	480	<50	190 (32), 1350 (36), 40000 (40)	88% (PC)	32	190	36	1350
M001	RAL	232	21	55 (2), 168 (13), 239 (15)	60% (SQ)	0	55	16	239
M002	None	228	<20	538 (24), 11000 (28)	100% (SQ)	24	538	29	11000
C001	EVG	20	<50	306 (24), 583 (28)	100% (SQ)	24	306	24	306
B005	RAL,EGV	432	<37	179 (13), 71 (14), 56 (16)	98% (PC)	13	179	14	71
B006	None	172	<37	355 (72), 1355 (76), 1397 (80), <37 (92)	100% (PC)	72	355	76	355
Median (IQR)		236 (186-402)				20 (11-28)	190 (102-343)	29 (20-34)	330 (181-3682)

UVL: undetectable viral load; ADH: adherence; PC: Pill count; SQ: Self questionnaire; GRT: Genotypic resistance test; GRM: genotypic resitance mutation

aco JL, et al. CROI 2017, Seattle (WA). Oral abstract #42

A5257. INSTI produced a more favorable lipid profile than ATVr or DRVr

Mean of changes from Baseline in Fasting Lipid Profile (mg/dL) Over Time.



Following ART initiation, fasting TG, non-HDL-C, and calculated LDL-C increased in the 2 RTV boosted PI arms, and decreased or remained stable in the RAL arm.

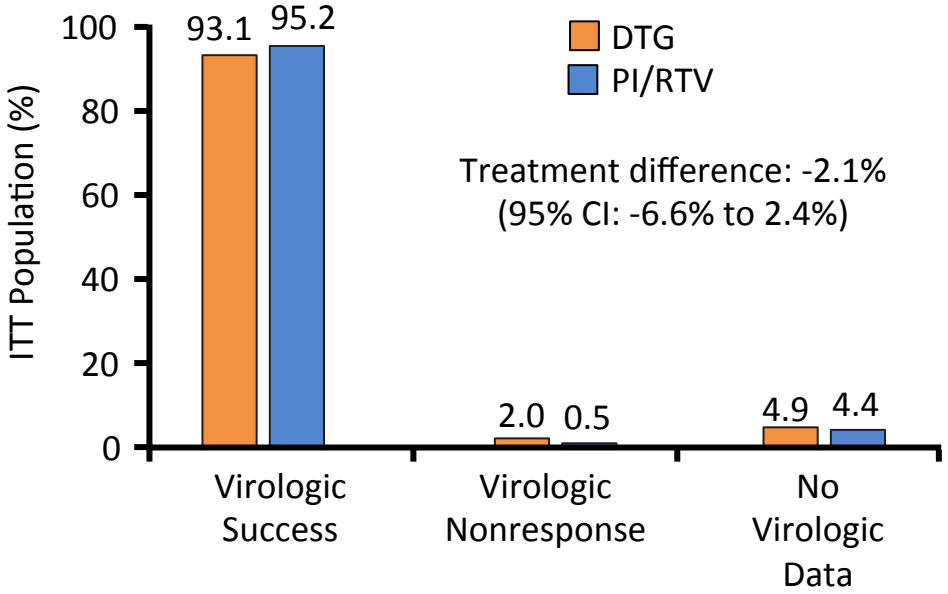
All pairwise comparisons between the ATV/RTV or DRV/RTV arm and the RAL arm showed **greater increases with ATV/RTV or DRV/RTV treatment compared to RAL**; no differences between ATV/RTV and DRV/RTV treatment were apparent.

As-treated and **sensitivity analyses excluding subjects on lipid lowering agents did not change results**.

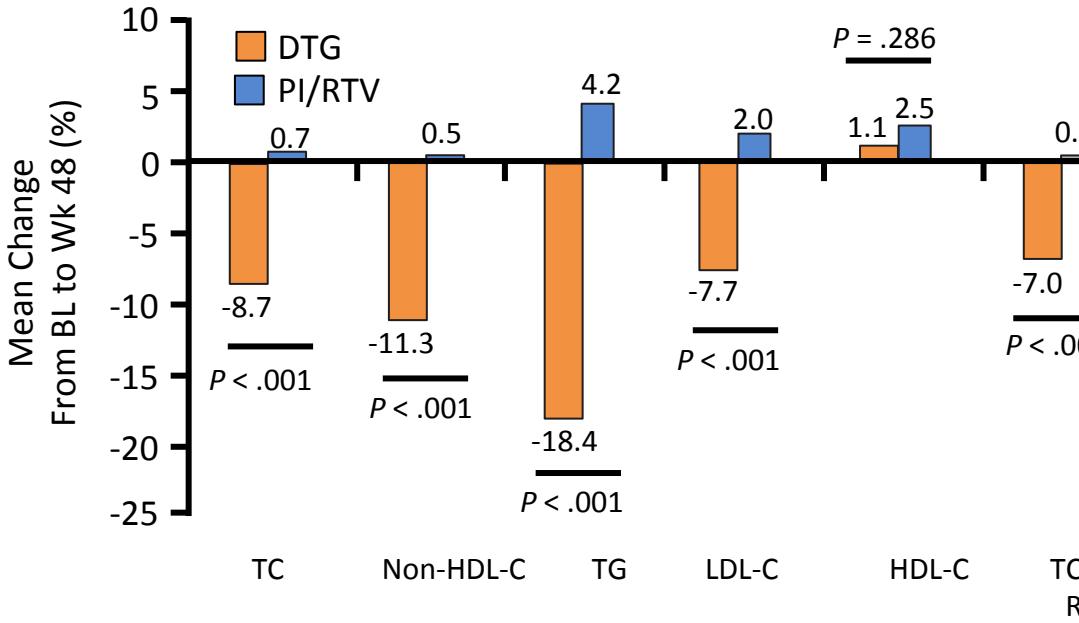
tokun I, et al. CROI 2014, Boston (MA). Abst.#746; Ofotokun I, et al. Clin Infect Dis, 2015

NEAT 022: Switch From Boosted PI to DTG in Suppressed Pts With High CV Risk

- Switching to DTG noninferior to continuing boosted PI through Wk 48



- Switching to DTG associated with improved lipid profile vs continuing boosted PI through Wk 48

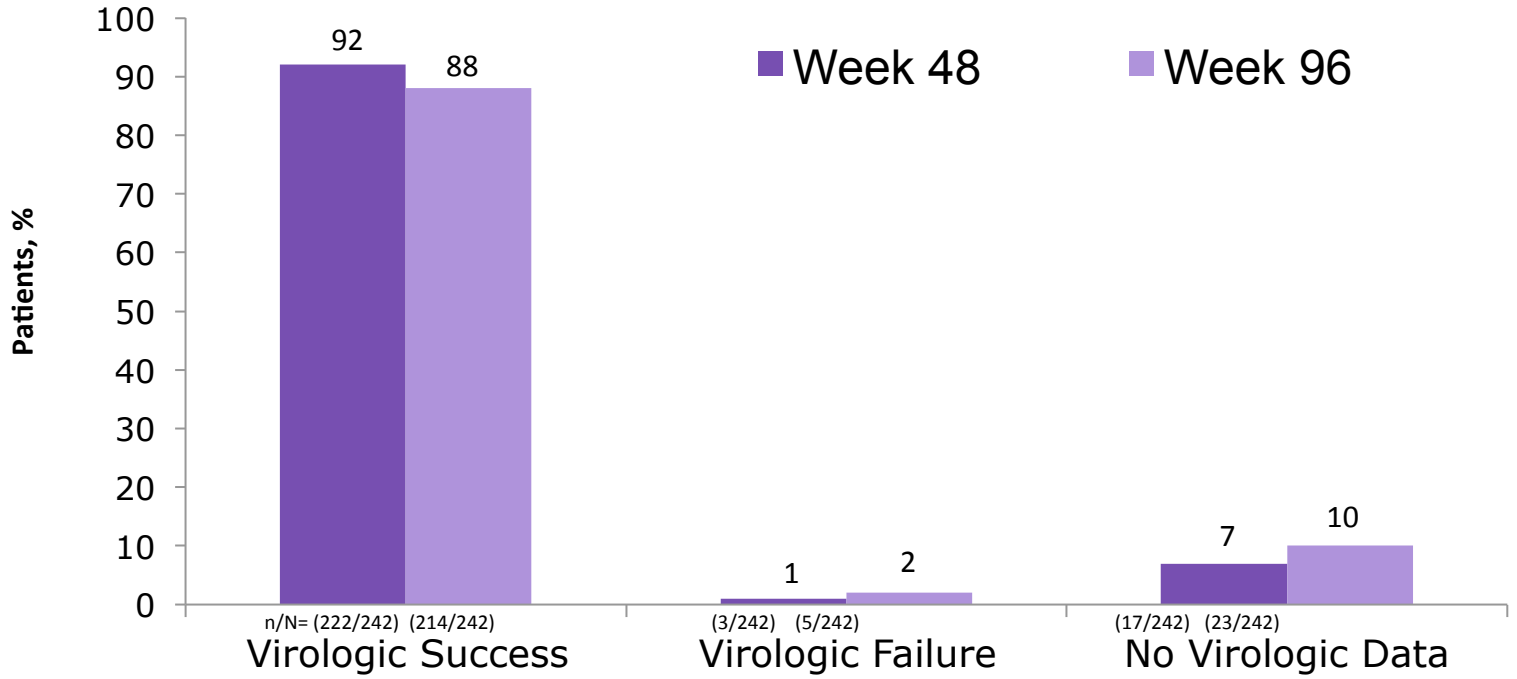


- No emergent resistance in pts with VF
- No significant differences in grade 3/4 AEs, serious AEs, AE-related d/c

ell JM et al. IAS 2017. Abstract TUAB0102.

Study 112: Suppressed adults with renal impairment switched to E/C/F/TAF

Virological outcomes (HIV-1 RNA <50 c/mL) at Week 96



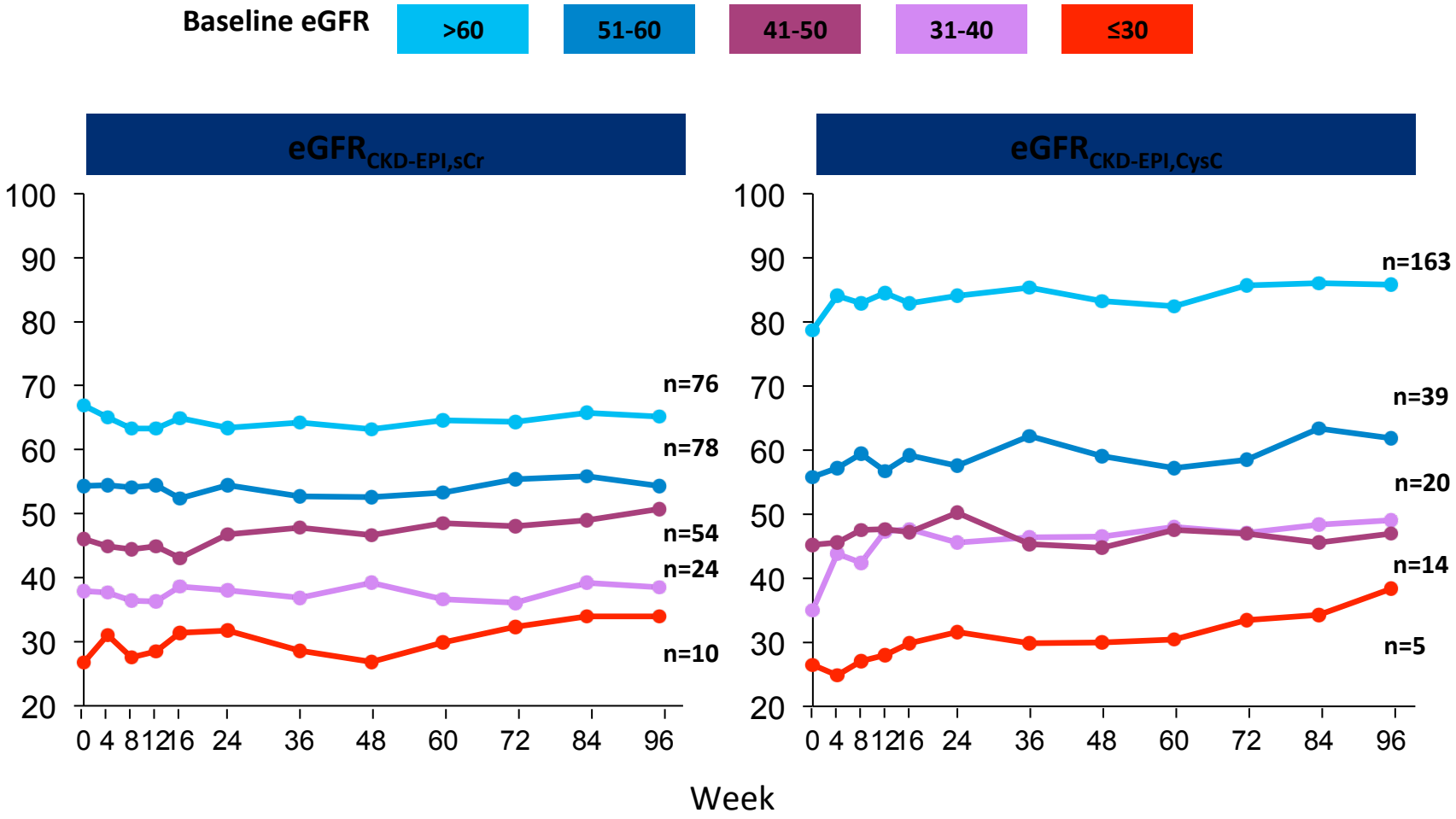
- **E/C/F/TAF maintained high rate of virological suppression through to Week 96**

*HIV-1 RNA<50 copies/mL; †HIV-1 RNA ≥50 copies/mL at Week 96 (n=2), discontinued due to lack of efficacy (n=2), took additional antiretroviral medications (n=1); ‡13 subjects discontinued due to adverse events; 10 subjects discontinued for other reasons (lost to follow-up, noncompliance, protocol violation) and last available HIV-1 RNA <50 copies/mL

F, et al. CROI 2016. Boston MA. #680; 2. Pozniak A, et al. CROI 2015. Seattle, WA. #795;
ta S, et al. ICAAC 2015. San Diego, CA. Oral; 4. Pozniak A, et al. JAIDS 2016. Publish Ahead of Print DOI:
97/Q AI.0000000000000908

tudy 112: Suppressed adults with renal impairment switched to E/C/F/TAF

Changes in eGFR by Baseline eGFR Strata through Week 96



One patient was excluded due to missing cysC data at baseline.

Summary of DDIs Between HCV and HIV Therapies

	SMV + SOF[1]	LDV/SOF[1]	DCV + SOF[1]	OBV/PTV/RTV + DSV[1]	EBR/GZR[1]	SOF/VEL[1]
ATV + RTV	X	≈	≈	√	X	≈
DRV + RTV	X	≈	√	≈[5]	X	≈
Tipranavir + RTV	X	X	X	X	X	X
EFV or ETR	X	√	≈	X	X	X
RPV	√	√	√	X	√	√
DTG or RAL	√	√	√	√	√	√
EVG + COBI	X	≈	√	X	X	≈
3TC/ABC	√	√	√[4]	√	√	√
TAF	√[2]	√[3]	√*	√*	√[2]	√
TDF	√	≈	√	√	√	≈

*No data.

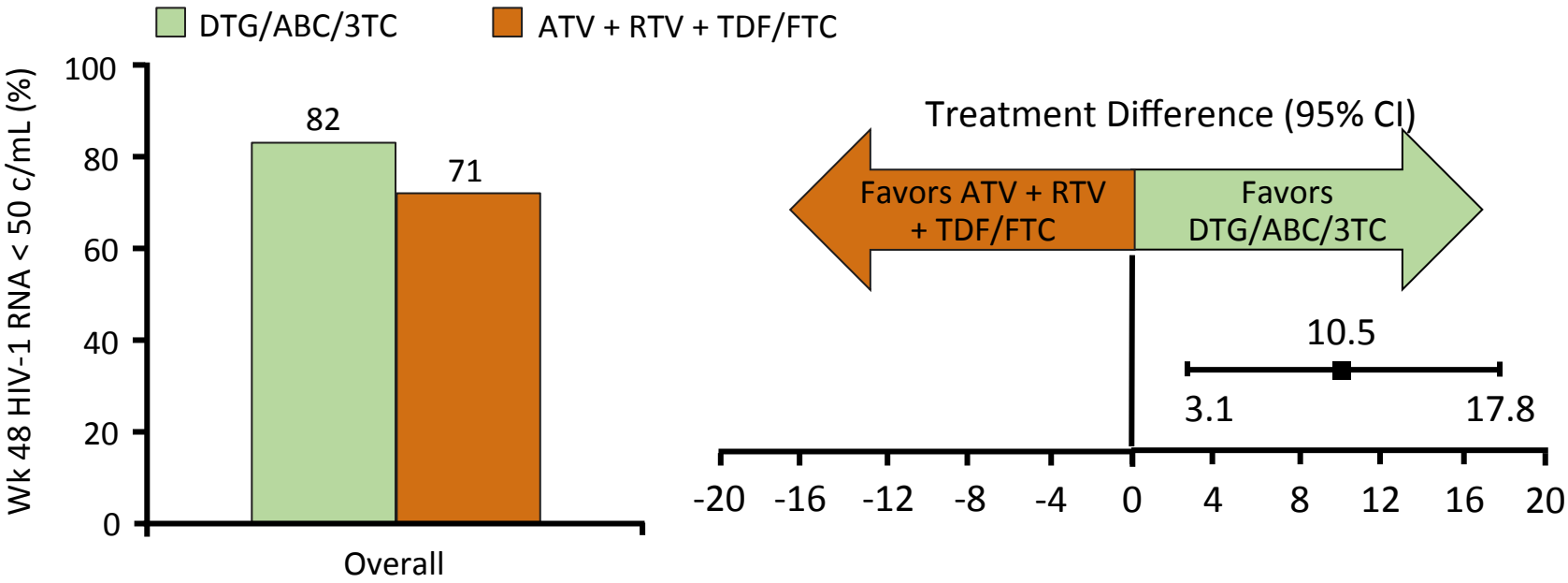
No clinically significant interaction expected

Potential interaction may require adjustment to dosage, timing of administration, or monitoring

Do not coadminister

1. AASLD/IDSA HCV Guidance. July 2016. 2. NY/NJ AETC. 2016. 3. Custodio J, et al. IDWeek 2015. Abstract 727. 4. Liverpool Drug Interactions Group. 5. Wyles D, et al. CROI 2016. Abstract 574.

ARIA: DTG/ABC/3TC Superior to ATV + RTV + TDF/FTC at Wk 48



- Superior efficacy driven by fewer discontinuations due to AEs and fewer virologic failures

Outcome, %	DTG/ABC/3TC (n = 248)	ATV+RTV+TDF/FTC (n = 247)
Discontinuations due to AEs	4	7
Virologic failure	6	14

, et al. Lancet HIV, 2017
, et al. AIDS 2016. Abstract THAB0205LB.

INSTI and therapeutic flexibility