Redefining Treatment Success!

Increasing role for switch?

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UCD DUBLIN

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HMRG
HIV Molecular Research Group

Scoil an Leighis agus Eolaíocht An Leighis UCD

Misericordia

Disclosures

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- Merck Sharpe and Dohme
- National Institutes of Health
- Wellcome Trust

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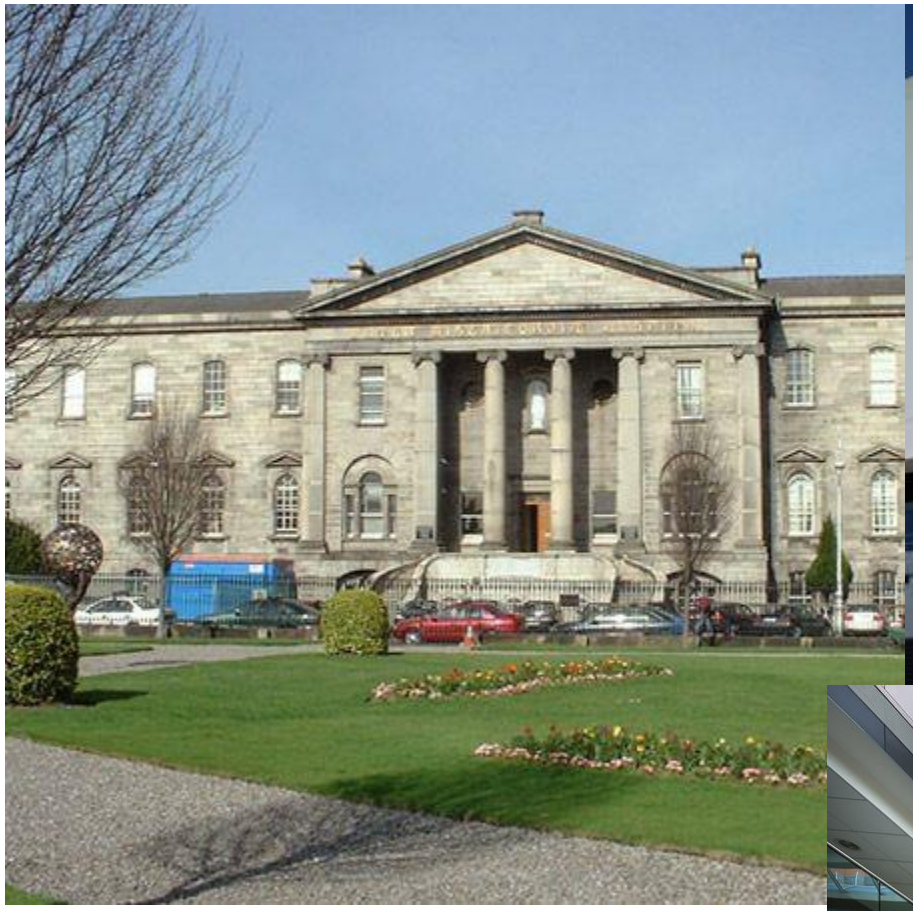

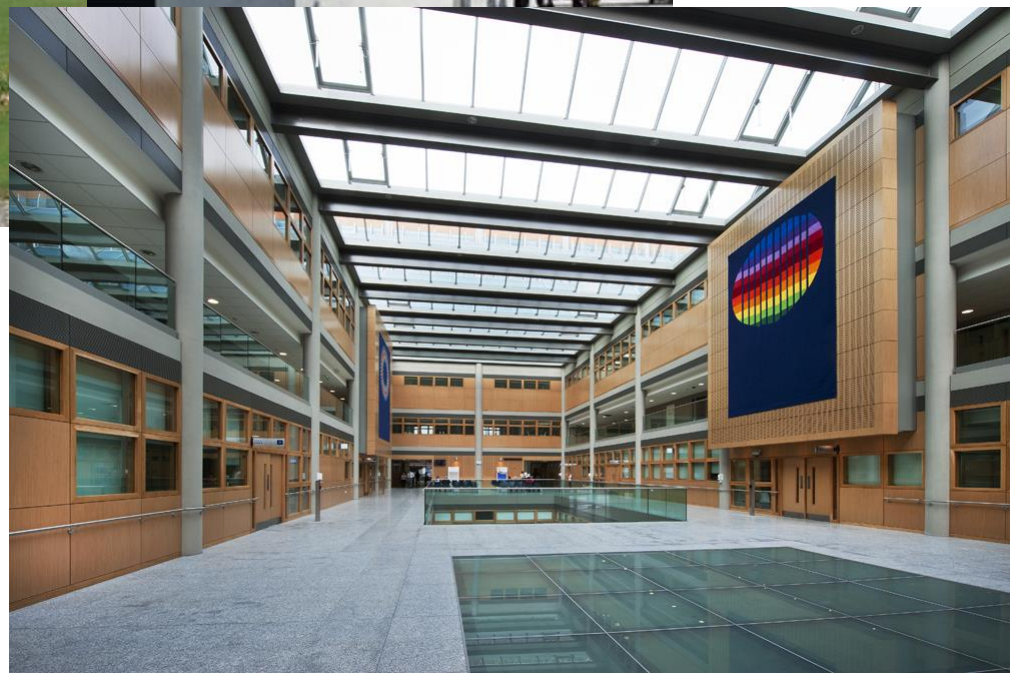

UCD DUBLIN

MMUH ID Cohort

Characteristics:		N=1012	
Sex:	Male	627	62
	Female	385	38
Age years Median (IQR)		42 (36-49)	
Ethnicity:	Caucasian	576	57
	African Origin	350	34
	South American	59	6
HIV Risk Factor:	Heterosexual	472	46.7
	IDU	182	18
	MSM	226	22.3
	Other	132	13.0
Year diagnosed:			
	<2000	130	12.8
	2000-2009	454	44.9
	≥2010	406	40.1

Tinago W. Personal Communication. Dec 2017.

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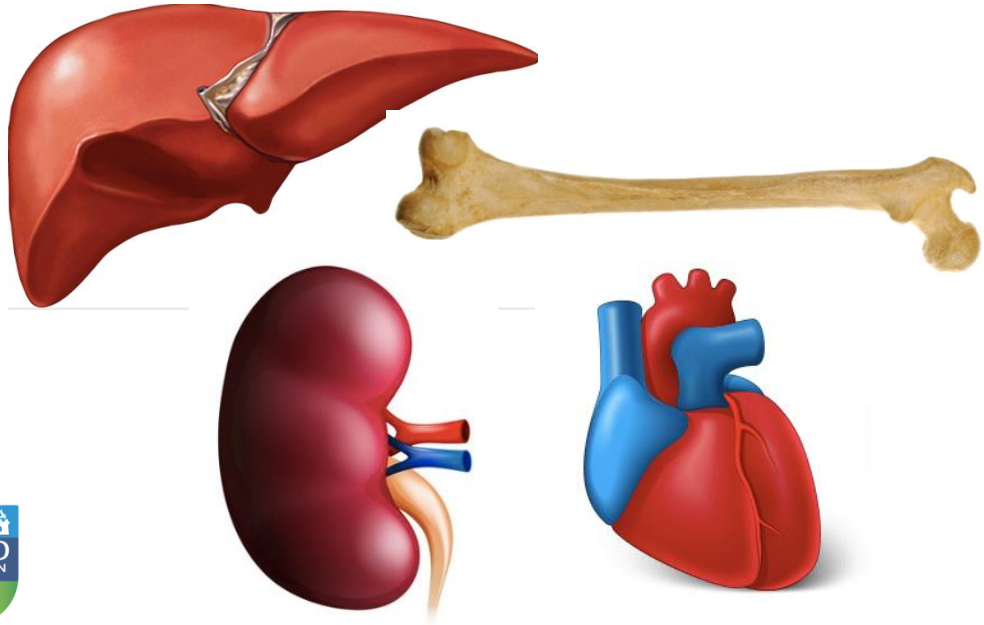
HIV Molecular Research Group

WE NEED SAFER DRUGS!!



UCD DUBLIN

Reasons to switch are increasing…..

- To decrease polypharmacy
- To simplify dosing (food effects) / monitoring
- To reduce potential for drug-drug interactions
- To manage / avoid adverse events
- Better safety in special circumstances - pregnancy
- To decrease cost (medications, labs, clinic visits)

Reasons *NOT* to switch?

- If it ain't broke, don't fix it
- 'Threshold' of toxicity / tolerability
- Can you be sure the switch will fix the problem?
- Potential to introduce new toxicities
- Will the switch be as effective?
- Virological failure (new resistance)
- Short-term gain, long-term costs – generics

Switching to InSTI as a ‘safer’ option

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Raltegravir

200mg

Elvitegravir

Stribild

Genvoya

Dolutegravir

Dolutegravir

Triumeq

* pictures do not represent actual size

UCD DUBLIN

Switching to InSTI as a ‘safer’ option

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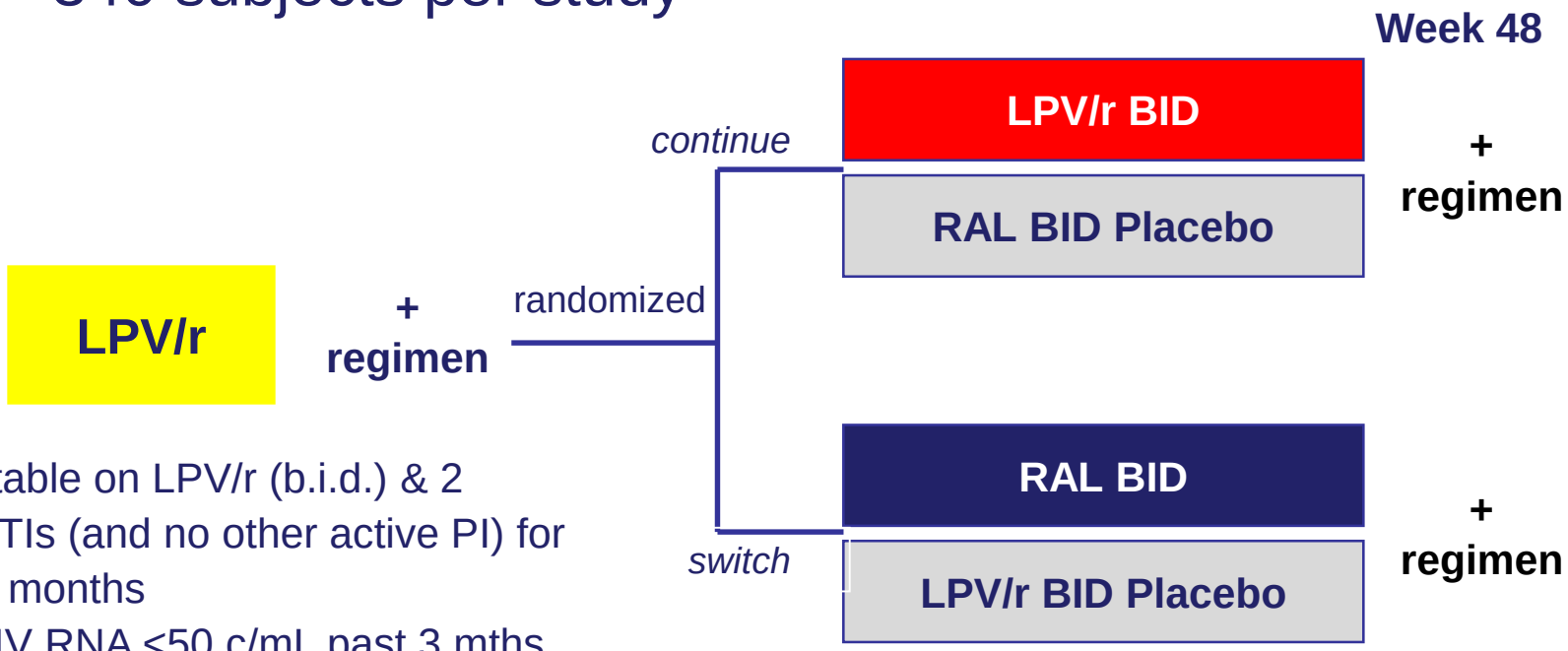
UCD DUBLIN

Switching to raltegravir

SWITCHMRK (032/033)

N= 340 subjects per study



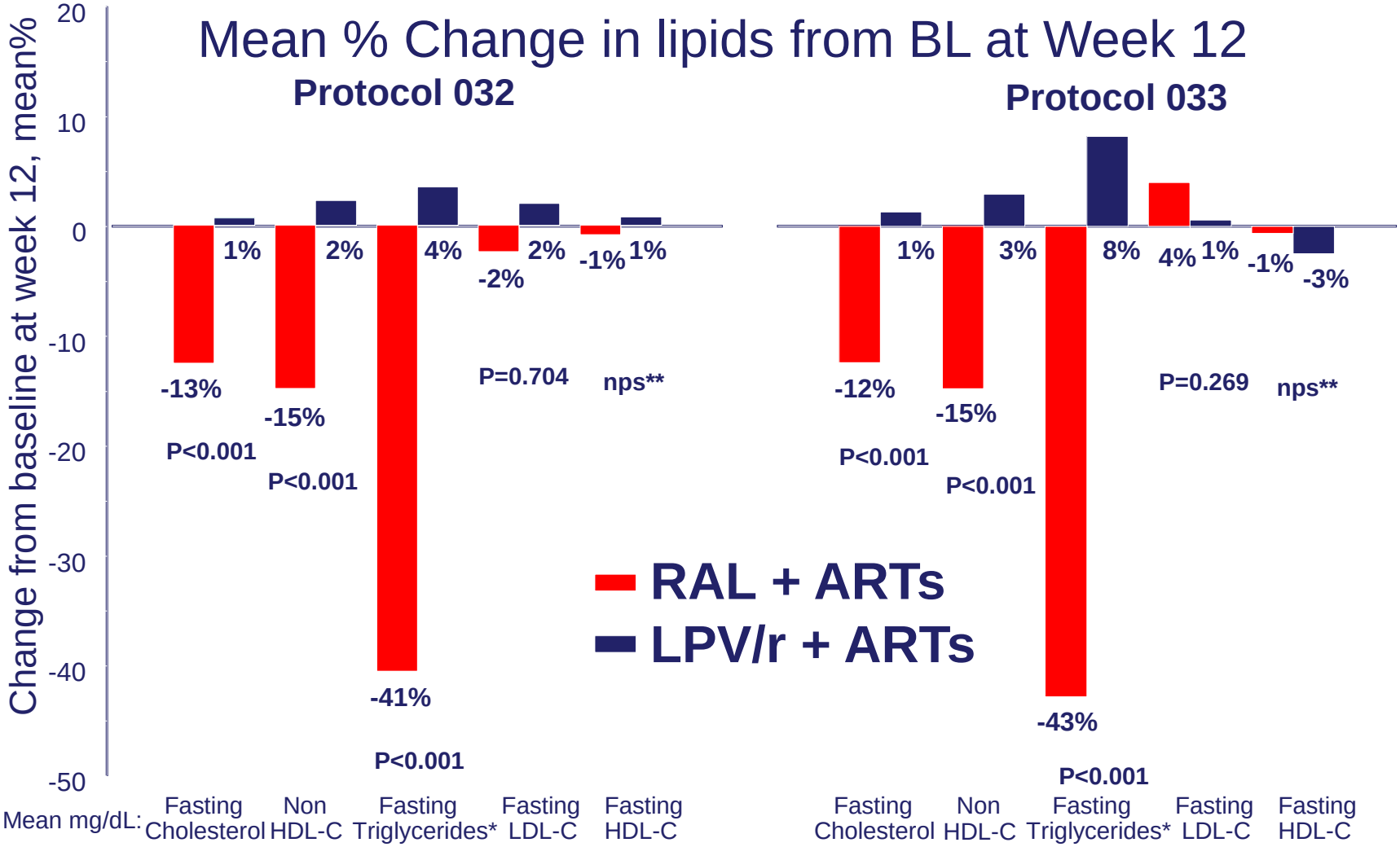
- Stable on LPV/r (b.i.d.) & 2 NRTIs (and no other active PI) for ≥ 3 months
- HIV RNA <50 c/mL past 3 mths
- Patients with prior virologic failure were not excluded
- No LLT past 12 weeks

<u>Primary endpoints:</u>
Week 12: Mean % change in lipids (Total-C, Triglycerides, non-HDL-C and LDL-C)
Week 24: Proportion with viral load <50 copies/mL by Non-completer = Failure (NC=F)

Eron J, et al. *Lancet*. 2010;375:396-407.

Switching to raltegravir

SWITCHMRK (032/033) study

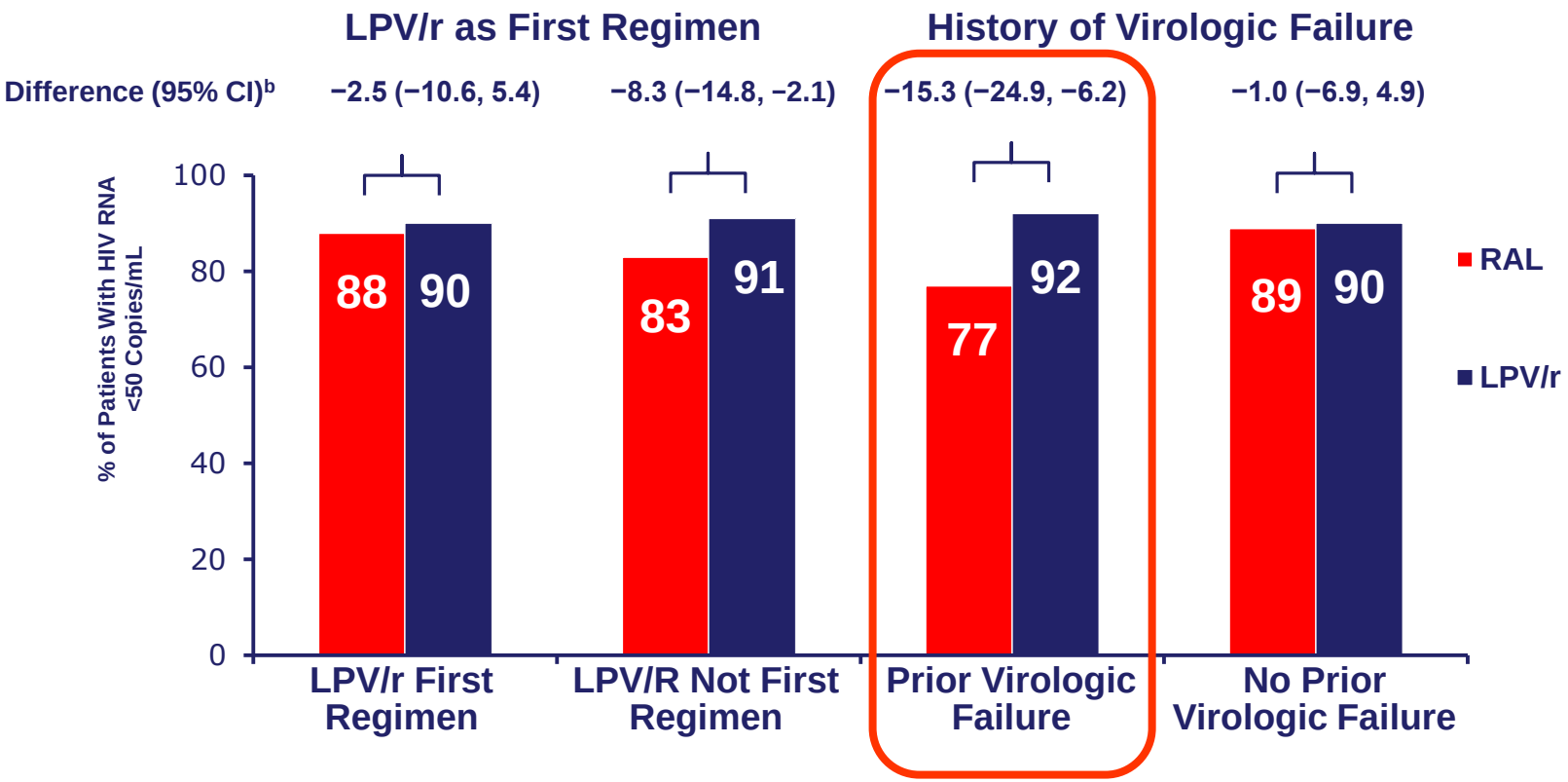


*Median Percent Change **Not prespecified for test

Eron J, et al. *Lancet*. 2010;375:396-407.

Switching to raltegravir

SWITCHMRK (032/033) study
Virological outcomes



CI = confidence interval; LPV/r = lopinavir/ritonavir; RAL = raltegravir. [a]All patients who did not complete the study were regarded as failures.

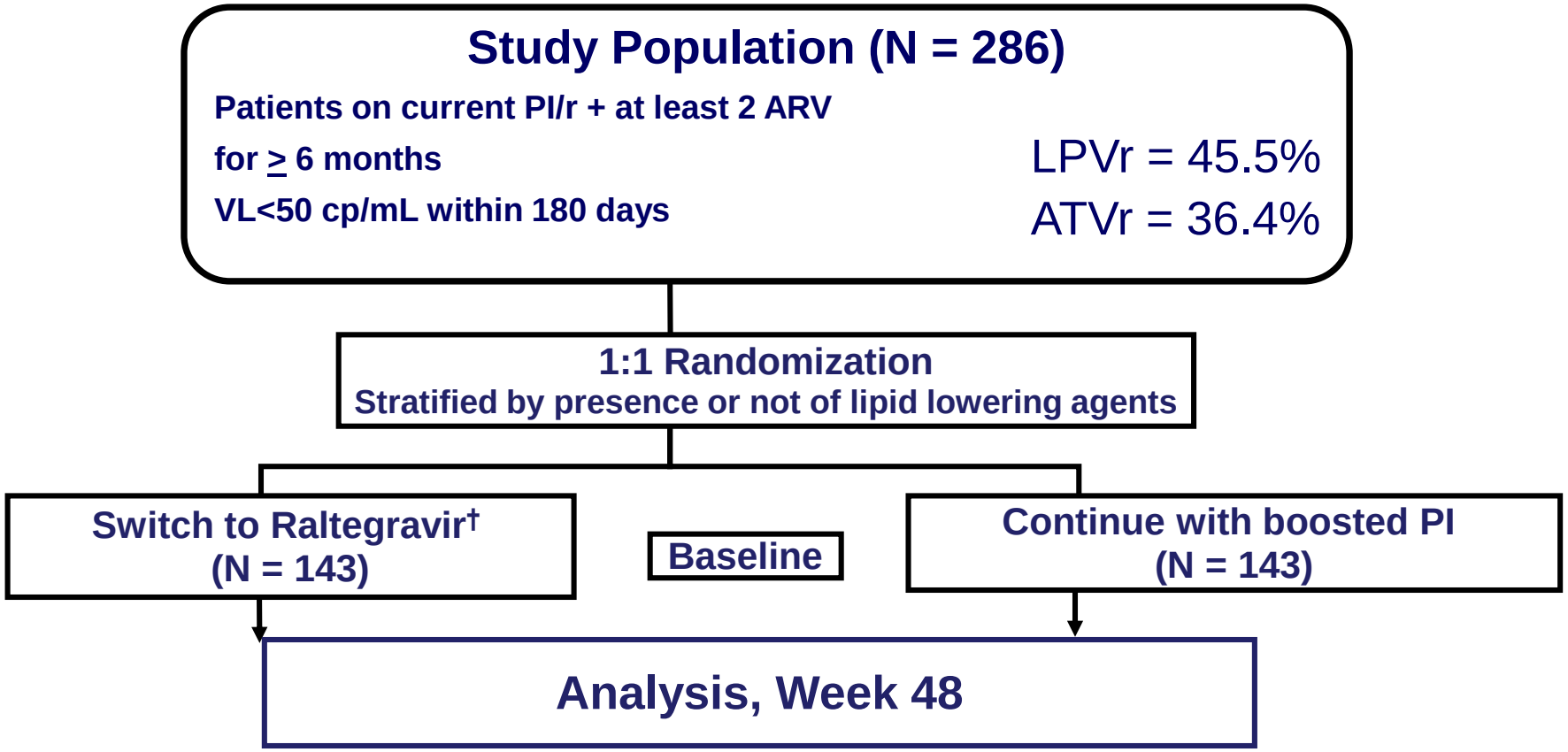
[b]Calculated by the method of Miettinen and Nurminen. cPlus existing baseline regimen.

Eron J, et al. *Lancet*. 2010;375:396-407.

Switching to raltegravir

SPIRAL study

Study design – open labeled RCT



*** Raltegravir 400mg BID (maintaining other antiretrovirals unchanged).**

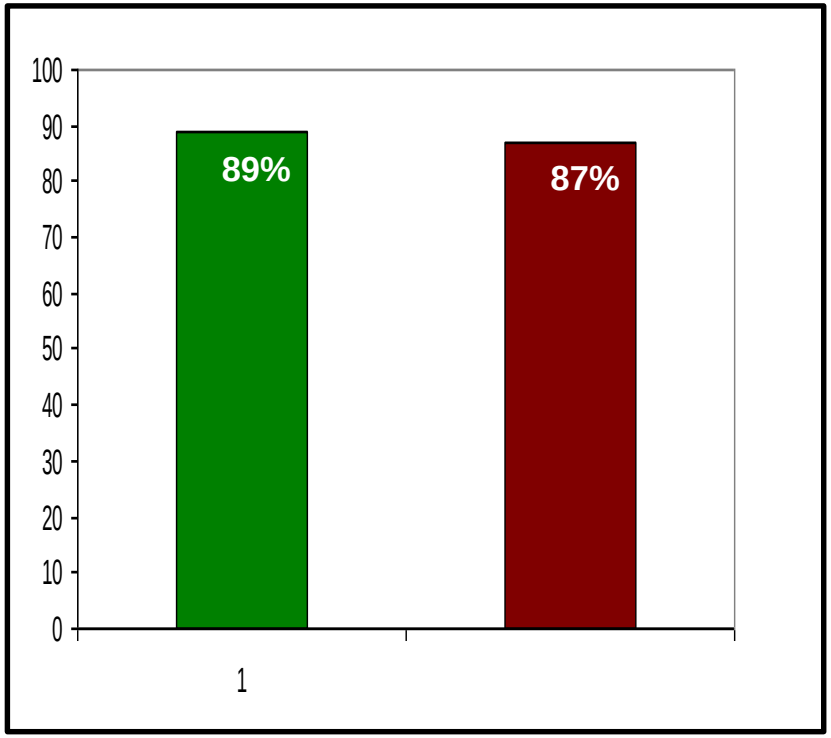
Martinez E et al. AIDS 2010Jul 17;24(11):1697-707

Switching to raltegravir

SPIRAL study
Virological outcomes[1]

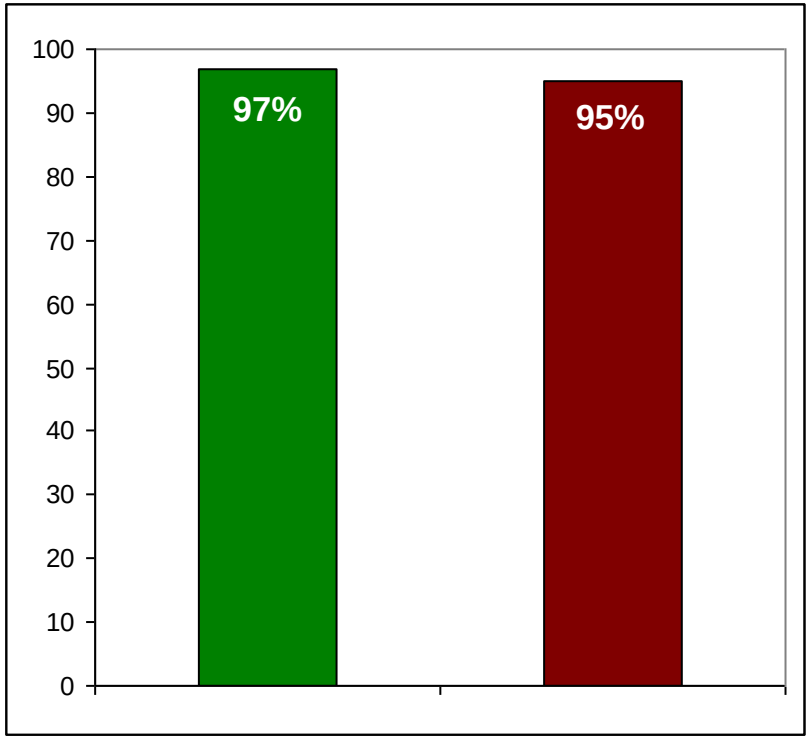
RALTEGRAVIR **PI/r**

Free of Treatment Failure (ITT, S=F)



Difference Estimate (95% CI) 2.6% (–5.2%, 10.6%)

Free of Virologic Failure (≥ 50 cp/mL) (OT)



Difference Estimate (95% CI) 1.8% (–3.5%, 7.5%)

Outcomes not influenced by previous virological failures[2]

1. Martinez E et al. AIDS 2010Jul 17;24(11):1697-707, 2. Blanco JL et al. Antivir Ther. 2015;20(5):487-92

Switching to raltegravir

Protocol 003
Double-blind, RCT

EFV QD vs RAL BID
96 week followup

83% RAL vs 84% EFV with HIVRNA<50c/ml @ wk96

TABLE 4. Summary of Adverse Events

	Raltegravir, 400 mg Twice a Day, (N = 160) n (%)	Efavirenz, 600 mg Every Day, (N = 38) n (%)
One or more clinical adverse events	146 (91.3)	35 (92.1)
Serious clinical adverse events	16 (10.0)	3 (7.9)
Discontinued due to clinical adverse event	2 (1.3)	1 (2.6)
Drug-related* clinical adverse events†	82 (51.3)	28 (73.7)
Diarrhea	11 (6.9)	4 (10.5)
Nausea	20 (12.5)	5 (13.2)
Vomiting	4 (2.5)	3 (7.9)
Flatulence	9 (5.6)	1 (2.6)
Dizziness	14 (8.8)	11 (28.9)
Headache	14 (8.8)	9 (23.7)
Abnormal dreams	10 (6.3)	7 (18.4)
Insomnia	13 (8.1)	4 (10.5)
Nightmares	0 (0.0)	4 (10.5)
Fatigue	8 (5.0)	2 (5.3)
Malaise	2 (1.3)	3 (7.9)
Anxiety	2 (1.3)	2 (5.3)
Lethargy	2 (1.3)	2 (5.3)
Disturbance in attention	1 (0.6)	2 (5.3)
One or more laboratory adverse events	38 (23.8)	11 (28.9)
Discontinued due to laboratory adverse event	1 (0.6)	0 (0.0)
Drug-related* laboratory adverse events†	19 (11.9)	3 (7.9)
Aspartate aminotransferase increased	7 (4.4)	2 (5.3)
Alanine aminotransferase increased	6 (3.8)	2 (5.3)

Markowitz M et al. JAIDS 2009; 52;:350-356

Switching to InSTI as a ‘safer’ option

Raltegravir

200mg

Elvitegravir

Stribid

Genvoya

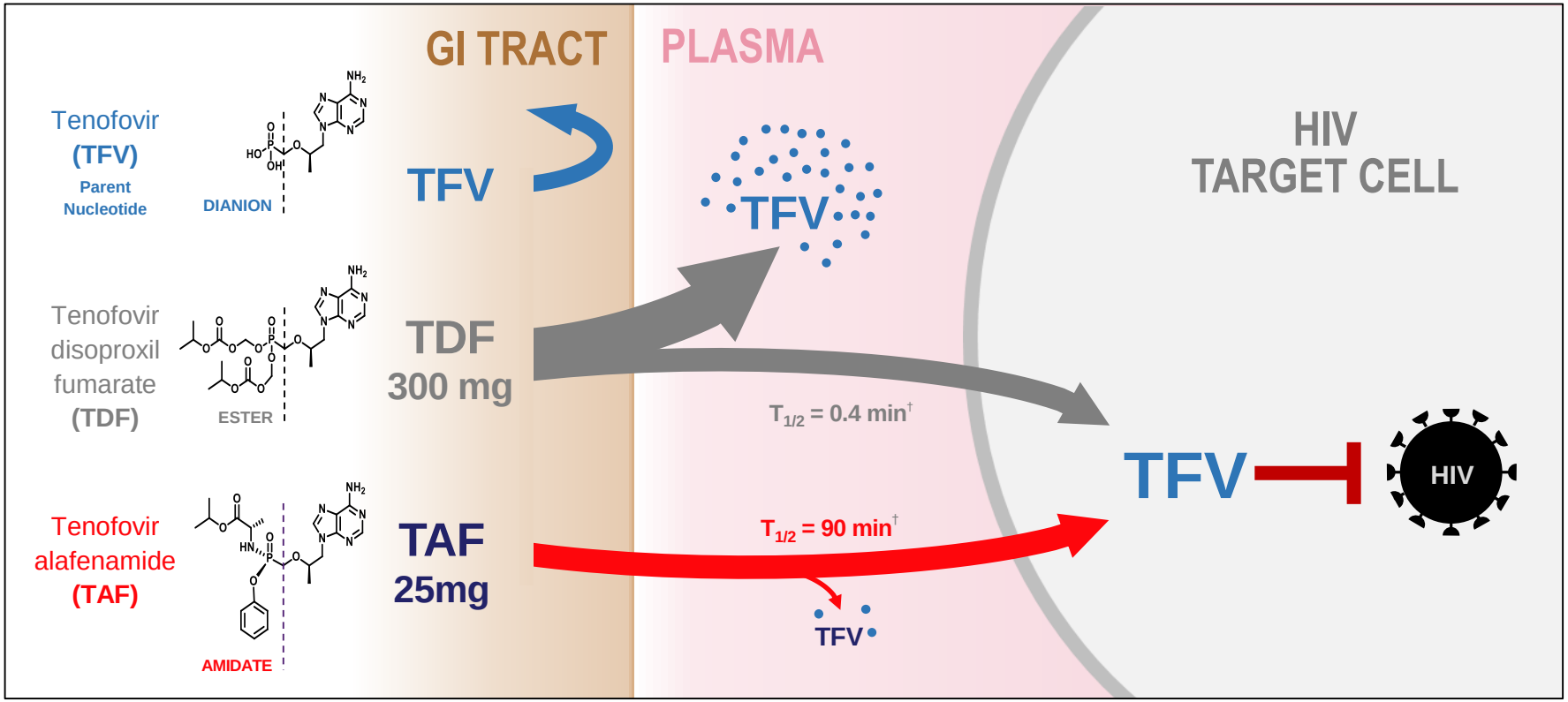
Dolutegravir

Dolutegravir

Triumeq

Tenofovir Alafenamide (TAF)

Tenofovir Alafenamide (TAF): Novel Prodrug of Tenofovir



91% lower TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV

† $T_{1/2}$ based on *in-vitro* plasma data

1. Lee W, et al. *Antimicr Agents Chemo* 2005;49(5):1898–906; 2. Birkus G, et al. *Antimicr Agents Chemo* 2007;51(2):543–50; 3. Babusis D, et al. *Mol Pharm* 2013;10(2):459–66;
4. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449–5; 5. Sax P, et al. *JAIDS* 2014;67(1):52–8; 6. Sax P, et al. Lancet 2015 [Epub ahead of print]

Gupta S, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0103

Switching to E/C/F/TAF (Genvoya)

Study 109: virologically suppressed adults switching from TDF-based regimen to Genvoya

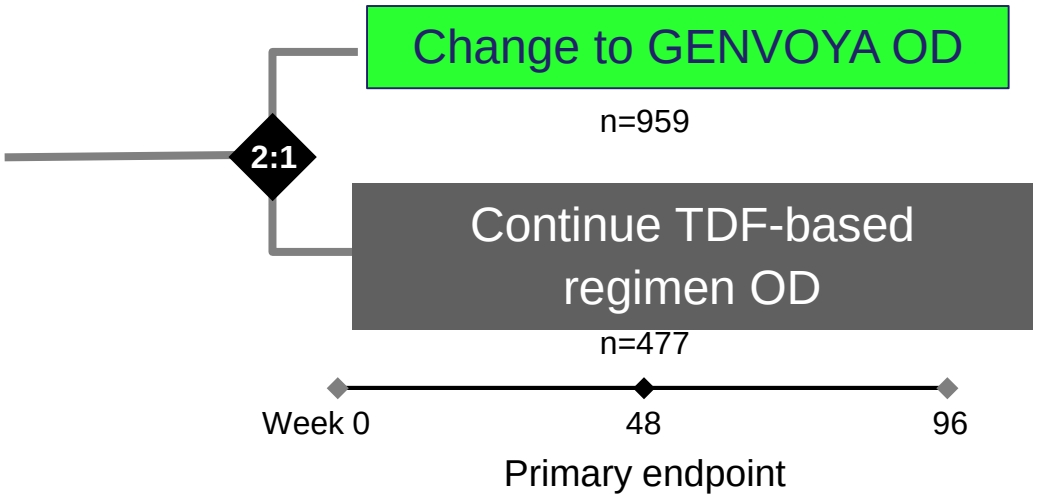
96 week, randomised, open-label, active-controlled Phase III study

Inclusion criteria:

- HIV-suppressed adults on ART (E/C/F/TDF, EFV/FTC/TDF, or boosted ATV + FTC/TDF)
- All patients were virologically suppressed* and had been on a TDF-based regimen for ≥96 weeks
- CrCl >50 mL/min

Primary endpoint:

- Proportion with HIV-1 RNA <50 copies/mL at Week 48



E, elvitegravir; C, cobisistat; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; EFV, efavirenz; ATV, atazanavir; OD, once daily; CrCl, creatinine clearance

* Virological suppression: plasma HIV-1 RNA <50 copies/mL

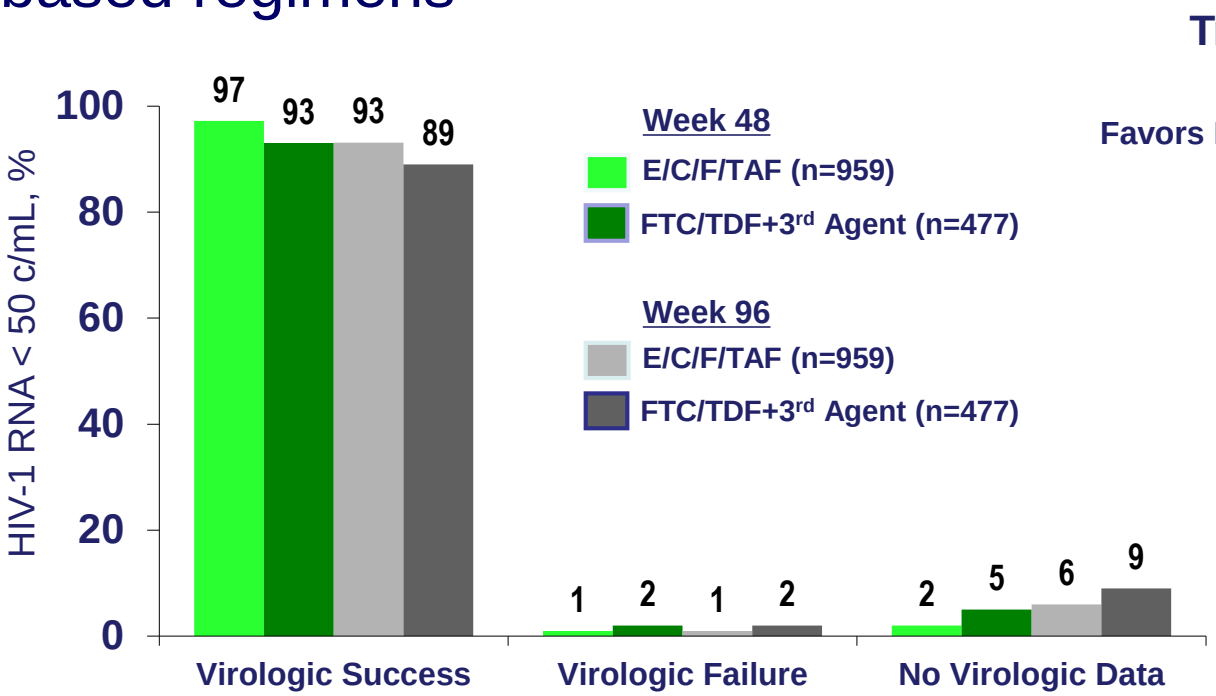
1. Mills A, et al. IAS 2015. Vancouver, Canada. Oral TUAB0102

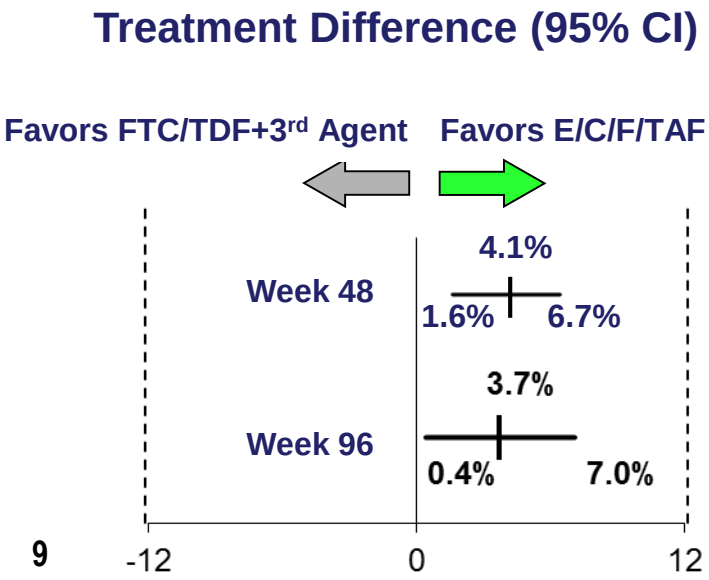
Switching to Genvoya

Study 109

Primary endpoint - switch to Genvoya non-inferior at week 48

Better virological success rates versus remaining on TDF-based regimens





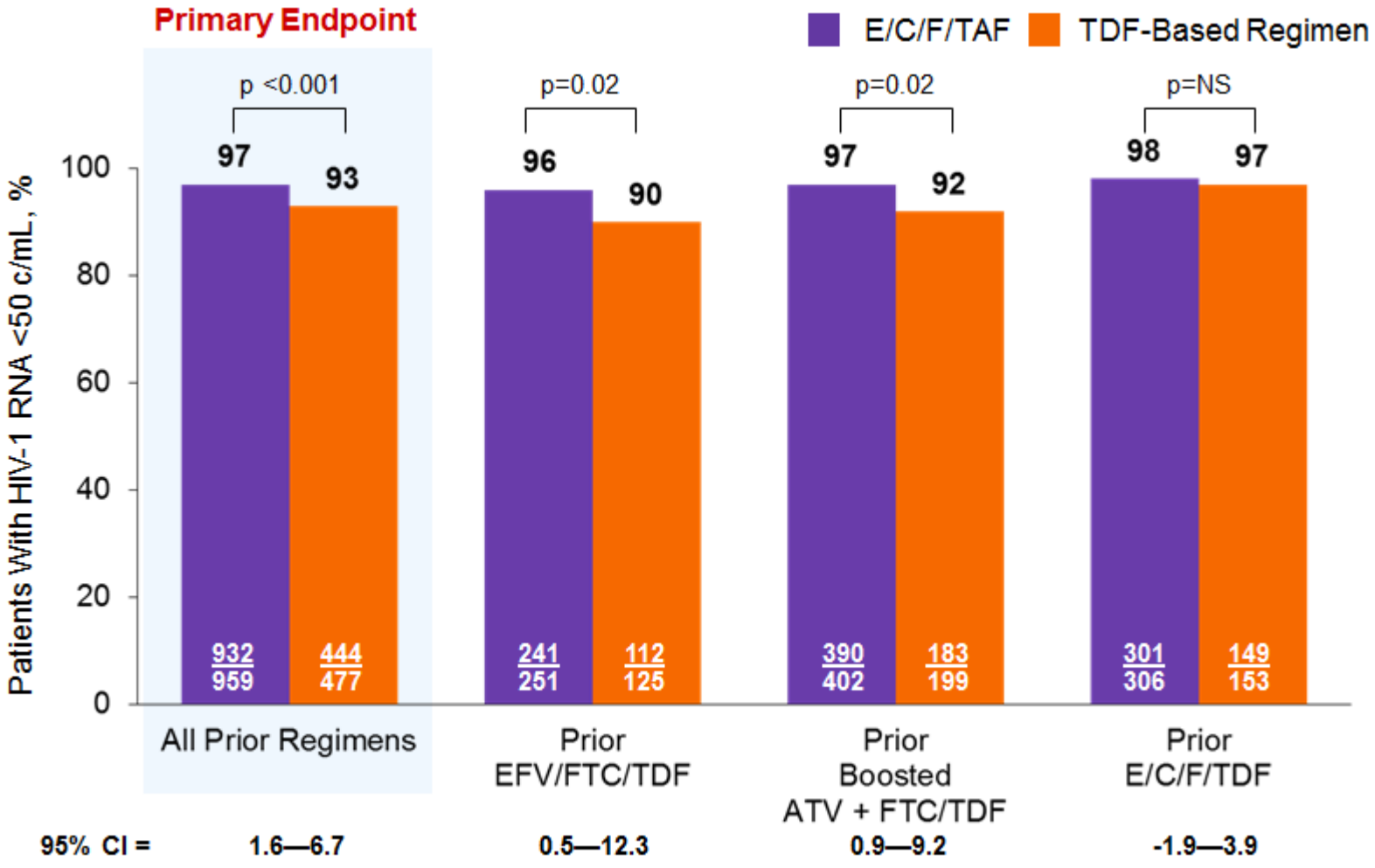
Switching to E/C/F/TAF was statistically superior in efficacy compared to continuing FTC/TDF + 3rd agent through Week 96

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

Switching to Genvoya

Study 109

Virological response based on switch regimen

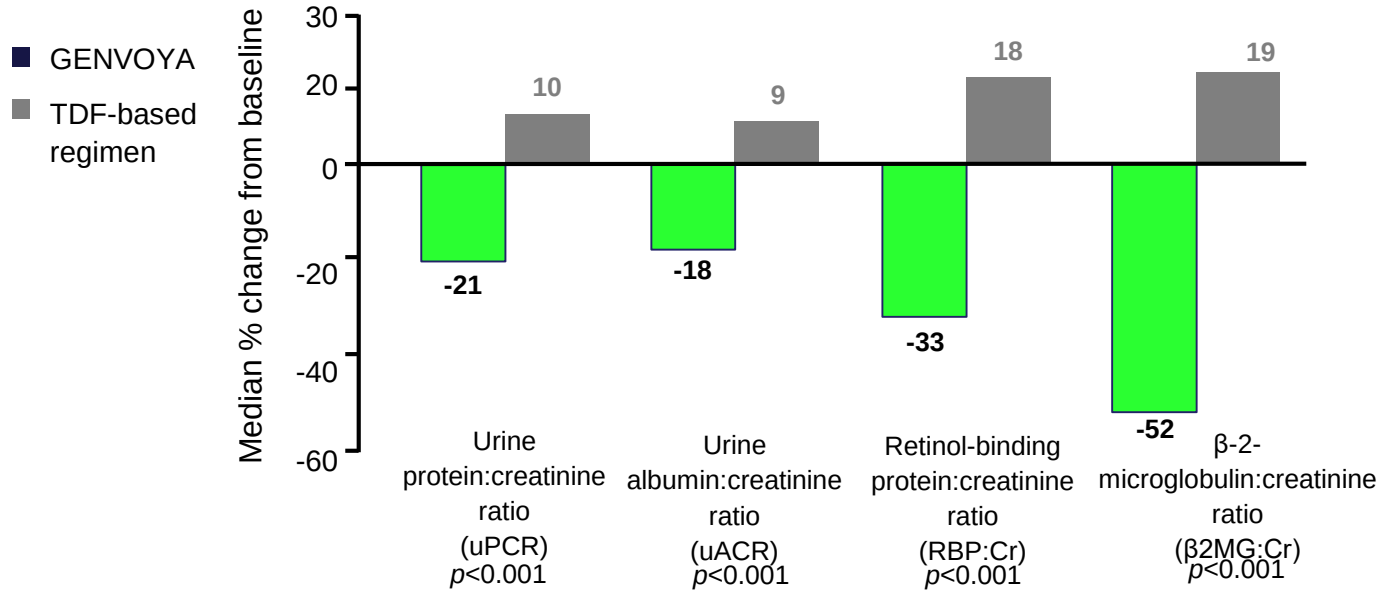


Mills A, et al. Lancet Infect Dis 2016; 16:43-52

Switching to Genvoya

Study 109

Statistically significantly lower quantitative proteinuria at week 48 versus remaining on TDF-containing regimens (all P<0.001)[1]

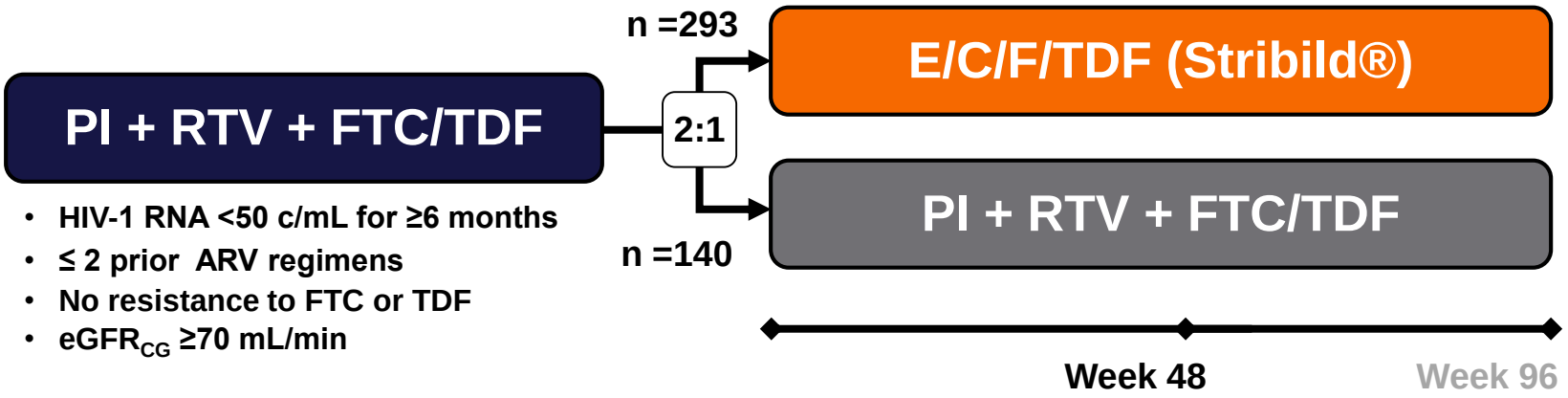


CrCl, creatinine clearance; TDF, tenofovir disoproxil fumarate

1. Mills A, et al. IAS 2015. Vancouver, Canada. Oral TUAB0102

Switching PI to Elvitegravir/c

STRATEGY PI – multicentre, randomised, open-label, 96 week study



- HIV-1 RNA <50 c/mL for ≥6 months
- ≤ 2 prior ARV regimens
- No resistance to FTC or TDF
- $eGFR_{CG}$ ≥70 mL/min

Primary endpoint: HIV-1 RNA <50 c/mL at Week 48 by Snapshot (noninferiority margin of 12%). If noninferiority is established, then superiority will be tested.

Secondary endpoint: Safety and tolerability at Week 48 & 96

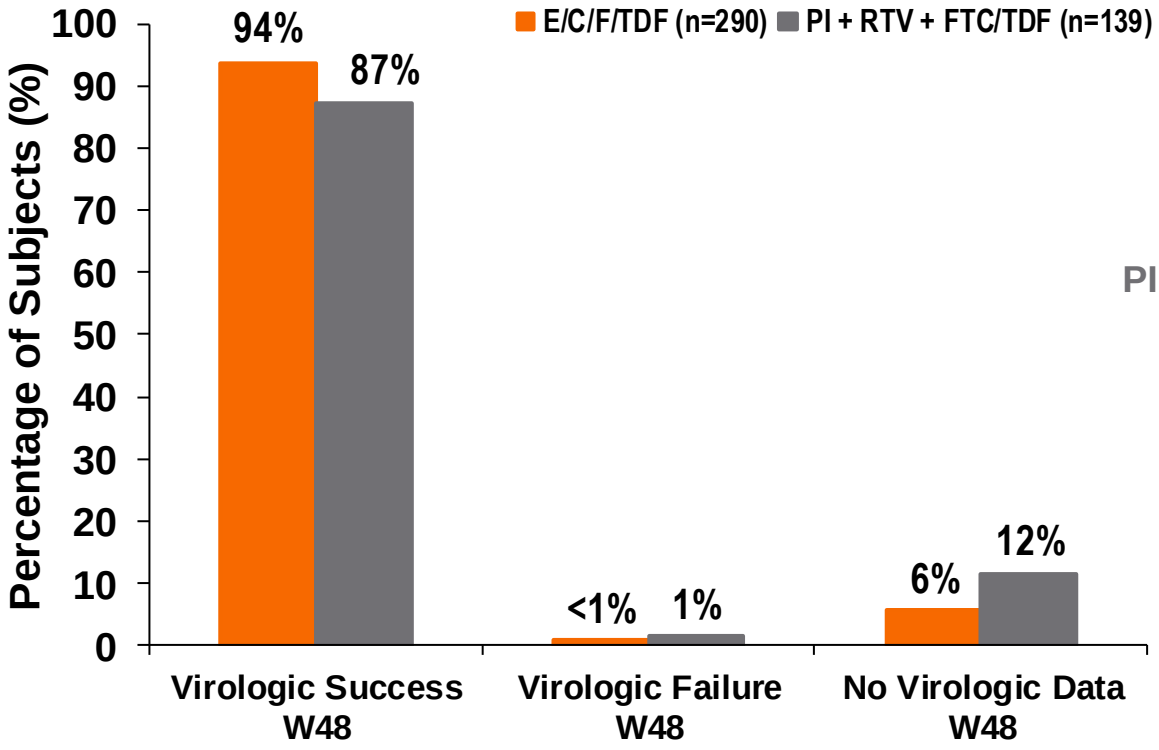
Other endpoints: Patient reported outcomes*

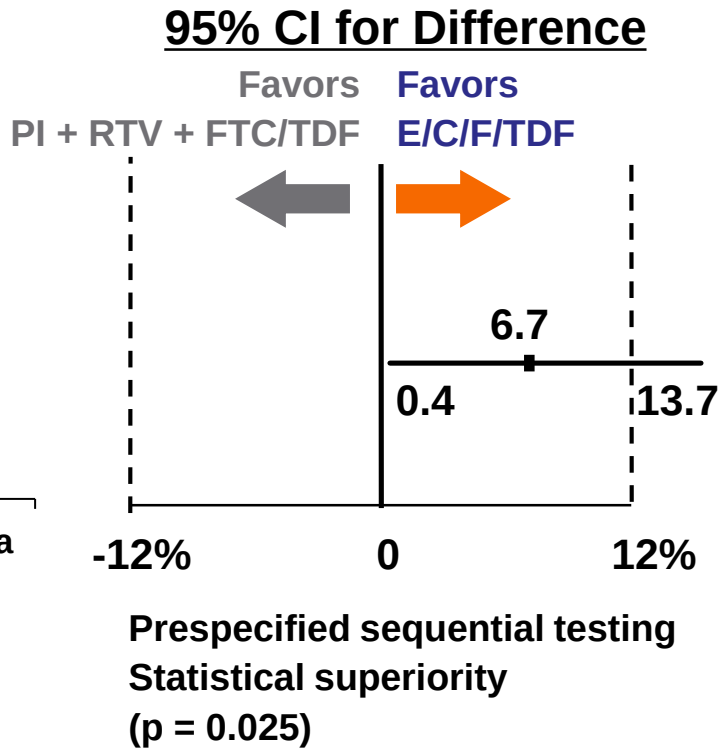
*HIV Symptom Index and HIV Treatment Satisfaction questionnaires
E/C/F/TDF: single-tablet regimen elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, tenofovir DF 300mg; Stribild®
PI + RTV + FTC/TDF: ritonavir-boosted protease inhibitor and emtricitabine/tenofovir DF
Study GS-US-236-0115 is registered with ClinicalTrials.gov, number NCT01475838.

Arribas J et al. CROI 2014. Abstract 551LB

Switching PI to Elvitegravir/c

STRATEGY PI – primary endpoint: HIVRNA <50 cps/ml





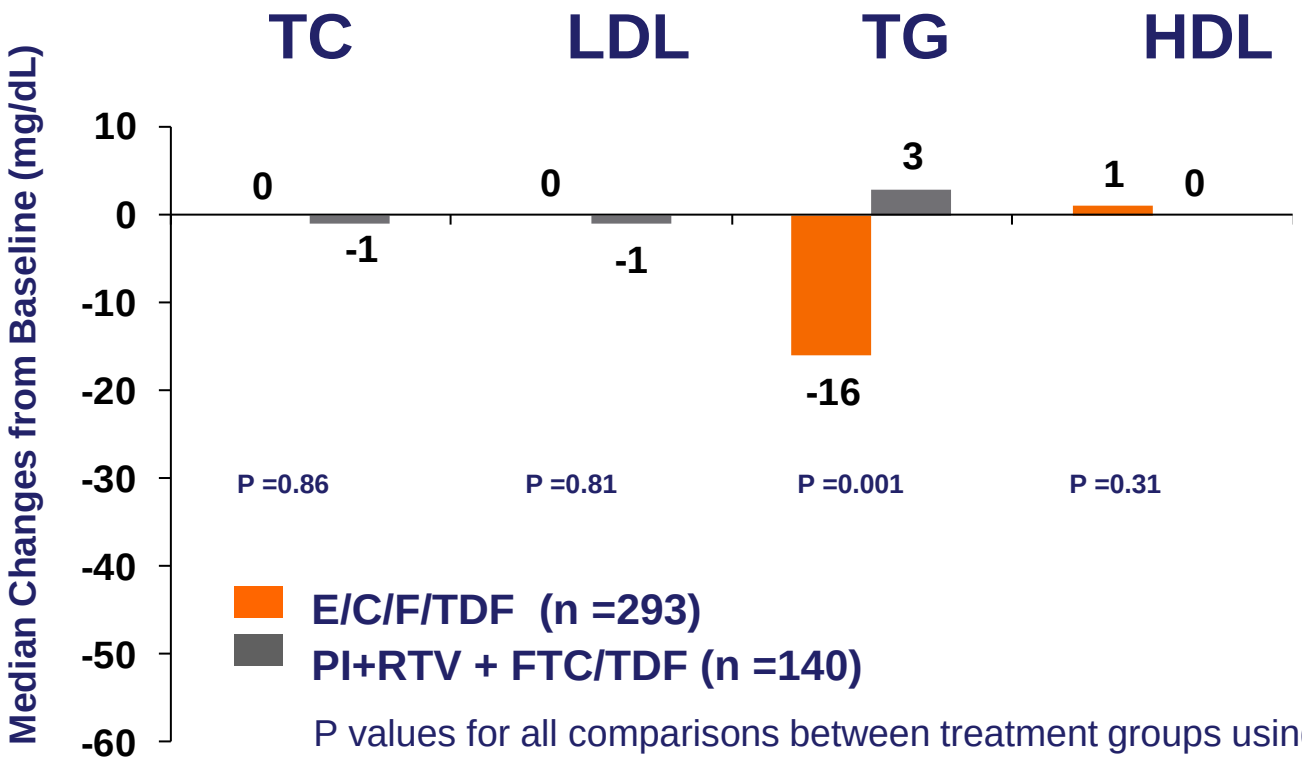
Prespecified sequential testing
Statistical superiority
(p = 0.025)

Full analysis set excluded subjects with protocol-prohibited mutations on historical genotype and those not on PI at randomization.

Arribas J et al. CROI 2014. Abstract 551LB

Switching PI to Elvitegravir/c

STRATEGY PI – change in fasting lipids



P values for all comparisons between treatment groups using ANOVA or Wilcoxon Rank Sum were not significant except for TG (p <0.001)

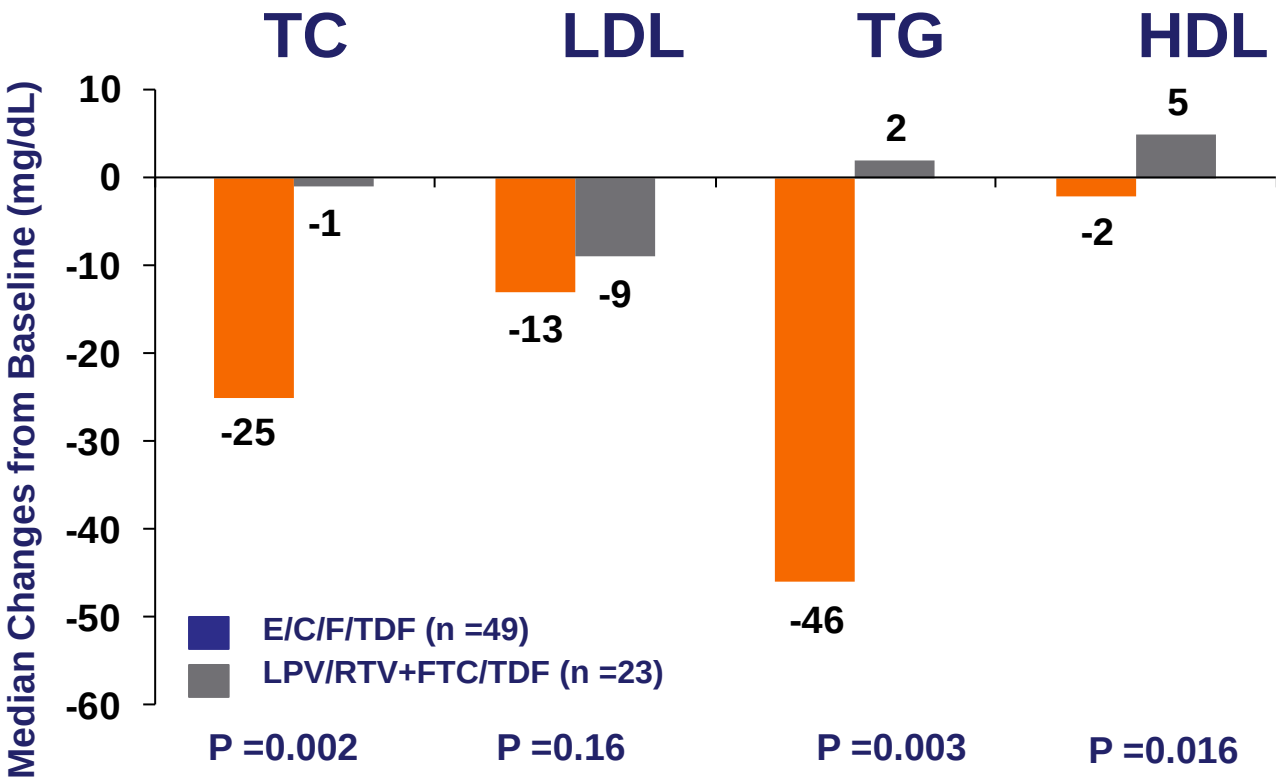
Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

Decreases from baseline in triglycerides at Week 48 after switching to E/C/F/TDF

1. Mills A, et al. IAS 2015. Vancouver, Canada. Oral TUAB0102

Switching PI to Elvitegravir/c

STRATEGY PI – change in fasting lipids with switch from LPVr



P values for all comparisons between treatment groups using Wilcoxon Rank Sum test

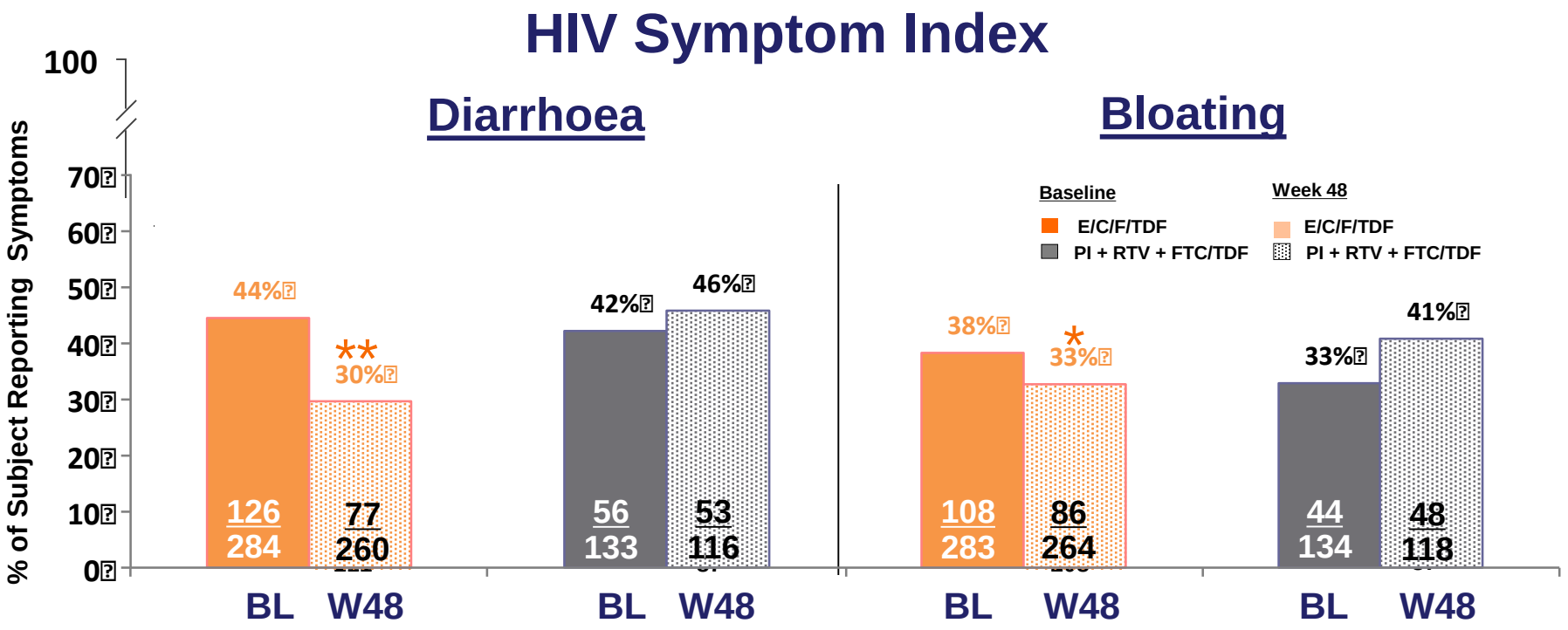
Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

Decreases from baseline in TC, TGs, and HDL at Week 48 after switching from LPV/RTV to E/C/F/TDF

1. Mills A, et al. IAS 2015. Vancouver, Canada. Oral TUAB0102

Switching PI to Elvitegravir/c

STRATEGY PI – patient reported outcomes



- Subjects who switched to E/C/F/TDF from PI + RTV + FTC/TDF had
  - Lower rates of diarrhea and bloating at Week 48 compared to baseline
  - Higher treatment satisfaction scores at Week 24 (mean: 23 vs. 15, p <0.001)^

*P <0.04 & **P <0.001 (comparison with baseline within each treatment group). Decreases noted at week 4 & sustained to week 48.
P <0.001, diarrhea & P=0.019, bloating (comparison of changes from baseline at week 48 between treatment group).
^ HIV Treatment Satisfaction questionnaire, score range: -30 to 30

Arribas J et al. CROI 2014. Abstract 551LB

Use of Genvoya in renal dysfunction

Study 112 - phase III, 96-week, single-arm, open-label study of virologically suppressed adults with mild to moderate renal dysfunction switching to GENVOYA[1]

Inclusion criteria:

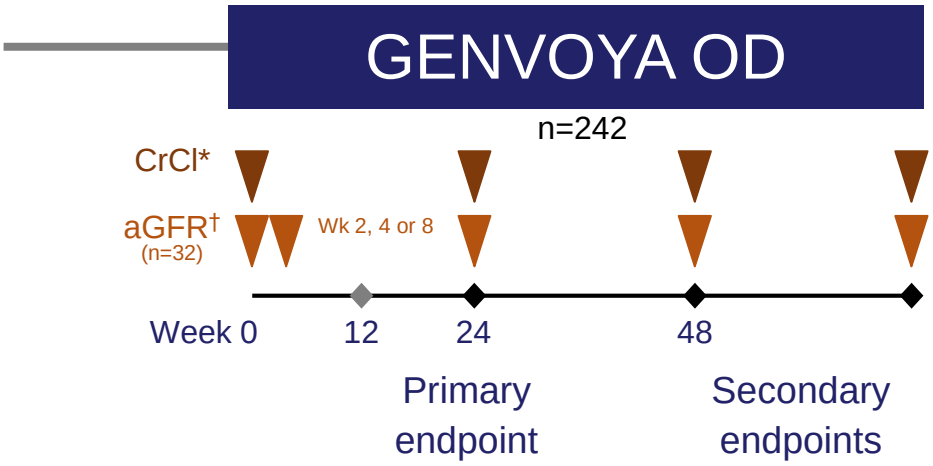
– HIV-suppressed adults with renal impairment (CrCl 30–69 mL/min)

– HIV-1 RNA <50 copies/mL for ≥6 months

– CD4 ≥50 cells/mm^3

Primary endpoint:

– Change from baseline in CrCl at Week 24**



*Creatinine clearance (CrCl) measured using the Cockcroft-Gault formula in all patients

†Actual GFR measured using iohexol plasma clearance in a subset of patients at 3 time points: baseline; Week 2, 4 or 8; and Week 24

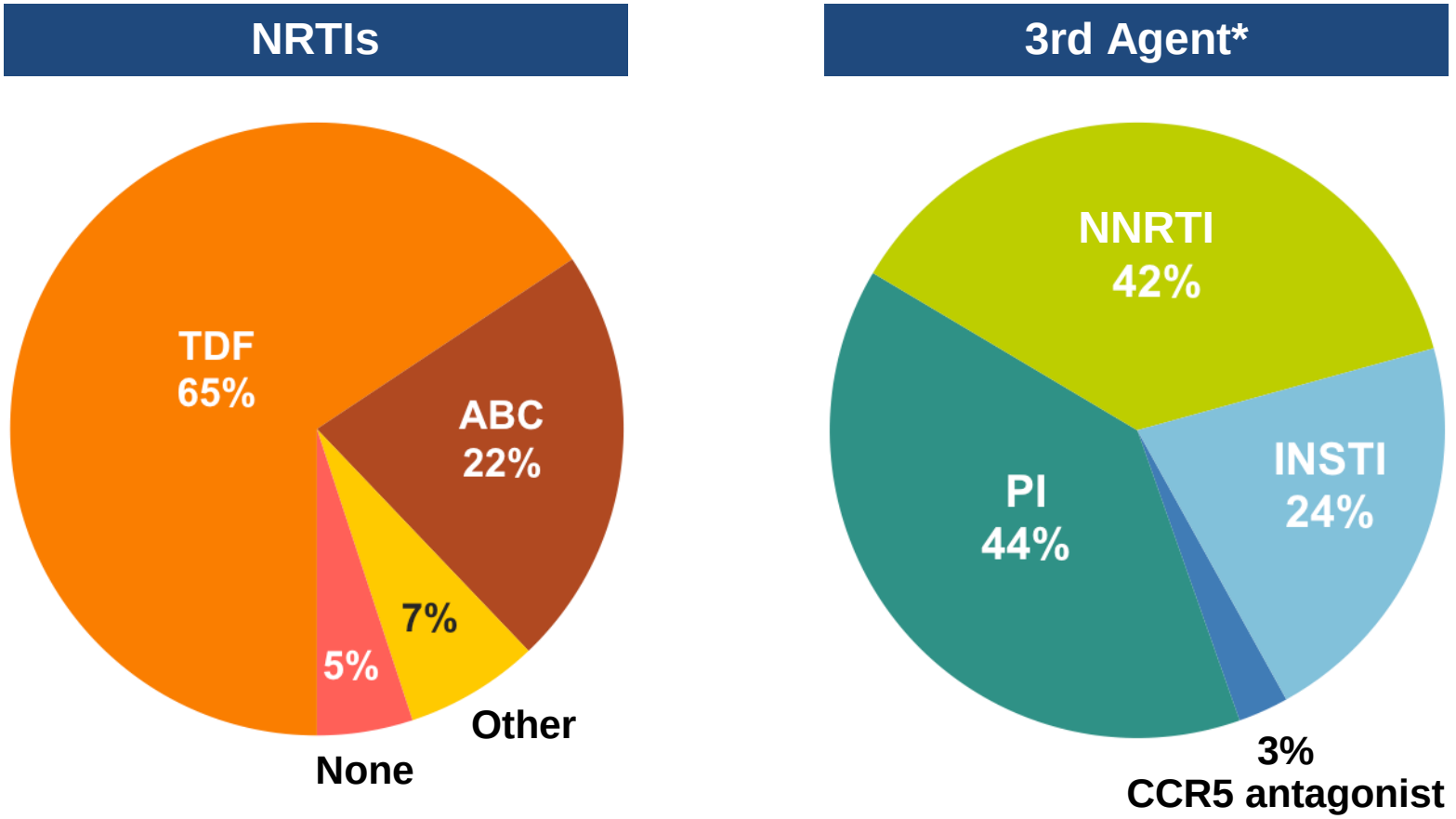
**Median (Q1, Q3) change in CrCl from baseline to Week 24 was -0.4 (-4.8, 4.5) mL/min

TDF, tenofovir disoproxil fumarate; OD, once daily; CrCl, creatinine clearance; aGFR, actual glomerular filtration rate

1. Pozniak A, et al. CROI 2015. Seattle, WA, USA. Poster 795

Use of Genvoya in renal dysfunction

Antiretroviral Treatment Prior to Switching to E/C/F/TAF

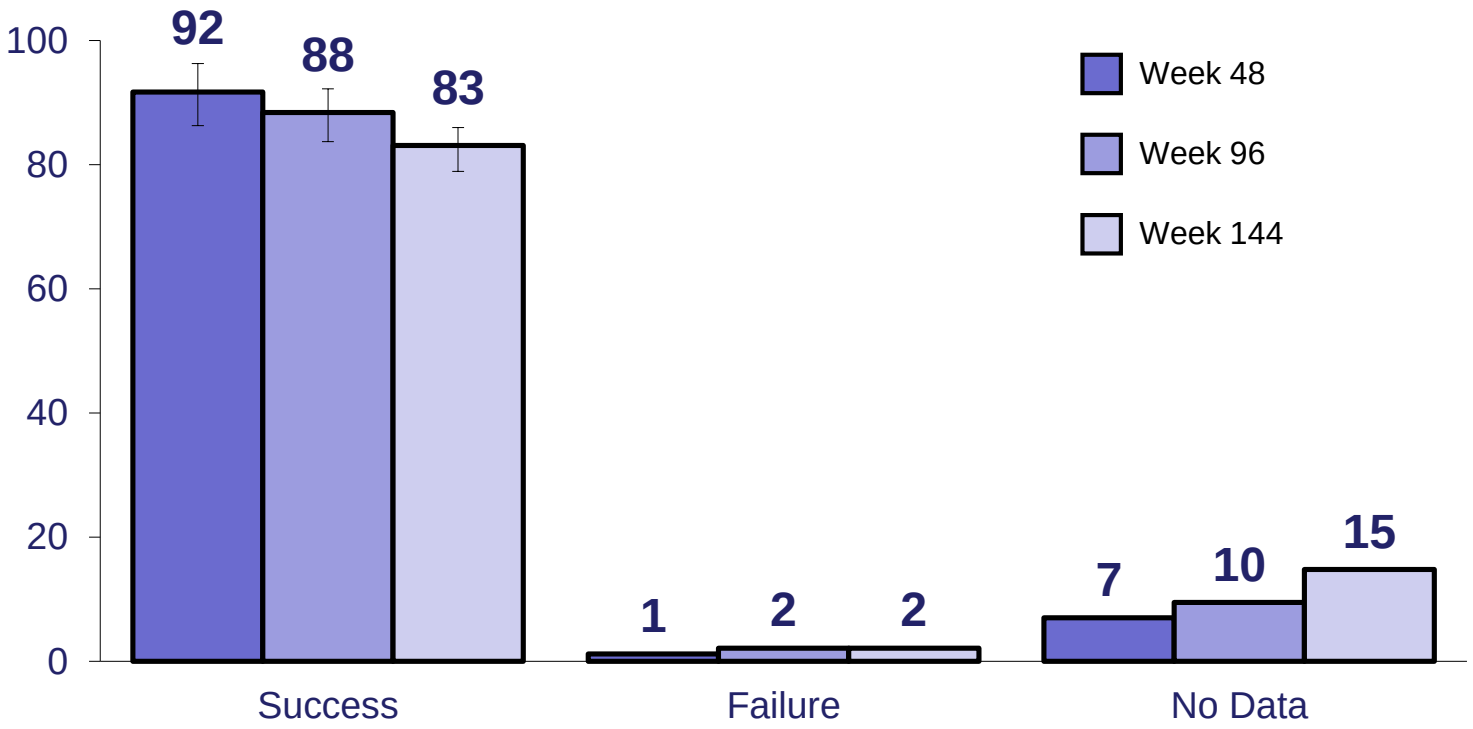


- *Some regimens included >1 3rd agent; therefore, total >100%. ABC, abacavir; CCR5, C-C chemokine receptor type 5; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

Post F et al. CROI 2016. Abstract #680.

Use of Genvoya in renal dysfunction

Primary endpoint change from baseline in CrCl at week 24
Genvoya maintains high rates of virological suppression at week 48, 96 & 144



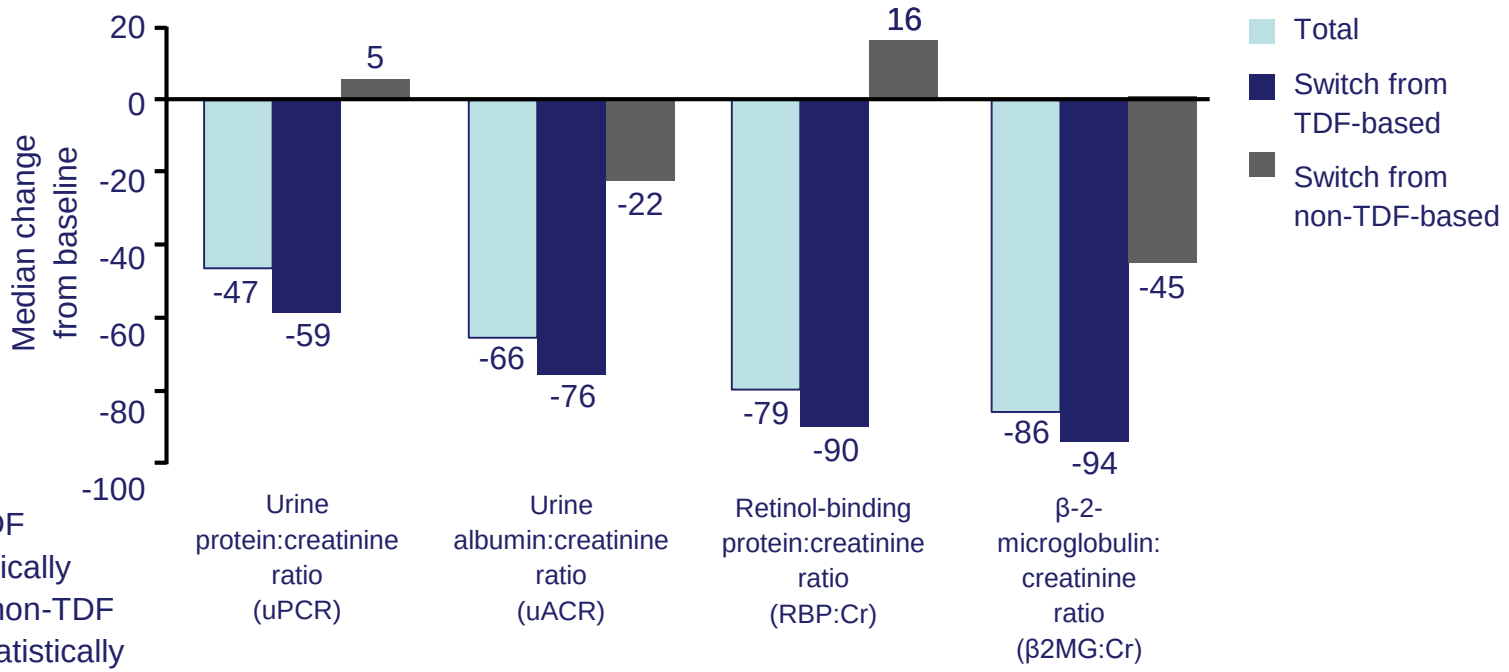
Discontinued drug due to AE or death 11 (5%) (2 treatment-emergent deaths were 71 yr old white male cardiac arrest and 73 yr old black male cardiopulmonary arrest); none of the deaths were study drug related per PI.) Discontinued drug due to other reasons and last available RNA was <40 19, (8%) (Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.)Missing data during study window: 5 (2%)

Pozniak A, et al. JAIDS 2016;71(5):530-7
Post F et al. JAIDS 201 Podzamzcer D, et al. IAS 2017 MOPEB02886

Use of Genvoya in renal dysfunction

Statistically significant improvements in markers of renal tubular function at week 48

Improvements most notable in those switching from TDF-based ART



All total and TDF changes statistically significant; all non-TDF changes not statistically significant

* at 48 weeks in Study 112

CrCl, creatinine clearance; TDF, tenofovir disoproxil fumarate

1. Gupta SK, et al. IAS 2015. Vancouver, Canada. Oral TUAB0103

Investigating the effect of antiretroviral switch to tenofovir alafenamide on lipid profiles in people living with HIV within the UCD ID Cohort

A. Lacey[1], W. Tinago[1], E. Alvarez Barco[1], A.J. Macken[1], G. Sheehan[2], J.S. Lambert[2], A.G. Cotter[1,2], P.W.G. Mallon[1,2]

[1]HIV Molecular Research Group, University College Dublin School of Medicine, Dublin, Ireland
[2]Mater Misericordiae University Hospital, Department of Infectious Diseases, Dublin, Ireland

UCD School of Medicine
Scoil an Leighis UCD

Mater Misericordiae
University Hospital

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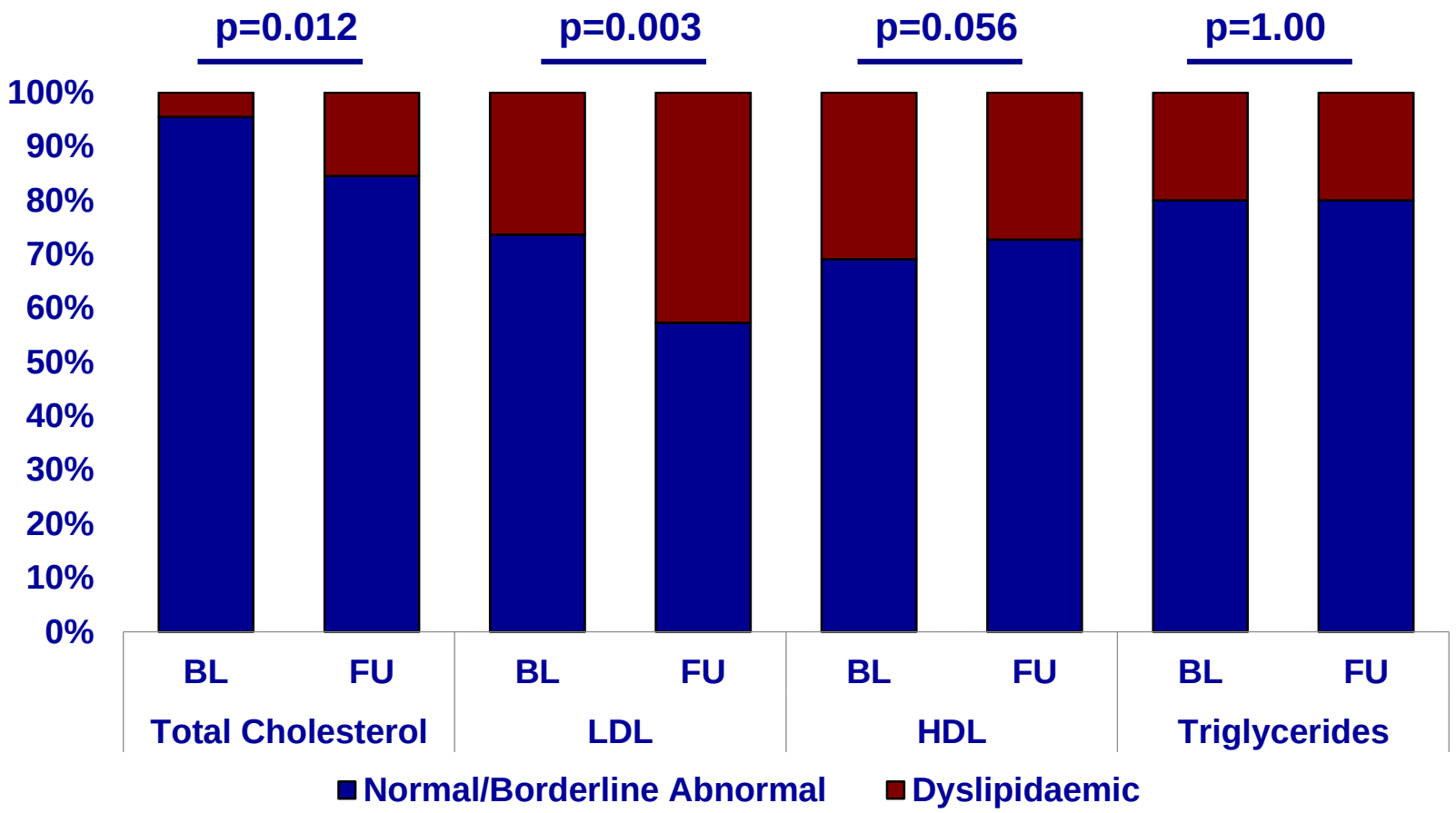
Baseline characteristics

Variables, n(%) (unless specified)	**Total switch to TAF (191)**	**Analysed (110)**	***P***
Age, median [IQR]	45 [37 – 51]	46 [39 – 53]	0.249
Male	128 (67%)	81 (73.6%)	0.171
Caucasian	130 (68.1%)	76 (69.1%)	0.853
African	51 (26.7%)	30 (27.3%)	0.949
Heterosexual acquisition	71 (37.2%)	42 (38.2%)	0.986
MSM acquisition	63 (33.0%)	40 (36.4%)	0.451
IVDU acquisition	46 (24.1%)	22 (20.0%)	0.415
HIV/HCV co-infection	42 (22.5%)	19 (17.3%)	0.279
Years since HIV diagnosis, median [IQR]	10 [5 – 15]	10 [5.25 – 14]	0.876

MSM: Men who have sex with men
IVDU: Intravenous drug users
HCV: Hepatitis C virus

Incidence of Dyslipidaemia



P-Values derived from McNer

Lacey A et al. EACS 2017

Switching to InSTI as a ‘safer’ option

Raltegravir

200mg

Elvitegravir

Stribid

Genvoya

Dolutegravir

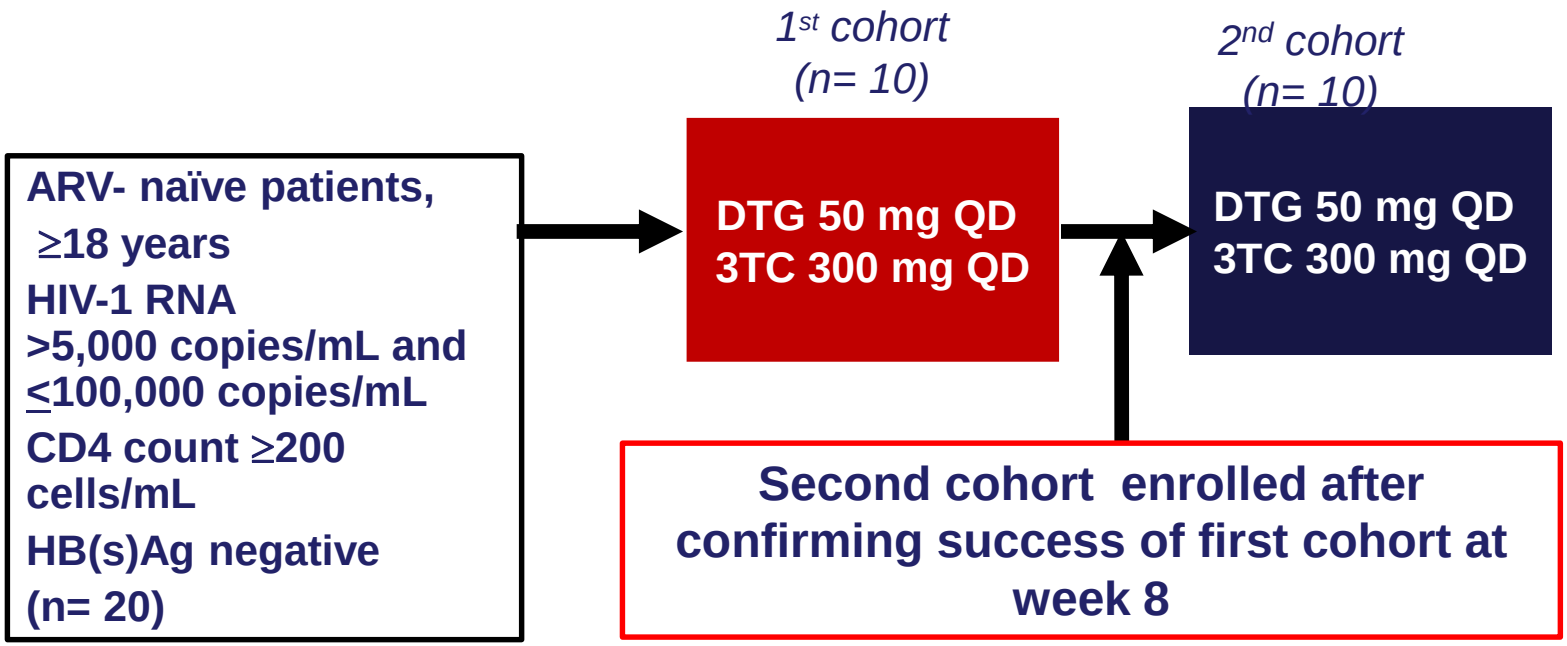
Dolutegravir

Triumeq

Dolutegravir / 3TC as a treatment option

PADDLE (***P***ilot ***A***ntiretroviral ***D***esign with ***D***olutegravir ***L***amivudin***E***)

Phase IV, pilot, open-label, single arm exploratory trial



Viral load was measured at baseline, days 2,4,7,10, and weeks 2,3,4,6,8,12, 24, 36 and 48*

** 96 week extension ongoing*

Cahn P et al. J Int AIDS Soc. 2017 May 9;20(1):21678

Dolutegravir / 3TC as a treatment option

#	SCR	BSL	DAY 4	DAY 7	W.2	W.3	W.4	W.6	W.8	W.12	W.24	W.36	W.48
1	5.584	10.909	383	101	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
2	8.887	10.233	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
3	67.335	**151.569**	1.565	1.178	97	53	< 50	< 50	< 50	< 50	< 50	< 50	< 50
4	99.291	**148.370**	3.303	432	178	55	< 50	< 50	< 50	< 50	< 50	< 50	< 50
5	34.362	20.544	1.292	570	107	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
6	16.024	14.499	1.634	162	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
7	37.604	18.597	819	61	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
8	25.071	24.368	1.377	Not done	105	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
9	14.707	10.832	516	202	< 50	< 50	< 50	< 50	< 50	< 50	< 50	SAE	
10	10.679	7.978	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
11	50.089	**273.676**	68.129	3.880	784	290	288	147	< 50	< 50	< 50	< 50	< 50
12	13.508	64.103	3.296	135	351	84	67	< 50	< 50	< 50	< 50	< 50	< 50
13	28.093	33.829	26.343	539	61	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
14	15.348	15.151	791	198	< 50	61	64	< 50	< 50	< 50	< 50	< 50	< 50
15	23.185	23.500	4.217	192	< 50	< 50	< 50	Not done	< 50	< 50	< 50	< 50	< 50
16	11.377	3.910	97	143	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
17	39.100	25.828	1.970	460	52	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
18	60.771	73.069	2.174	692	156	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
19	82.803	**106.320**	2.902	897	168	76	< 50	< 50	< 50	< 50	< 50	PDVF	
20	5.190	7.368	147	56	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50

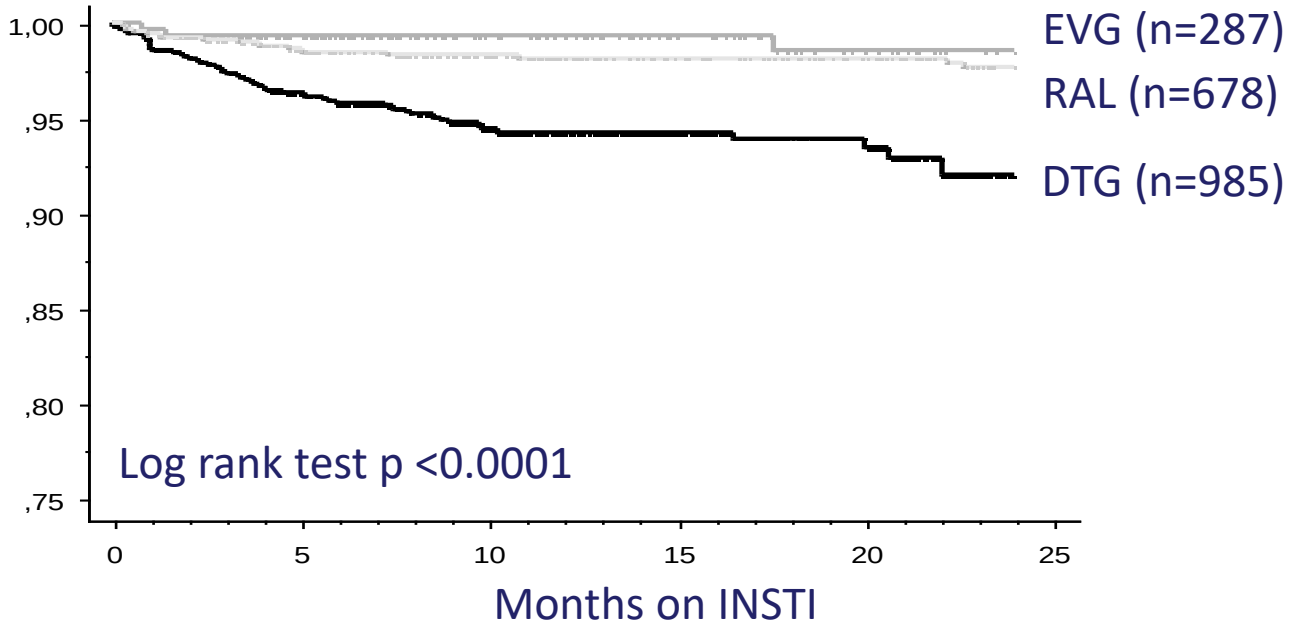
CD4 increase: Median (IQR) : 267 (180-462)

Cahn P et al. J Int AIDS Soc. 2017 May 9;20(1):21678

Dolutegravir and tolerability

Discontinuation due to neuropsychiatric AEs

	Dolutegravir n=985	Elvitegravir n=287	Raltegravir n=678
Neuropsychiatric % (n)	5.0 % (49)	1.0 % (3)	2.1 % (14)
Insomnia, sleep disturbances	36	2	4
Poor concentration, slow thinking	8	0	0
Dizzyness	13	1	3
Headache, paraesthesia	16	1	6
Depression	7	0	1



Sabranski et al. HIV Med. 2017 Jan;18(1):56-63.

Summary

The approach to treatment of long-term HIV continues to evolve

Treatment approaches moving to convenience, tolerability and avoidance of long-term toxicity

Optimal choice of ART focused around age-related conditions

Knowledge of an individual's risk becoming more important

- have a reason for switch
- set your target to achieve
- know the past treatment history

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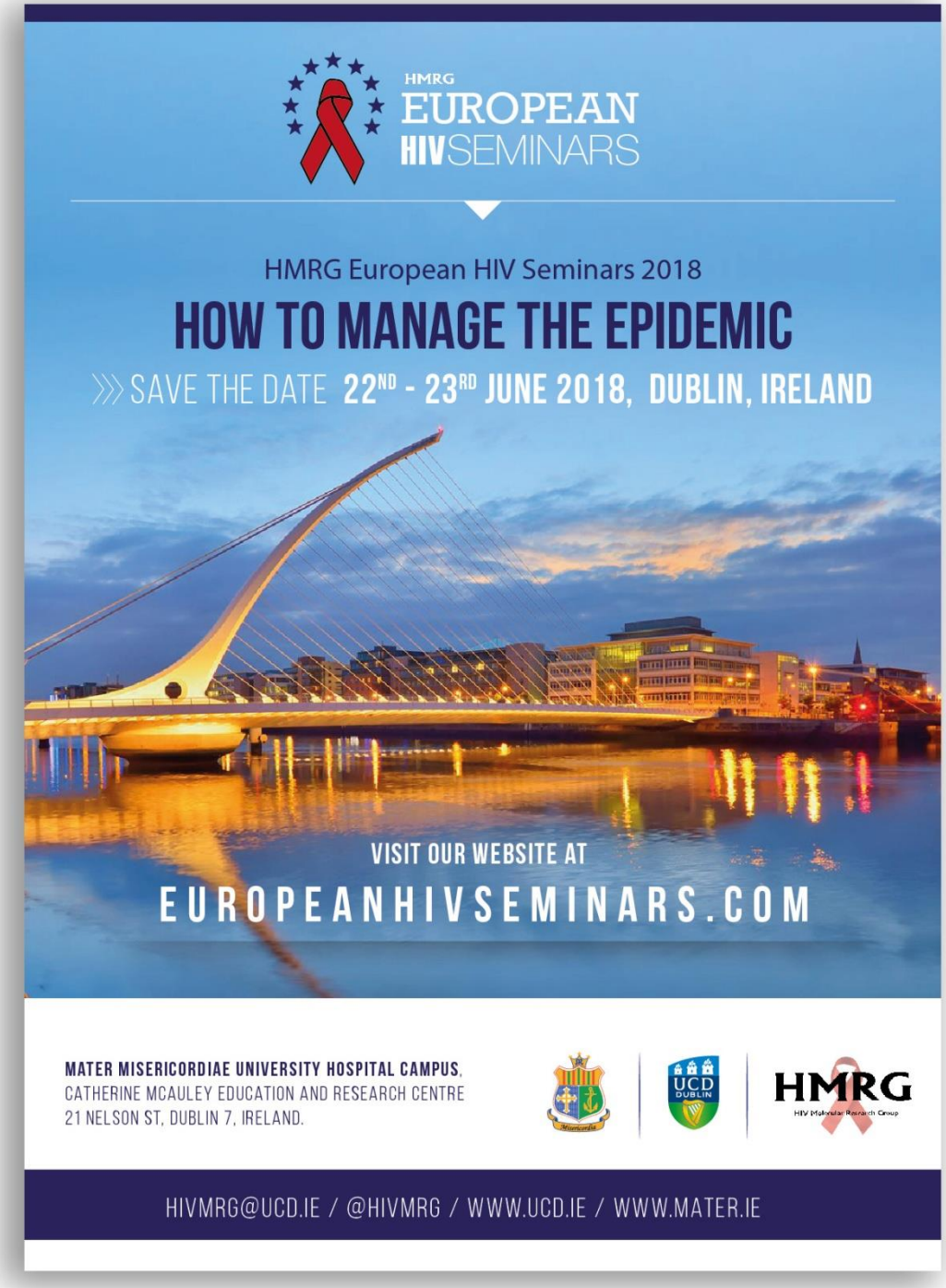

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