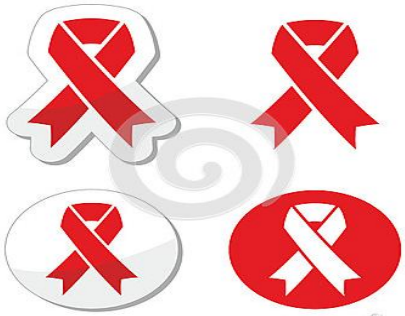
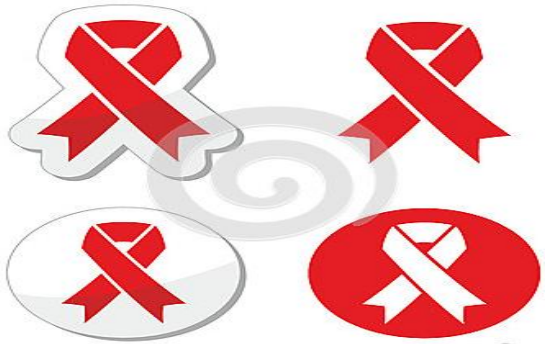


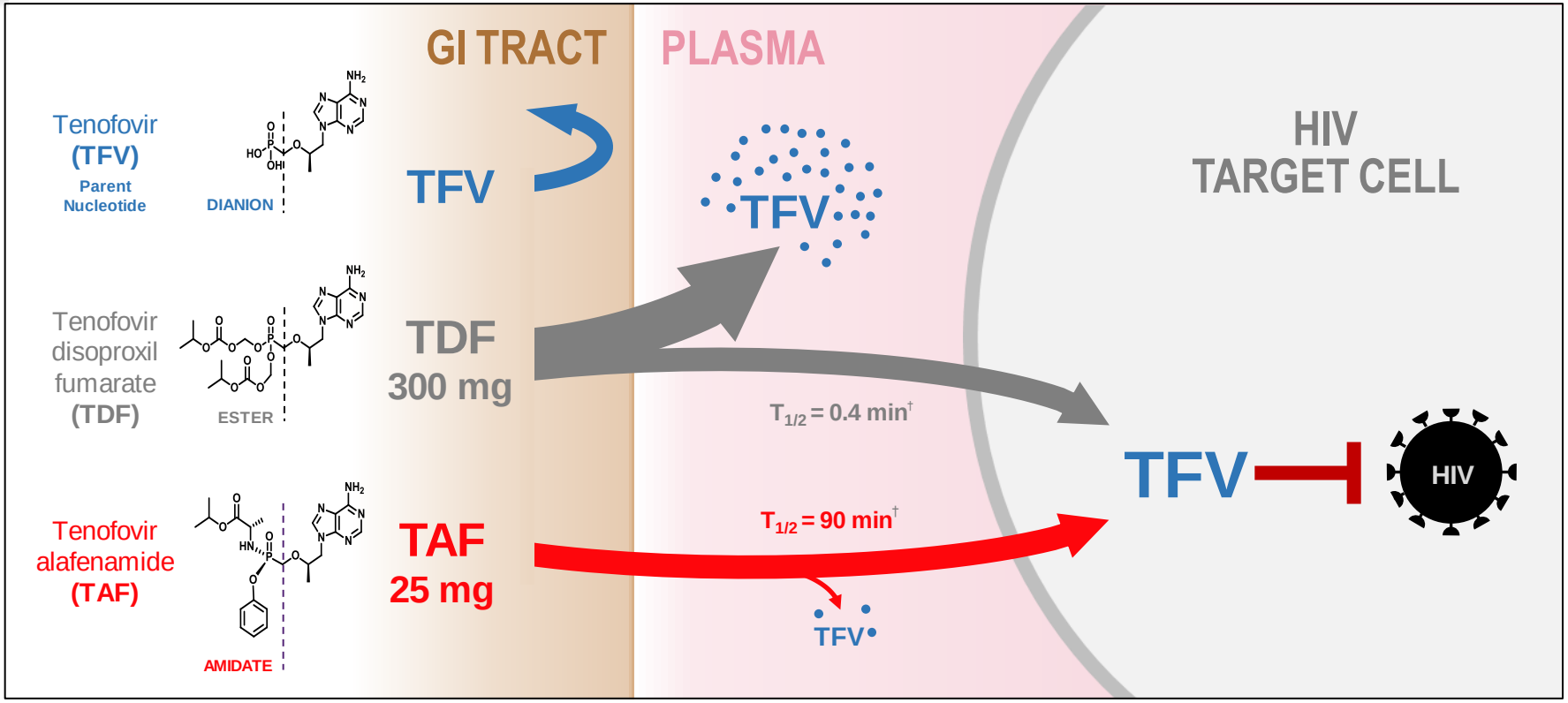
La terapia della infezione da HIV-AIDS: novità terapeutiche 2016

TERESA BINI
Clinic of Infectious Diseases
Department of Health Sciences
San Paolo Hospital
University of Milan



Vecchie molecole, nuove formulazioni

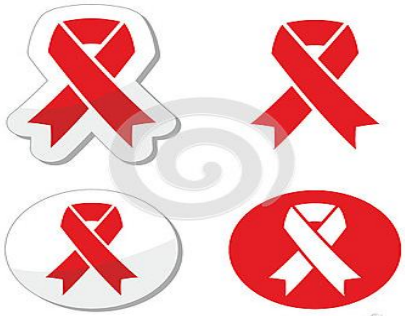
Tenofovir alafenamide (TAF): novel prodrug of tenofovir



- TAF is more stable in plasma compared with TDF[1]
- Intact TAF transits directly into target cells where it is intracellularly activated to tenofovir disphosphate (TFV-DP)[1–3]
- TAF at an equivalent dose of 25 mg (10 mg in boosted regimens) has 91% lower circulating plasma TFV levels compared to TDF 300 mg[4–6]

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

1. Lee W et al. Antimicr Agents Chemo 2005;49(5):1898–1906; 2. Birkus G et al. Antimicr Agents Chemo 2007;51(2):543–550; 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 Apr 15 [Epub ahead of print]

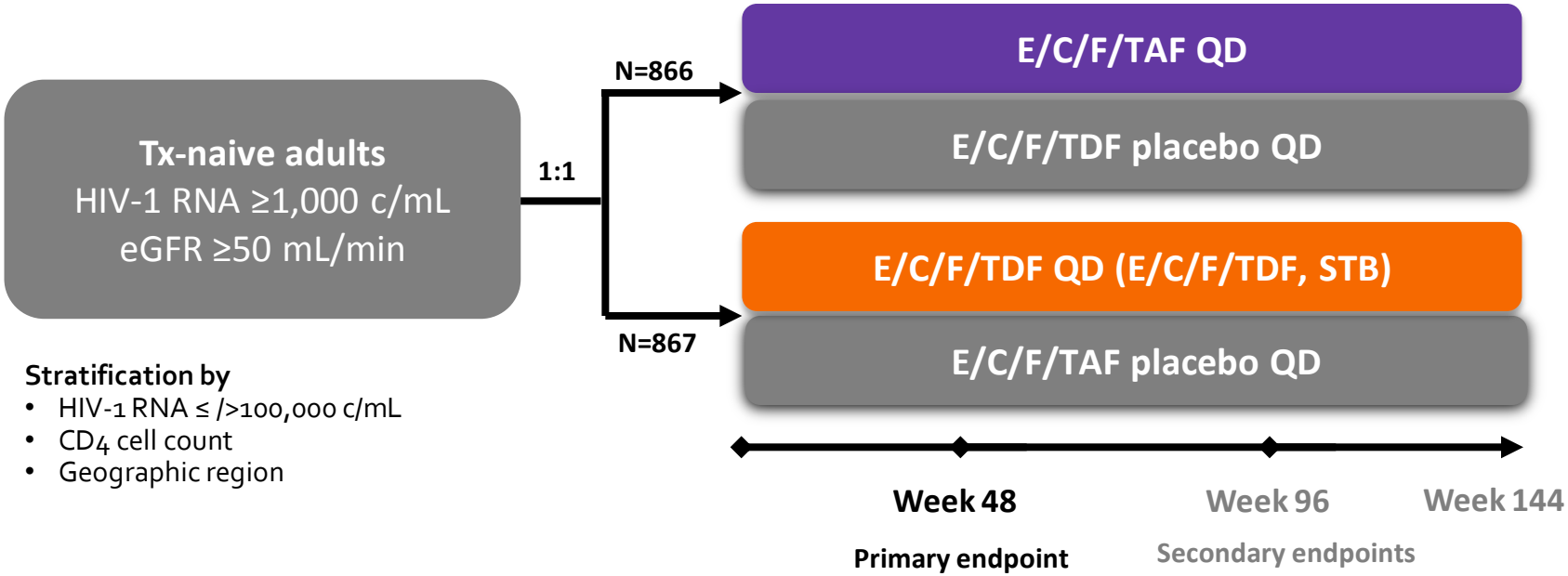


‡

E/C/F/TAF
nei pazienti naive

Study design

Two Phase III, international, randomised, double-blind, active-controlled studies



Stratification by
- HIV-1 RNA ≤ />100,000 c/mL
- CD_4 cell count
- Geographic region

Primary endpoint**

Non-inferiority (12% margin) of E/C/F/TAF to E/C/F/TDF based on HIV-1 RNA <50 copies/mL^ at Week 48 by FDA Snapshot analysis*

ClinicalTrials.gov identifier: NCT01780506 and NCT01797445.

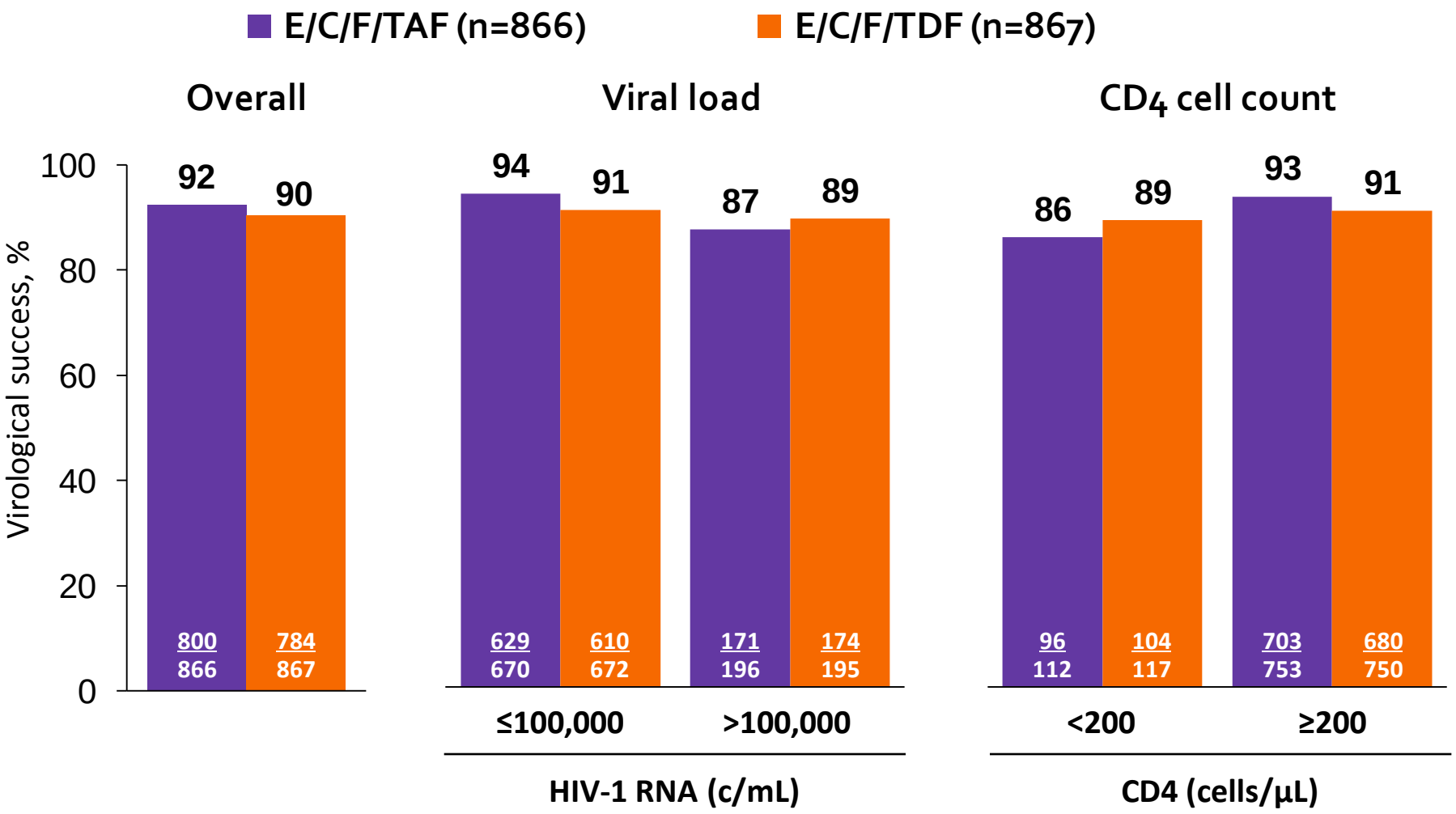
*Combined efficacy analysis was pre-specified. **SCr, proteinuria, hip and spine BMD were pre-specified Week 48 safety endpoints. ^Taqman 2.0 assay Study 104 (North America, EU, Asia) and Study 111 (North America, EU, Latin America).

E/C/F/TAF: elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir DF

1. Sax P et al. Lancet. 2015 Jun 27;385(9987):2606–15; 2. Sax P et al. CROI 2015. Seattle, WA. #143LB

Studies 104 and 111: ART-naive patients, Week 48 combined analysis

Efficacy by baseline HIV-1 RNA and CD4 cell count

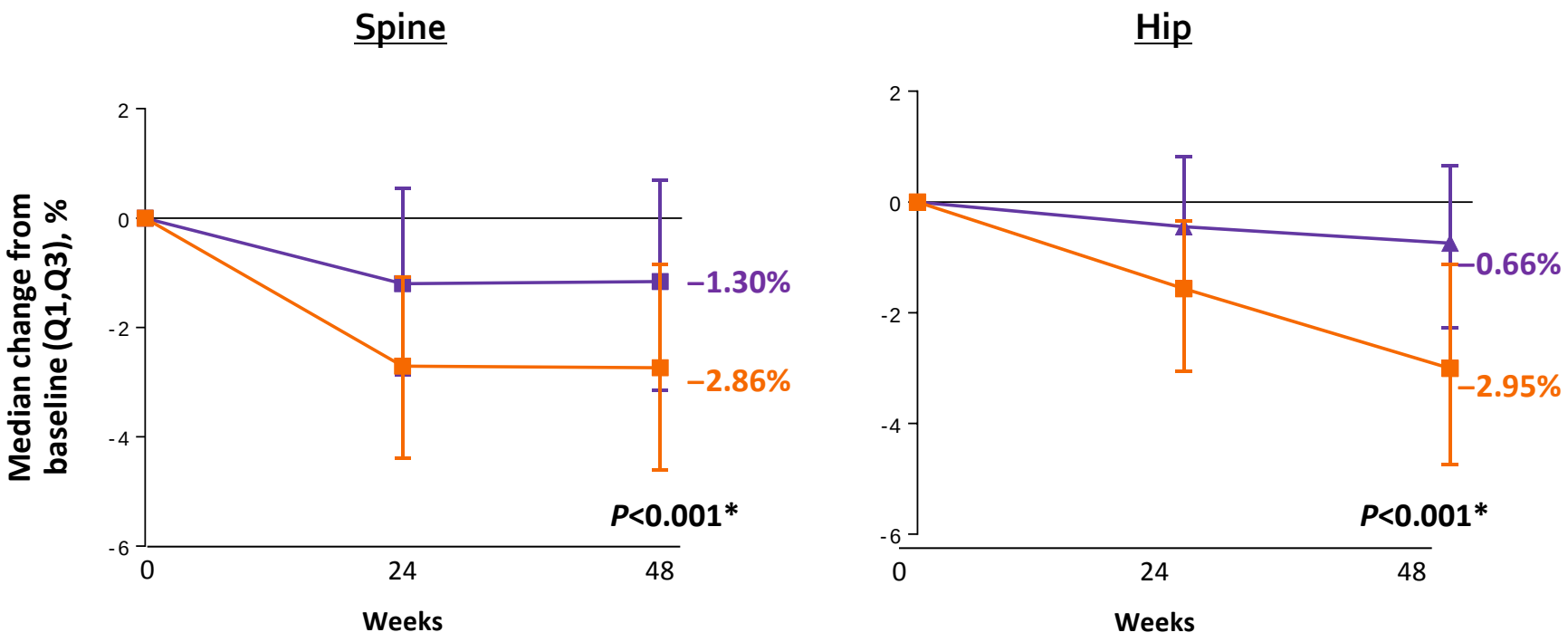


High rates of virological success across low and high BL VL and CD4 cell count

Sax P et al. Lancet. 2015 Jun 27;385(9987):2606–15

Studies 104 and 111: ART-naive patients, Week 48 combined analysis

Changes in spine and hip BMD through Week 48



E/C/F/TAF	n=845	797	784	836	789	780
E/C/F/TDF	n=850	816	773	848	815	767

*Comparison of E/C/F/TAF vs E/C/F/TDF at Week 48

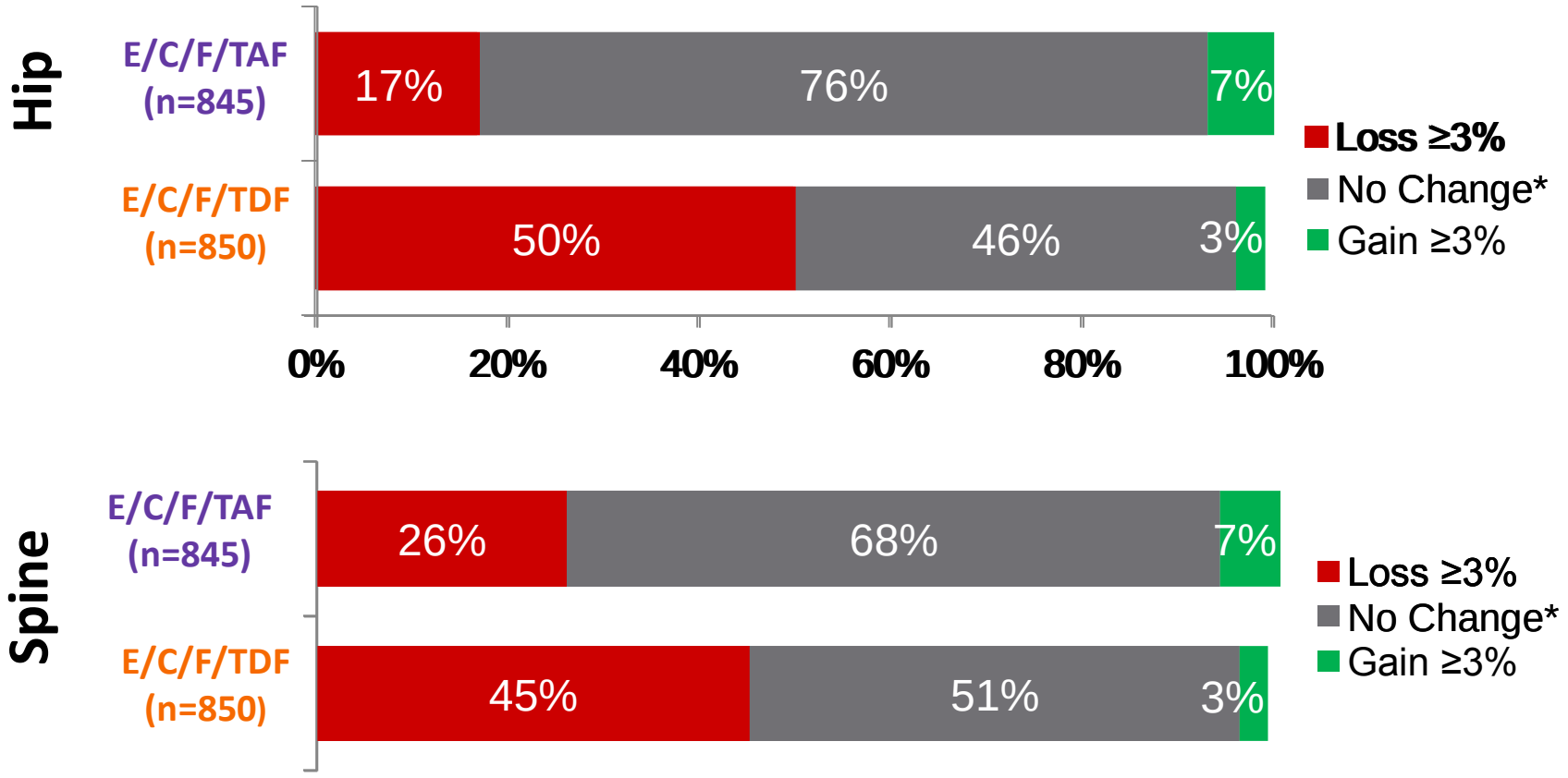
Significantly less decreases in spine and hip BMD in the E/C/F/TAF group at Week 48

BMD = bone mineral density

Sax P et al. Lancet. 2015 Jun 27;385(9987):2606–15

Studies 104 and 111: ART-naive patients, Week 48 combined analysis

BMD categorical changes at Week 48



*No change = -3% to +3%

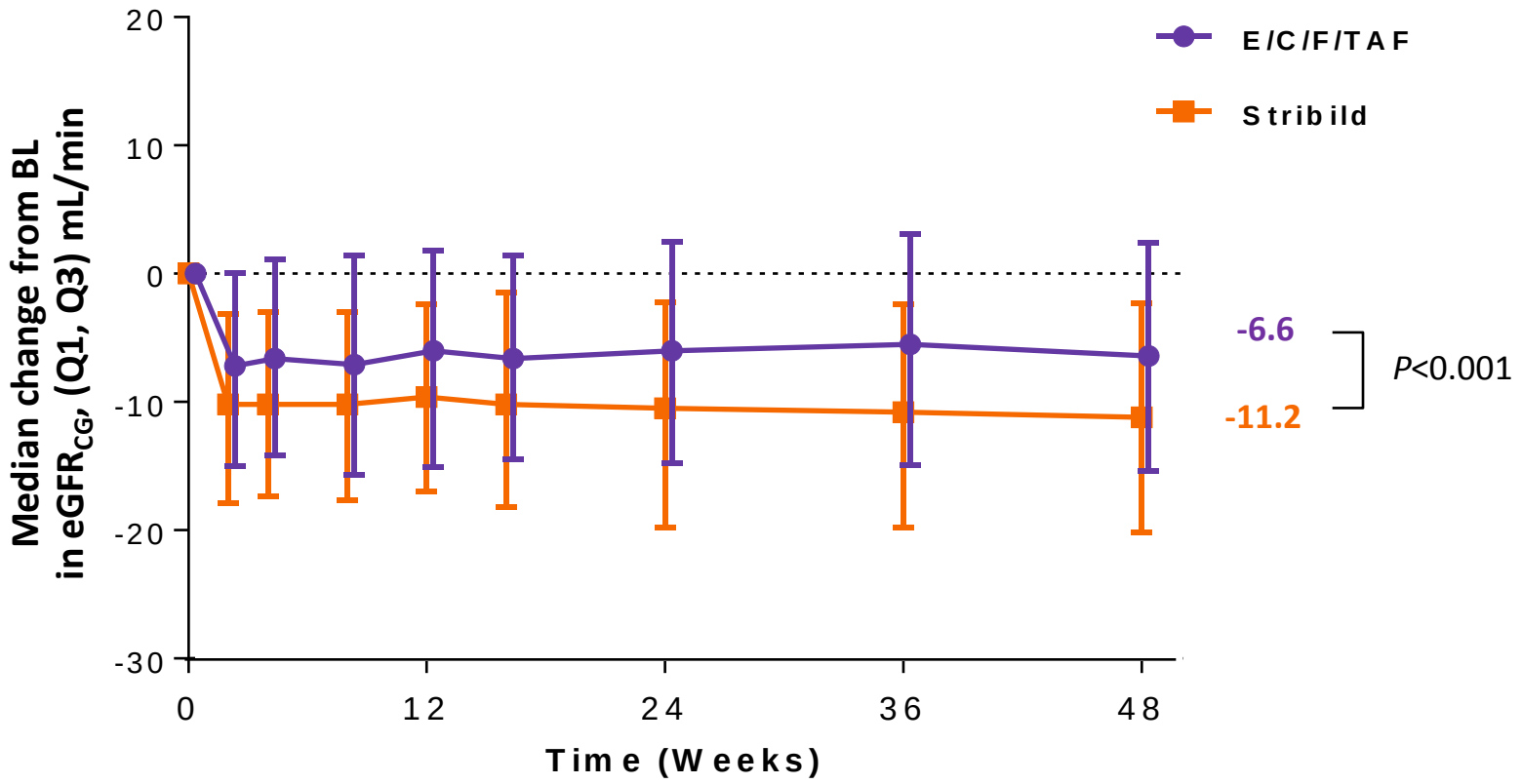
BMD = bone mineral density

Adapted from Sax P et al. Lancet. 2015 Jun 27;385(9987):2606–15

‡

Studies 104 and 111: ART-naive patients, Week 48 combined analysis

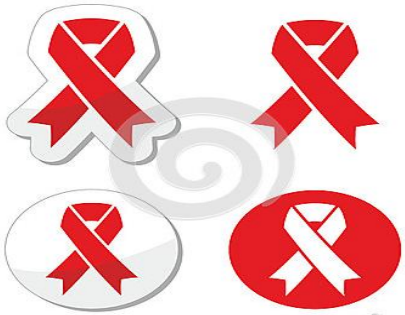
Changes in eGFR (Cockcroft-Gault) through Week 48



Less GFR decrease with E/C/F/TAF compared to E/C/F/TDF (p<0.001)

Pattern of early decline (2 weeks) then stable eGFR is consistent with cobicistat inhibition of tubular secretion of creatinine

Sax P et al. Lancet. 2015 Jun 27;385(9987):2606–15



E/C/F/TAF
in semplificazione

Switching to F/TAF (Tenofovir Alafenamide) from F/TDF (Tenofovir DF) based Regimen Study 311-1089: 48-Week Data

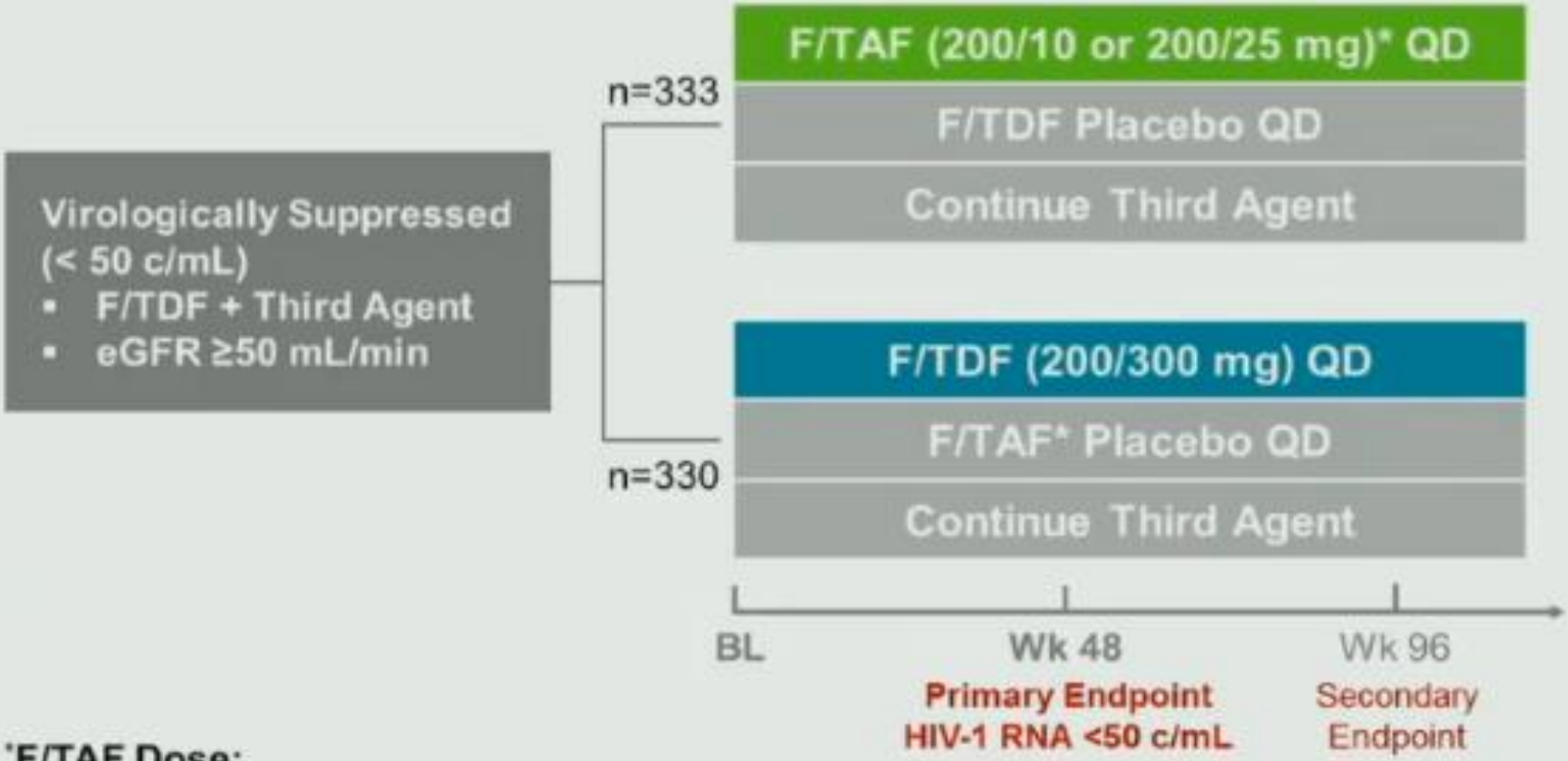
Joel Gallant[1], Eric Daar[2], Francois Raffi[3], Cynthia Brinson[4], Peter Ruane[5], Edwin DeJesus[6], Mingjin Yan [7], Andrew Plummer[7], Andrew Cheng[7], Martin S Rhee[7]

[1]Southwest CARE Center, Santa Fe, NM; [2]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA; [3]CHU Hotel Dieu-CHU De Nantes, Nantes, France; [4]Central Texas Clinical Research, Austin, TX; [5]Ruane Medical and Liver Health Institute, Los Angeles, CA; [6]Orlando Immunology Center, Orlando, FL; [7]Gilead Sciences, Foster City, CA

Abstract 29
CROI 2016, Boston

Switch from F/TDF to F/TAF

- Randomized, double-blind, double-dummy, active-controlled study

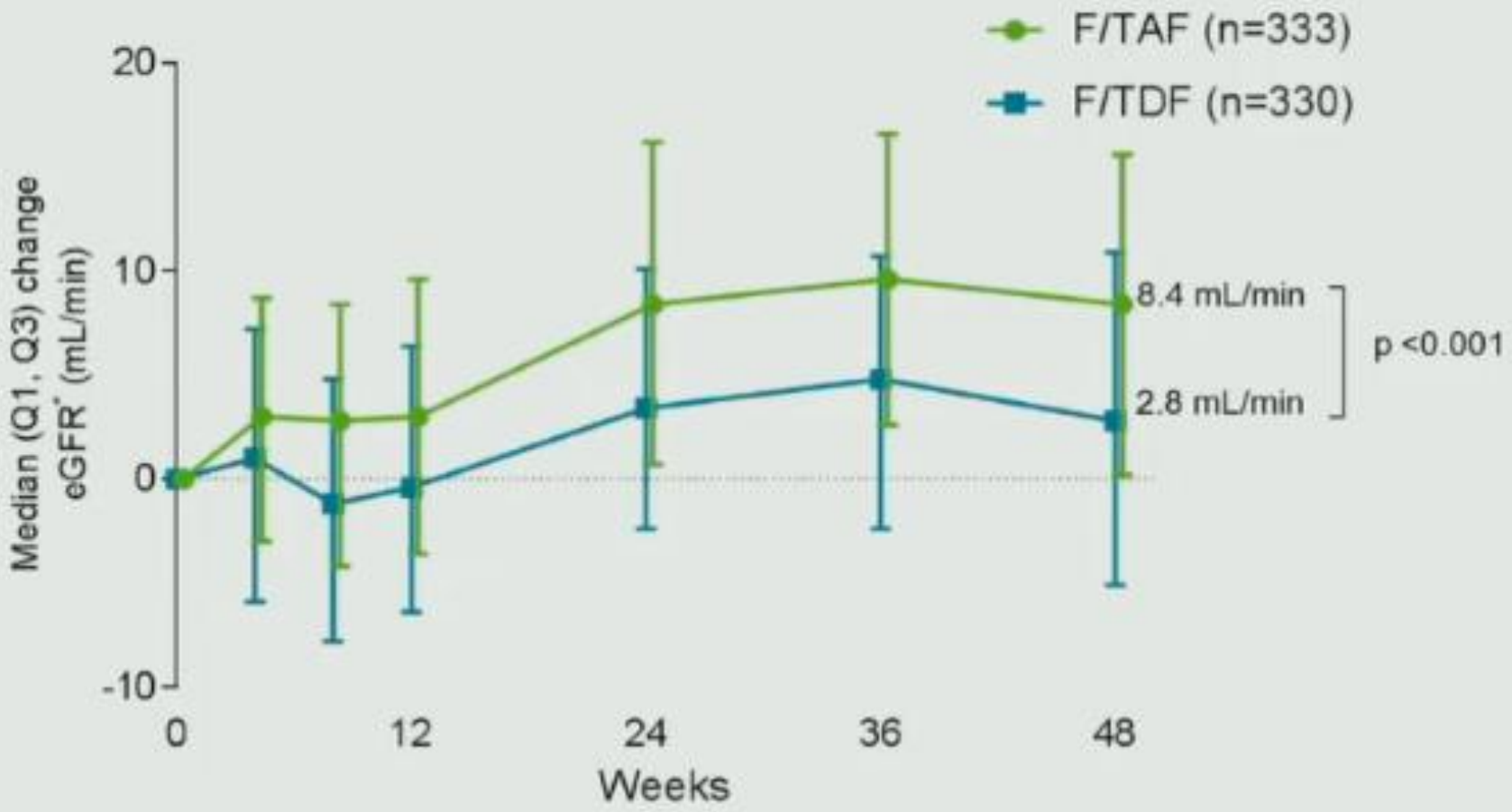


*F/TAF Dose:

- 200/10 mg with boosted PIs
- 200/25 mg with unboosted third agents

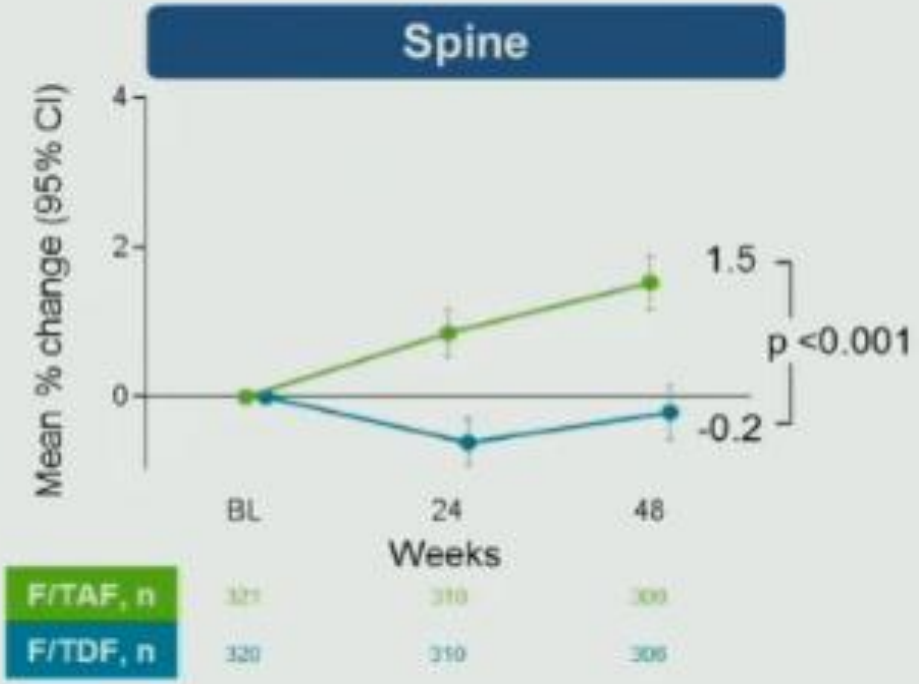
Virologic Success in Select Subgroups

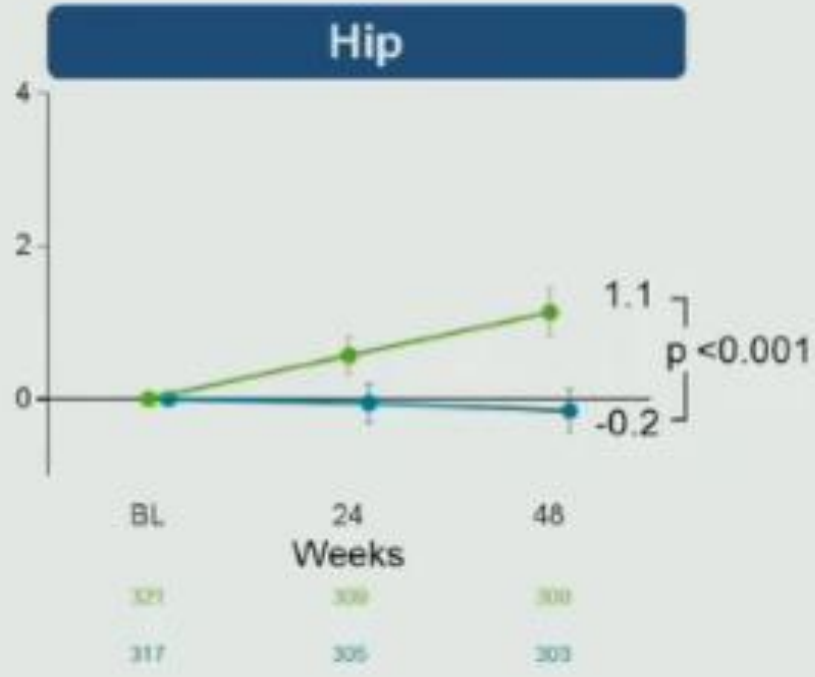
Changes in eGFR



*eGFR calculated with Cockcroft-Gault equation

Change in Bone Mineral Density through Week 48





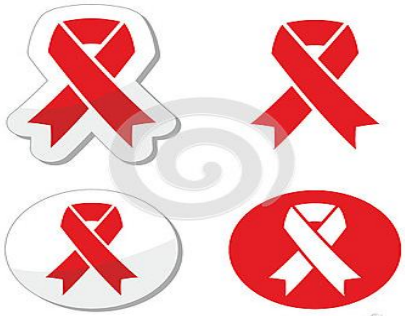
≥ 3% BMD increase at Week 48

F/TAF	30%
F/TDF	14%

p<0.001

	17%
	9%

p=0.003

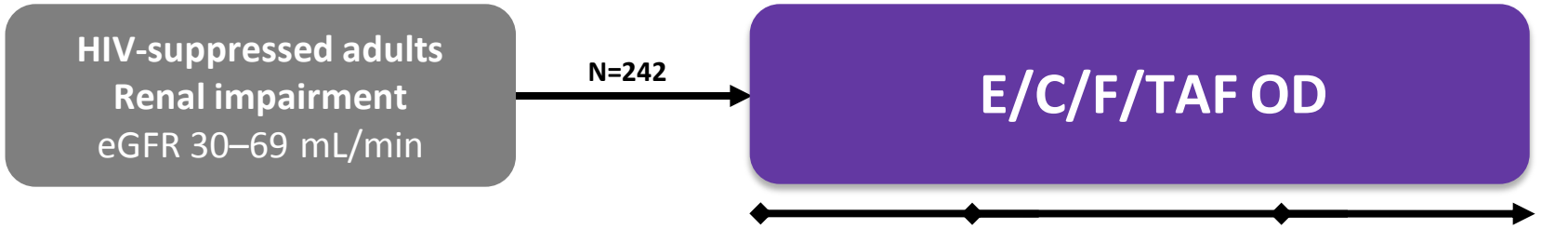


E/C/F/TAF nei pazienti virologicamente soppressi con alterazione della funzionalità renale

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

Study design

Phase III, 96-week, multi-centred, single-arm, open label study



Key inclusion criteria
- CD4 ≥50 cells/µL
- No HCV or HBV infection
- HIV-1 RNA <50 c/mL for ≥6 months

ClinicalTrials.gov identifier: NCT01818596

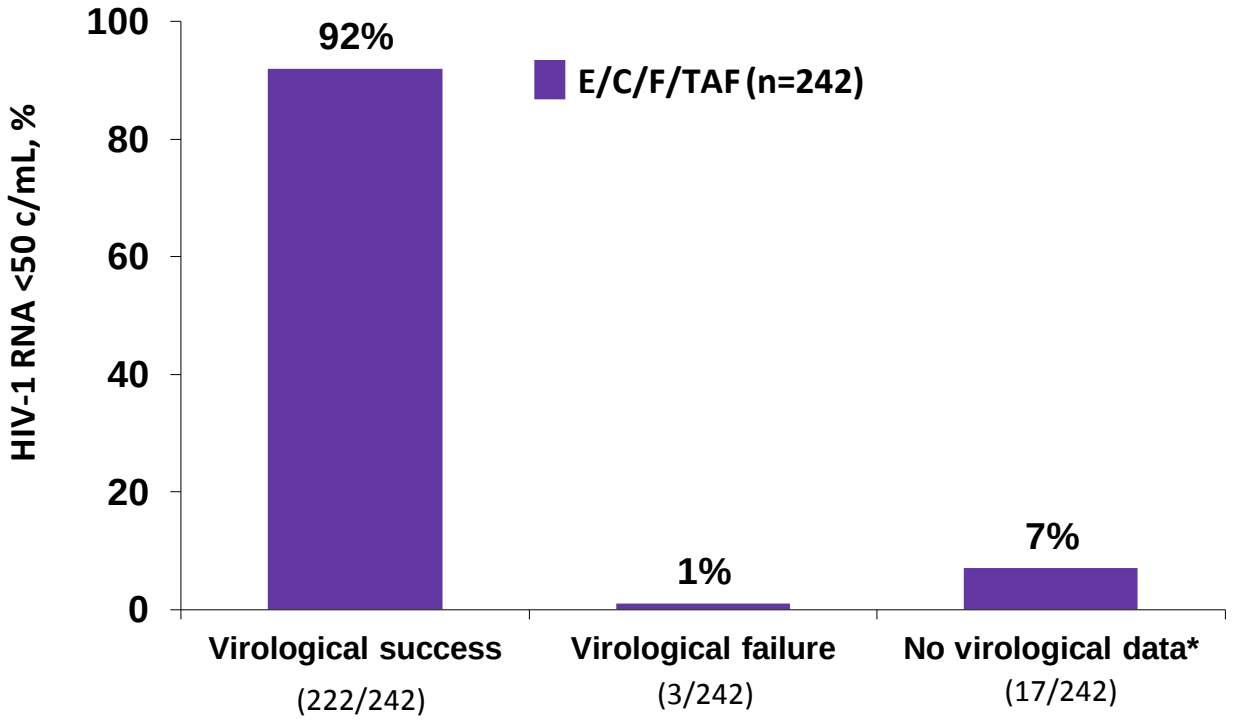
Primary endpoint
- Change from baseline in glomerular filtration rate*† at Week 24

Secondary endpoints
- Efficacy, safety, and tolerability observed through Weeks 48 and 96
- Proportion of subjects with HIV-1 RNA <50 c/mL by FDA Snapshot analysis

*eGFR was measured using the Cockcroft-Gault formula ($eGFR_{CG}$) in all patients
†aGFR was measured at three timepoints (baseline, Week 2, 4 or 8 and Week 24) in a subset of patients

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

Virological outcomes (HIV-1 RNA <50 c/mL) at Week 48



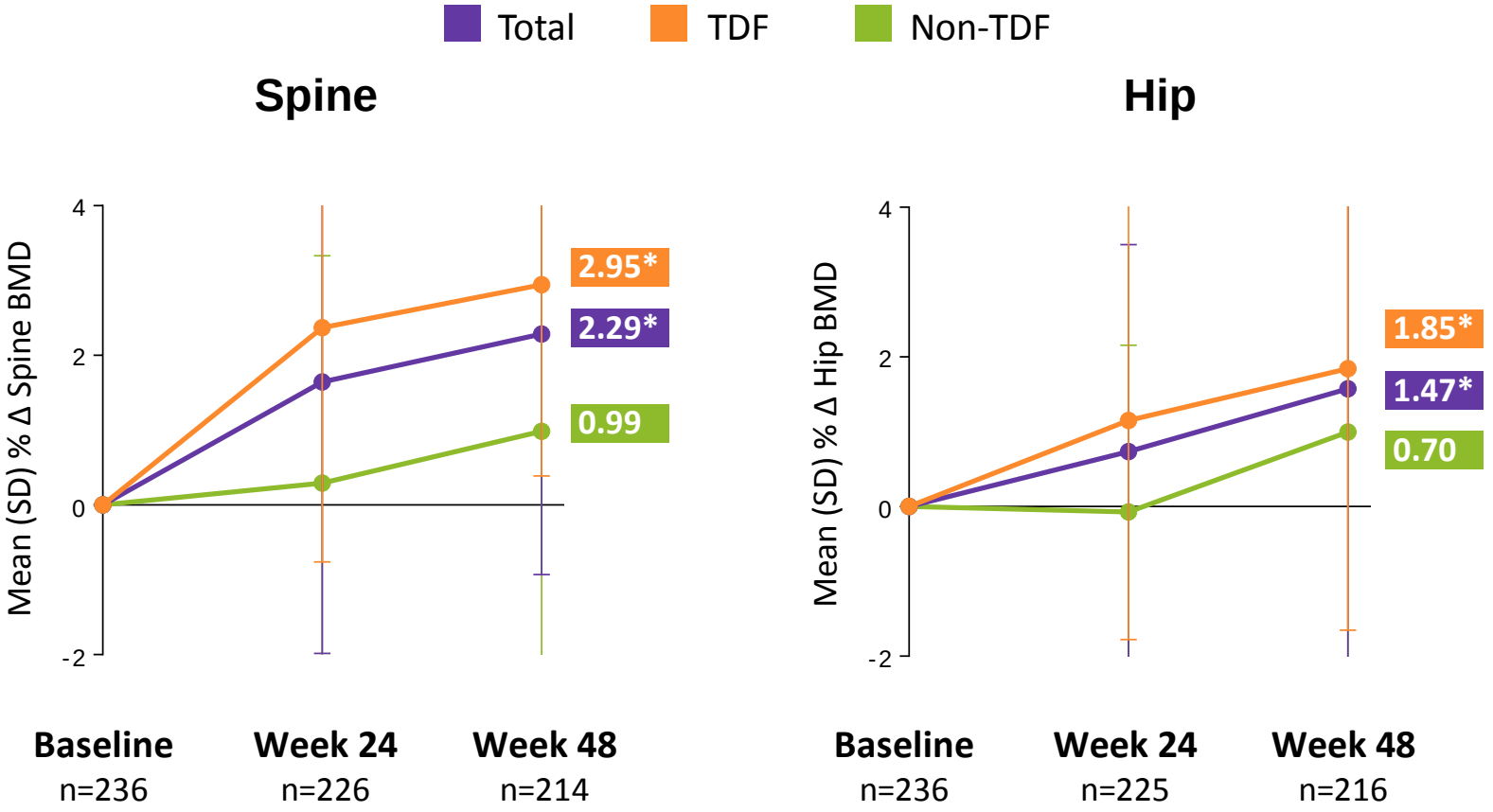
*Seven subjects discontinued through Week 48 due to adverse events, seven discontinued due to administrative reasons, and three had missing virological data but were on study drugs

E/C/F/TAF maintained high rate of virological suppression at Week 48

Virological suppression defined as HIV-RNA <50 copies/mL

Study 112: Suppressed adults with renal impairment switched to E/C/F/TAF
Total and sub-group analysis by pre-switch ARV regimen (TDF vs. Non-TDF)

Change in spine and hip BMD through Week 48



Progressive increases in spine and hip BMD through Week 48

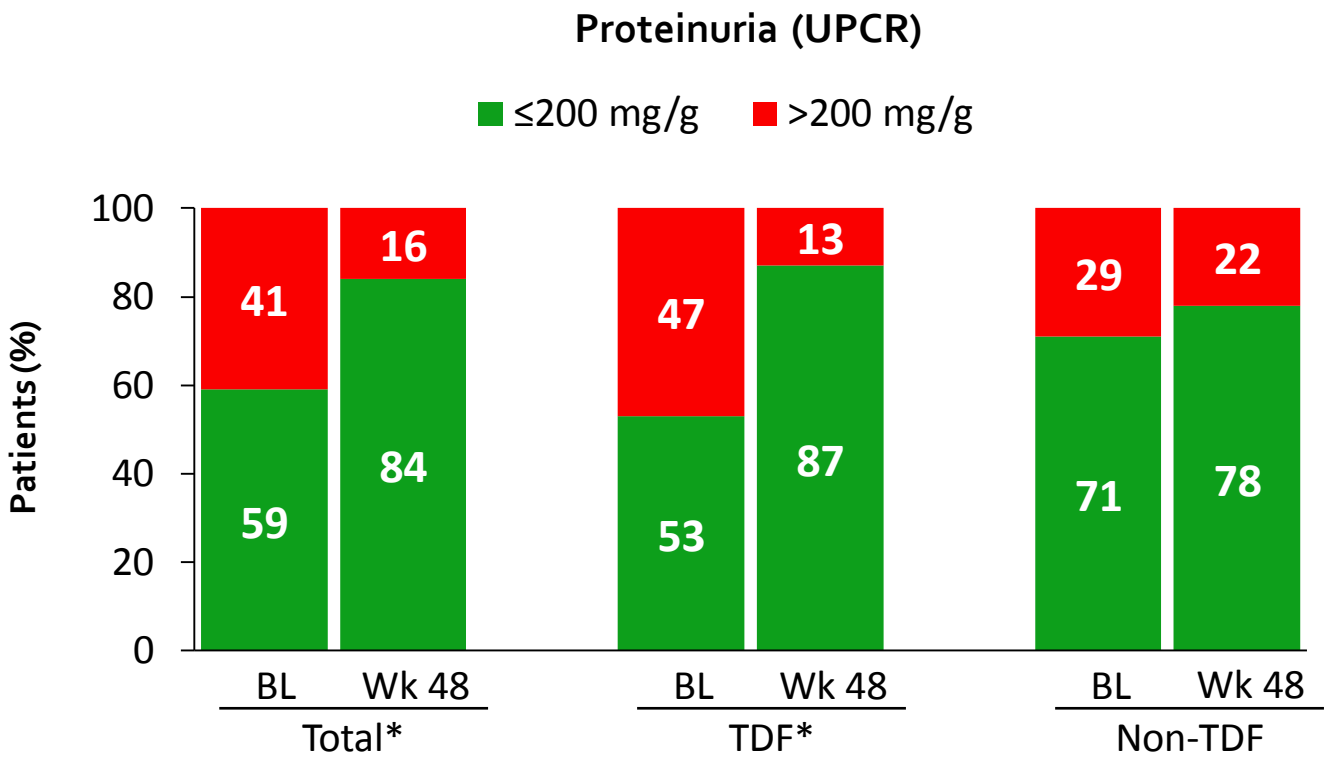
BMD=bone mineral density

*p<0.05 by two-sided Wilcoxon signed-rank test (Wk 48 vs. Baseline)

Study 112: Suppressed adults with renal impairment switched to E/C/F/TAF
Sub-group analysis by pre-switch ARV regimen (TDF vs. Non-TDF)

‡

Clinically significant proteinuria: baseline to Week 48



Significant improvements in clinically significant proteinuria following switch to E/C/F/TAF from a TDF-based regimen

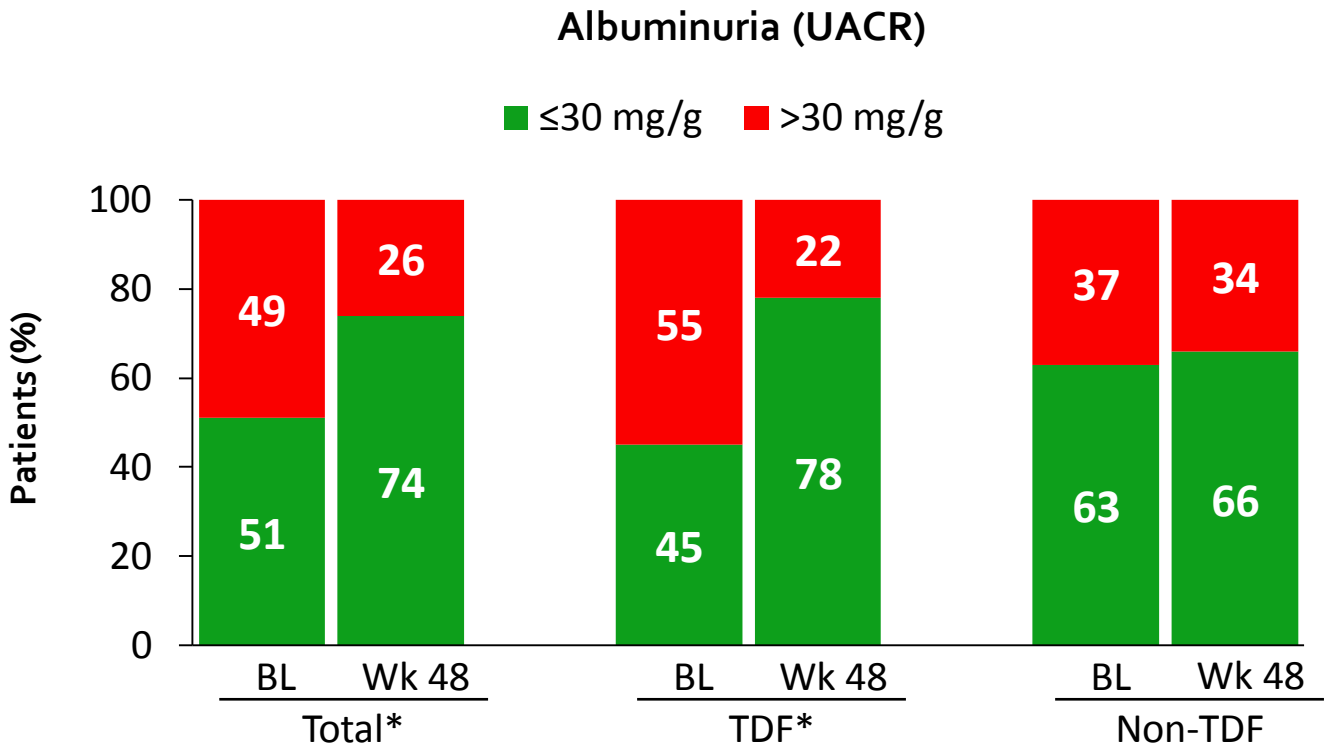
*Total and TDF changes statistically significant (Week 48 vs. baseline)

UPCR = Urine Protein:Creatinine Ratio

BL = Baseline

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

Clinically significant albuminuria: baseline to Week 48



Significant improvements in clinically significant albuminuria following switch to E/C/F/TAF from a TDF-based regimen

UACR = Urine Albumin:Creatinine Ratio
BL = Baseline

*Total and TDF changes statistically significant (Week 48 vs. Baseline).

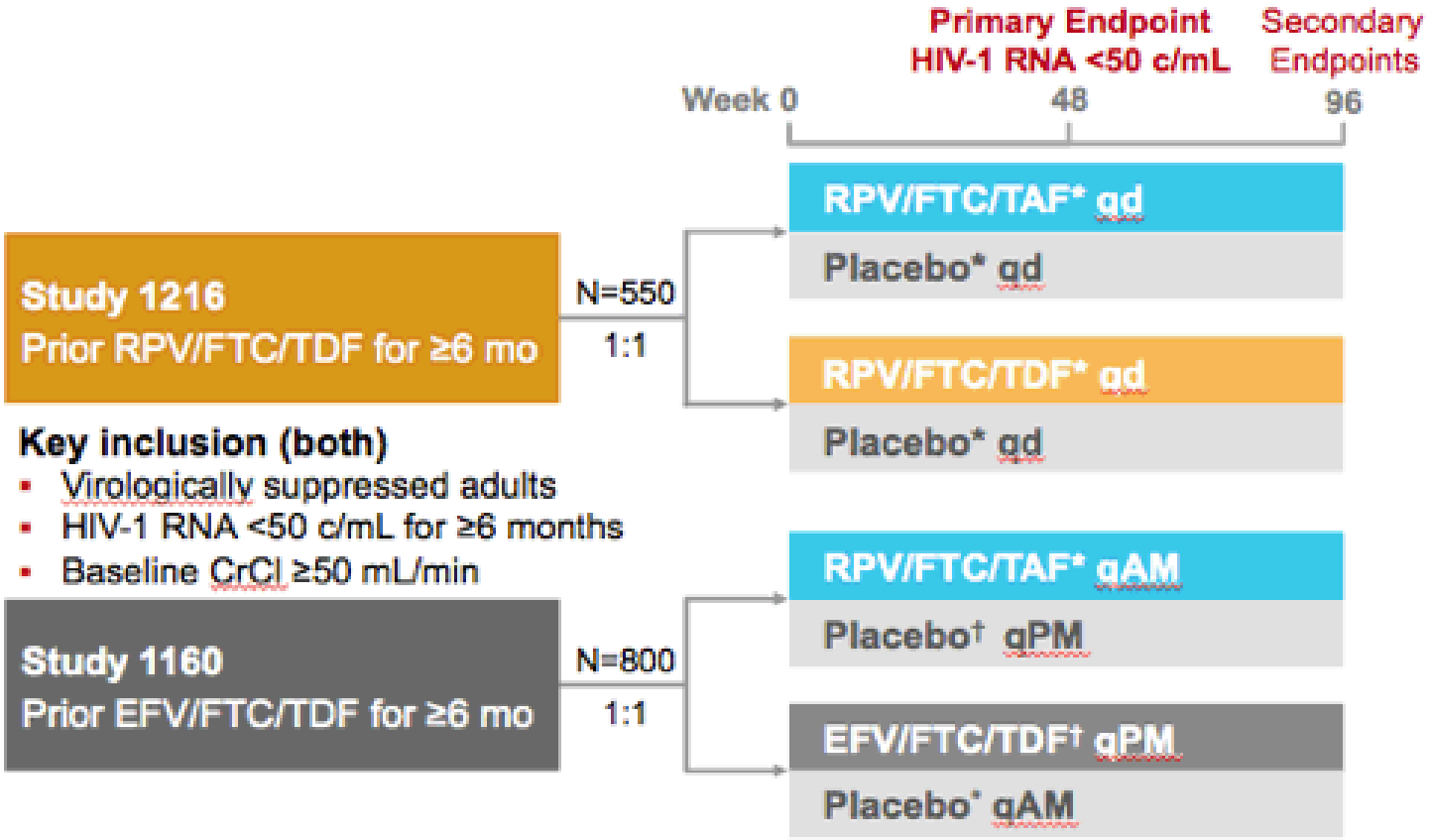
48 Week Results from two studies: Switching to RPV/FTC/TAF from EFV/FTC/TDF (Study 1160) or RPV/FTC/TDF (Study 1216)

Chloe Orkin,[1] Edwin DeJesus,[2] Moti Ramgopal,[3] Gordon Crofoot,[4] Peter Ruane,[5] Anthony LaMarca,[6] Anthony Mills,[7] Bernard Vandercam,[8] Joseph De Wet,[9] Jurgen Rockstroh,[10] Adriano Lazzarin,[11] Bart Rijnders,[12] Daniel Podzamczer,[13] Anders Thalme,[14] Marcel Stoeckle,[15] Danielle Porter,[16] Hui Liu,[16] Andrew Cheng,[16] Erin Quirk,[16] Devi SenGupta,[16] Huyen Cao[16]

[1]Royal London Hospital, London, UK; [2]Orlando Immunology Center, Orlando, Florida, USA; [3]Midway Immunology and Research Center, Fort Pierce, Florida, USA; [4]The Crofoot Research Center, Houston, Texas, USA; [5]Ruane Medical & Liver Health Institute, Los Angeles, California, USA; [6]Therafirst Medical Centers, Fort Lauderdale, Florida, USA; [7]Southern California Men's Medical Group, Los Angeles, California, USA; [8]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [9]Spectrum Health Care, Vancouver, British Columbia, Canada; [10]Universitätsklinikum Bonn, Germany; [11]Ospedale San Raffaele, Milano, Italy; [12]Erasmus University Medical Center, Rotterdam, the Netherlands; [13]Hospital Universitari de Bellvitge, Barcelona, Spain; [14]Karolinska Universitetssjukhuset, Solna, Sweden; [15]Universitätsspital Basel, Switzerland; [16]Gilead Sciences, Inc., Foster City, California, USA

HIV Glasgow 2016

Study Designs
Studies 1216 and 1160

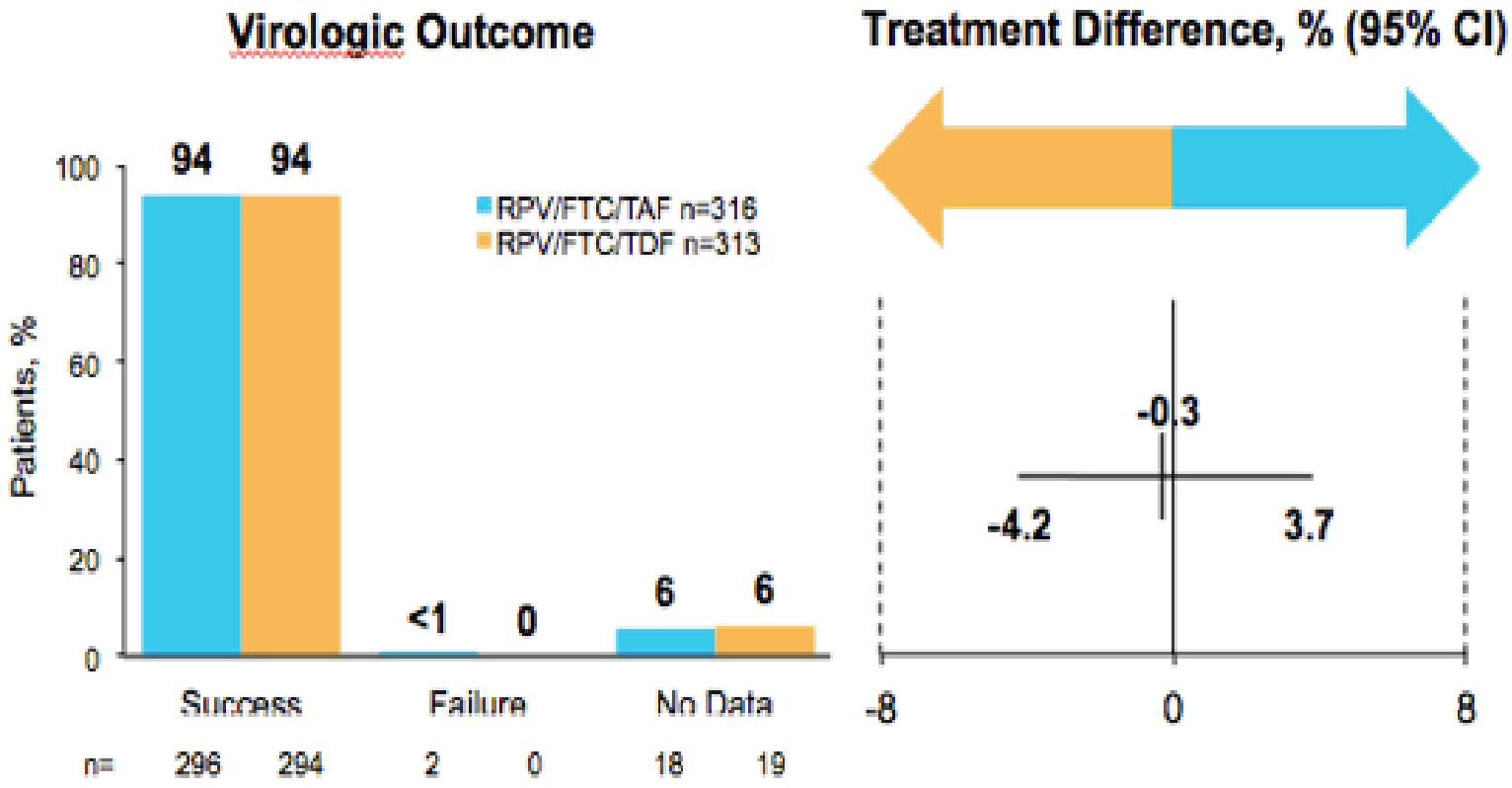


Randomized, double-blind, active-controlled studies

*Given with food (no restrictions specified); †Given without food

Virologic Suppression at Week 48 (FDA snapshot)

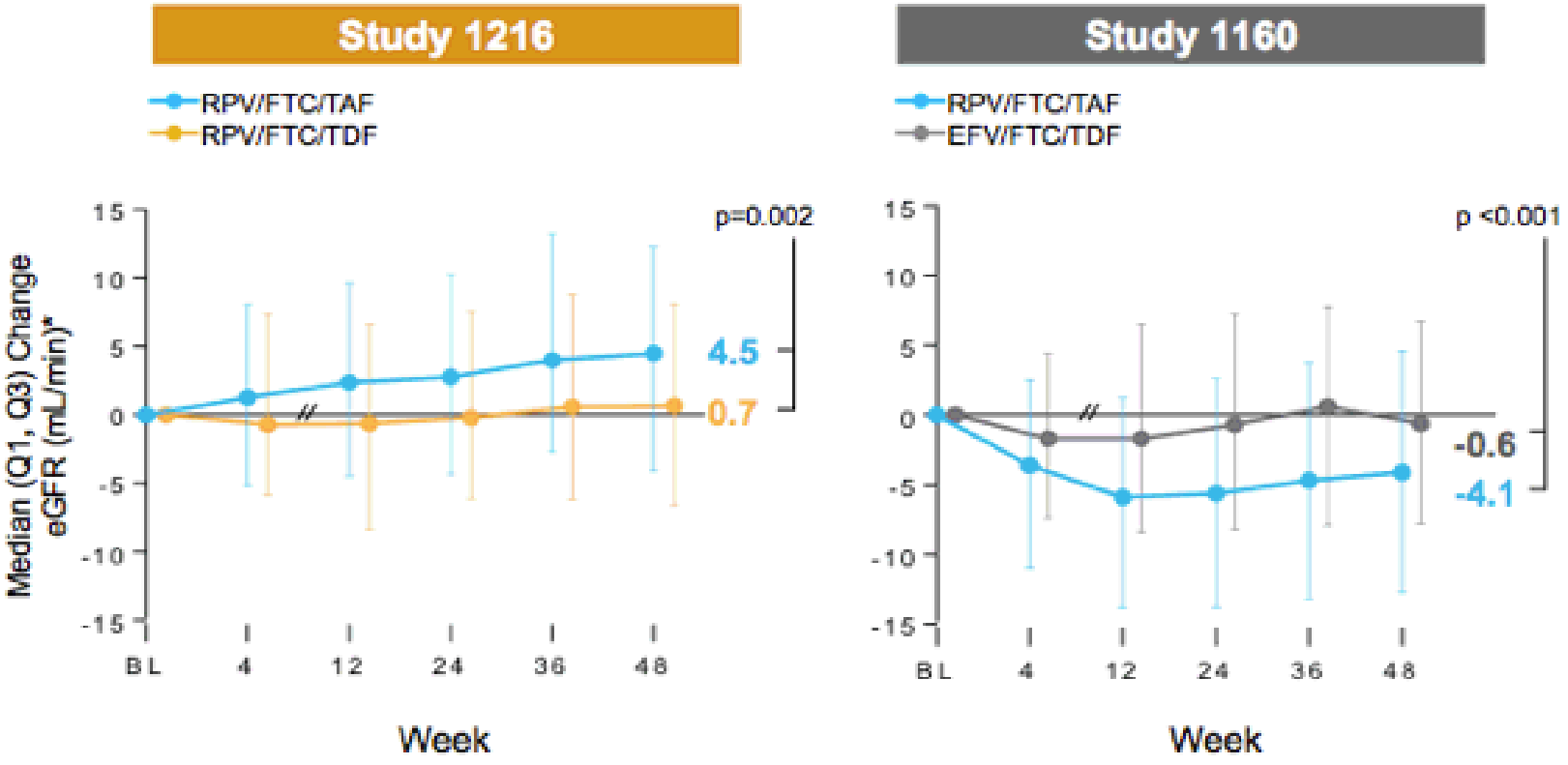
Study 1216



- Efficacy was comparable across age, sex, geographic region
- No emergent resistance mutations were detected in either group

Change in eGFR at Week 48

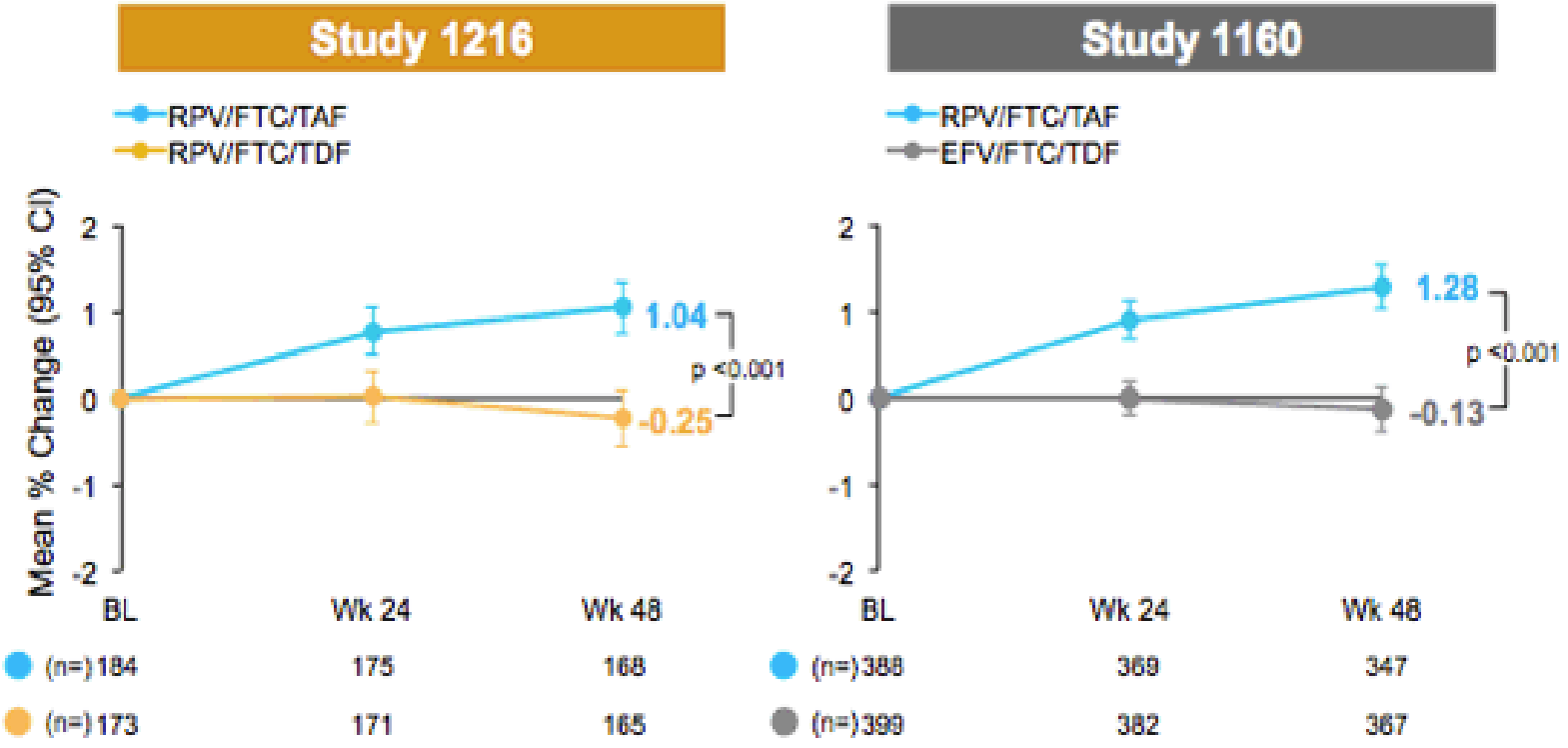
Studies 1216 and 1160



*eGFR calculated with Cockcroft-Gault equation.

Change in Hip BMD through Week 48

Studies 1216 and 1160

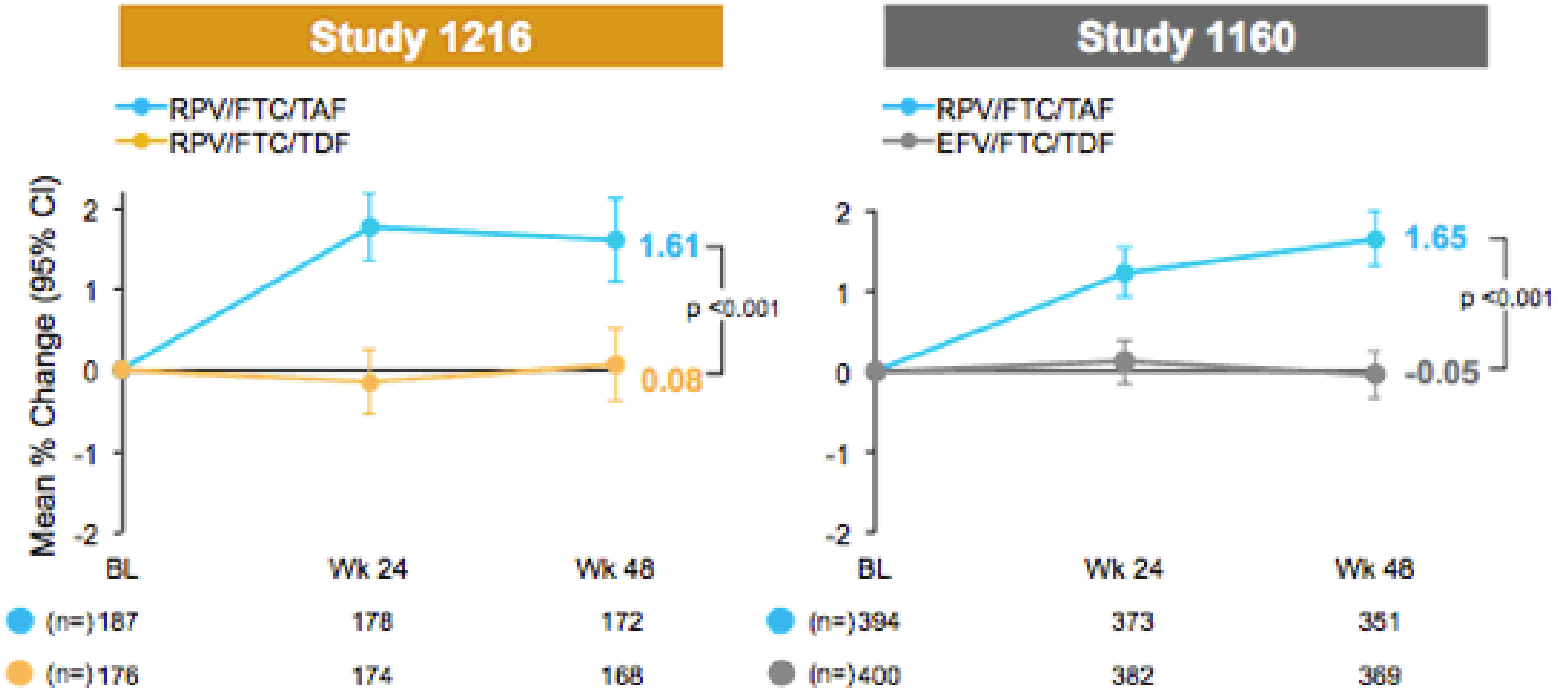


	RPV/FTC/TAF	RPV/FTC/TDF	
≥3% increase	16%	4%	p<0.001
≥3% decrease	3%	7%	p=0.13

RPV/FTC/TAF	EFV/FTC/TDF	
19%	6%	p<0.001
2%	10%	p<0.001

Change in Spine BMD Through Week 48

Studies 1216 and 1160

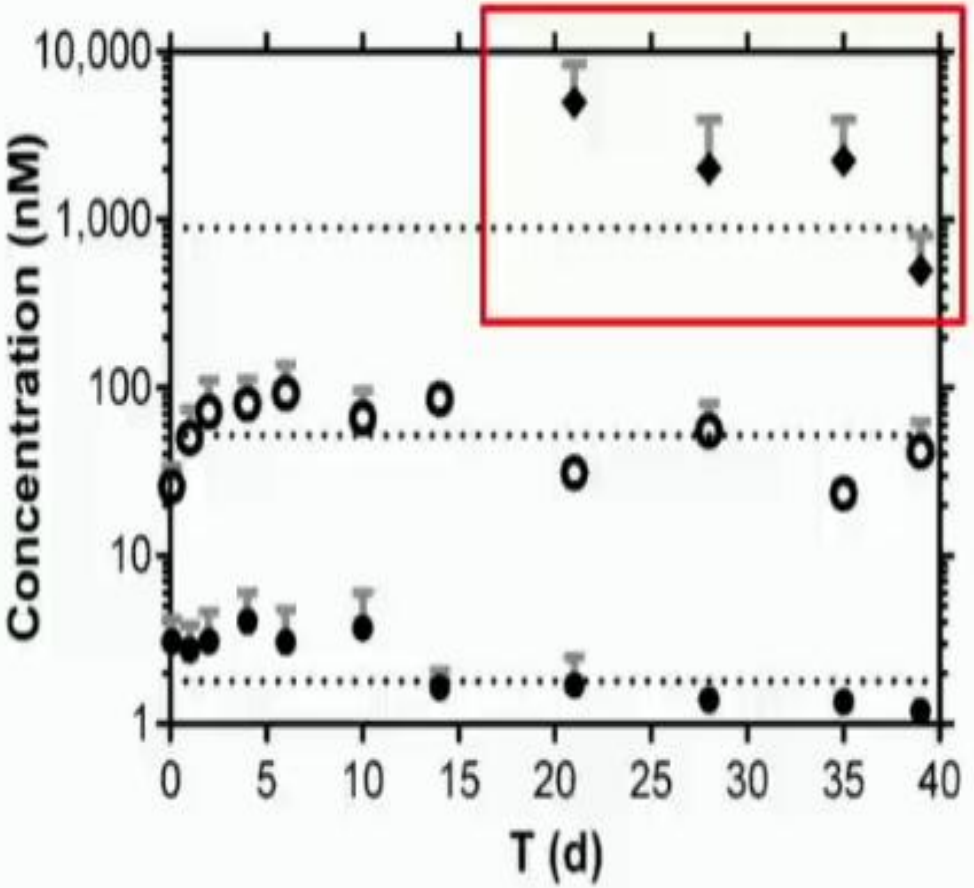


	RPV/FTC/TAF	RPV/FTC/TDF	
≥3% increase	27%	11%	p<0.001
≥3% decrease	6%	13%	p=0.044

RPV/FTC/TAF	EFV/FTC/TDF	
29%	13%	p<0.001
7%	14%	p=0.001

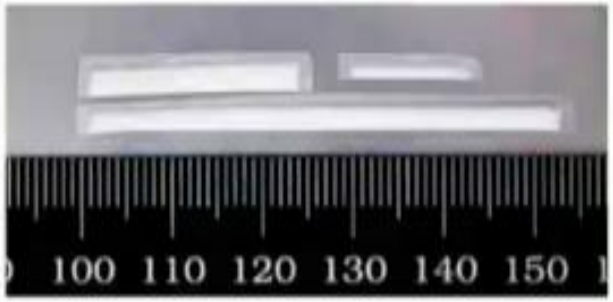
Implantable Formulations (1)

Tenofovir alafenamide silicone tubing implant

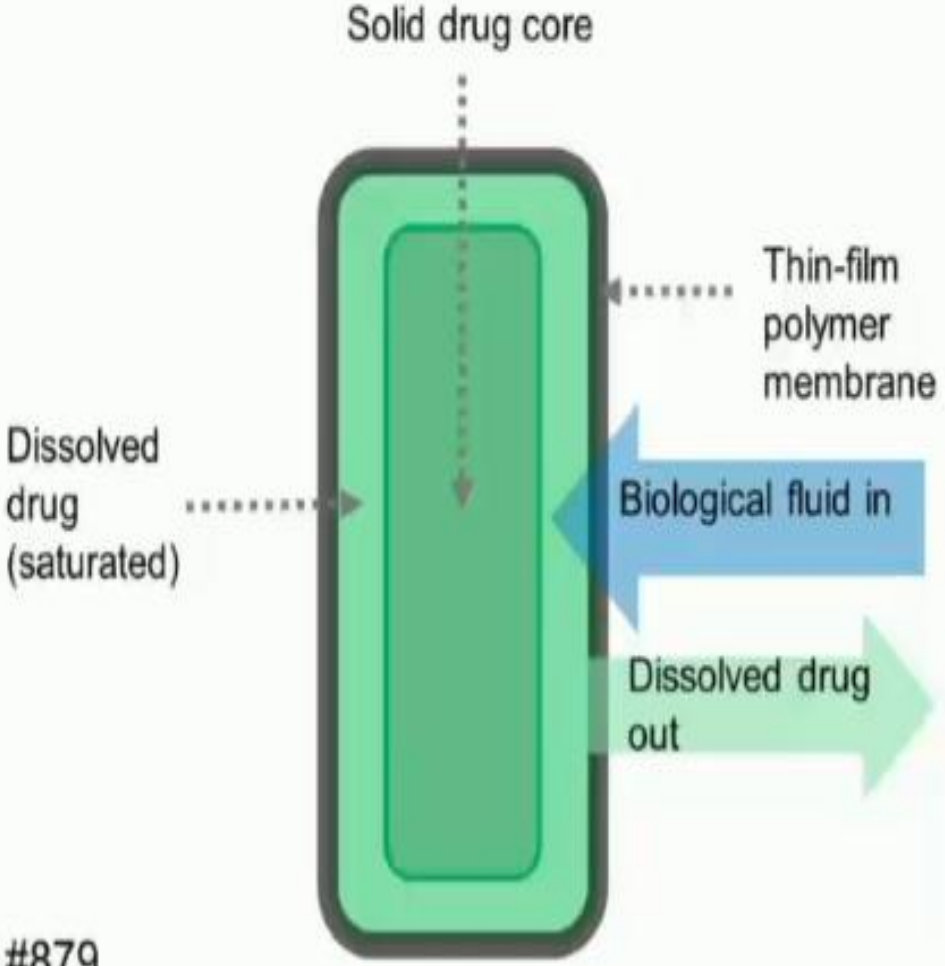


Gunawardana M et al. Antimicrob Agents Chemother 2015

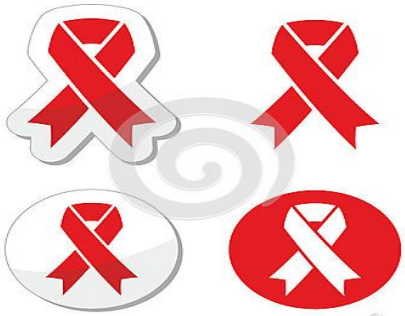
Implantable Formulations (2)



Tenofovir alafenamide polycaprolactone biodegradable implant

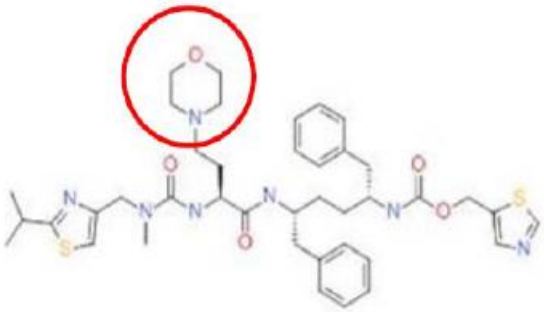


Schlesinger EB et al. CROI 2016 Abstract #879

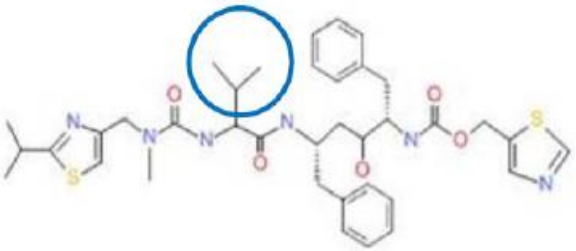


REZOLSTA (Prezista/Cobicista)
e
EVOTAZ (Reyataz/Cobicistat)

Cobicistat is structurally similar to ritonavir..



Cobicistat



Ritonavir

... it has no intrinsic anti-HIV activity
(EC50 > 30µmol/L)
...Cobi has similar inhibition to ritonavir on CYP3A4...

Mathias AA et al., American Society for Clinical Pharmacology and Therapeutics, Vol 87:3 ; March 2010

Ritonavir: vantaggi e svantaggi

- **ritonavir prolunga l'emivita terminale plasmatica dei PI co somministrati** e ne **aumenta la concentrazione di valle (C trough)**, consentendo ai PI di essere assunti BID o QD

- **tuttavia il ritonavir, si associa ad un aumentato rischio di iperlipidemia con aumento nel lungo termine del rischio cardiovascolare**

- i disturbi gastrointestinali come diarrea o nausea sono piuttosto comuni

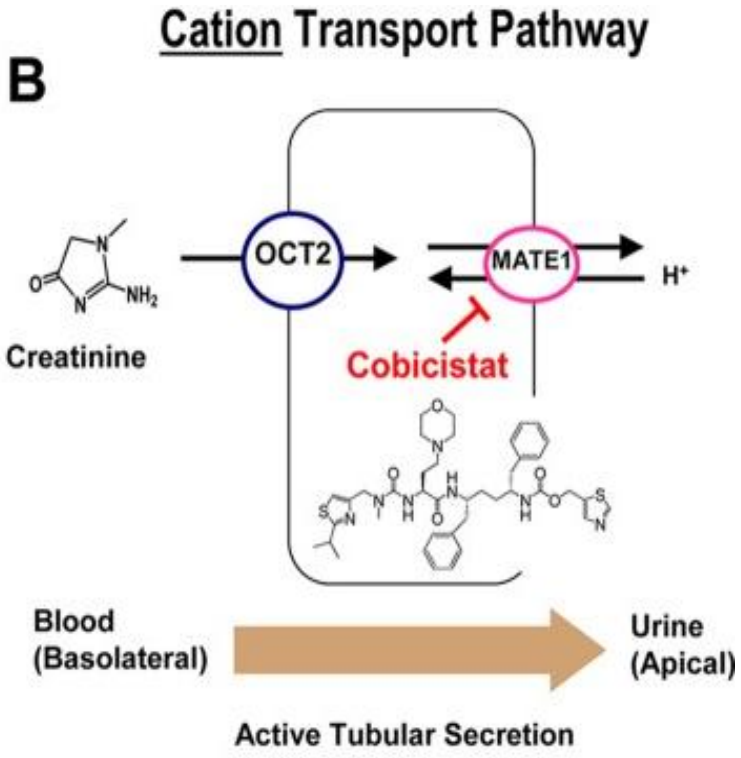
- le DDI sono numerose a causa dell'effetto di RTV sul sistema CYP450 - sia di inibizione che di induzione

Cobicistat : vantaggi e svantaggi

- **un'alternativa al ritonavir** per intolleranza, per l'opportunità di regimi STR e FDC (tenofovir / emtricitabina, cobicistat e elvitegravir, atazanavir o darunavir)
- **un'inibizione più specifica** del citocromo P450 3A (CYP3A) rispetto a ritonavir
- **non ha attività antivirale** contro l'HIV
- **ha un profilo diverso di interazione tra farmaci**

Cobicistat e funzionalità renale

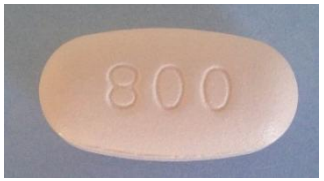
- **Cobicistat riduce la clearance stimata della creatinina** (eGFR) a **causa dell'inibizione della secrezione.**
- **La Creatinina viene rimossa dal sangue principalmente dai reni per filtrazione glomerulare, ma anche per secrezione tubulare prossimale.**
- **Il riassorbimento tubulare di creatinina è davvero poco rilevante se non nullo**
- **L'eGFR (tasso presunto di filtrazione glomerulare) viene calcolato con la concentrazione di creatinina sierica** e **alcune o tutte le seguenti variabili: sesso, età, peso e razza anche senza una raccolta urine delle 24 ore**
- **Quindi la clearance della creatinina è sovrastimata a causa dell'apporto 'extra' della secrezione tubulare**



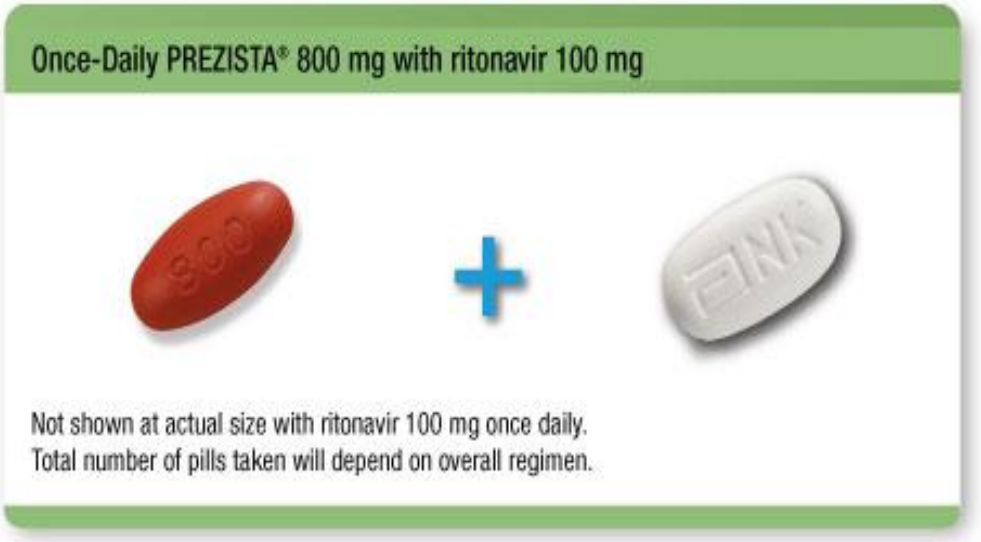
ATV + COBI and DRV + COBI Clinical Overview

	ATV + COBI[1]	DRV + COBI[2]
Indication	**EVOTAZ EU SmPC**: EVOTAZ is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults without known mutations associated with resistance to atazanavir	**REZOLSTA EU SmPC**: REZOLSTA, is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adults aged 18 years or older. Genotypic testing should guide the use of REZOLSTA
Posology	The recommended dose of EVOTAZ is one tablet once daily taken orally with food	*ART-naïve patients* The recommended dose regimen is one film-coated tablet of REZOLSTA once daily taken with food. *ART-experienced patients* One film-coated tablet of REZOLSTA once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs)* and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106 /l (see section 4.1). DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V. In all other ART-experienced patients or if HIV-1 genotype testing is not available, the use of REZOLSTA is not appropriate and another antiretroviral regimen should be used.
Special warnings		Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

REZOLSTA = DRV/cobi



Invece di:



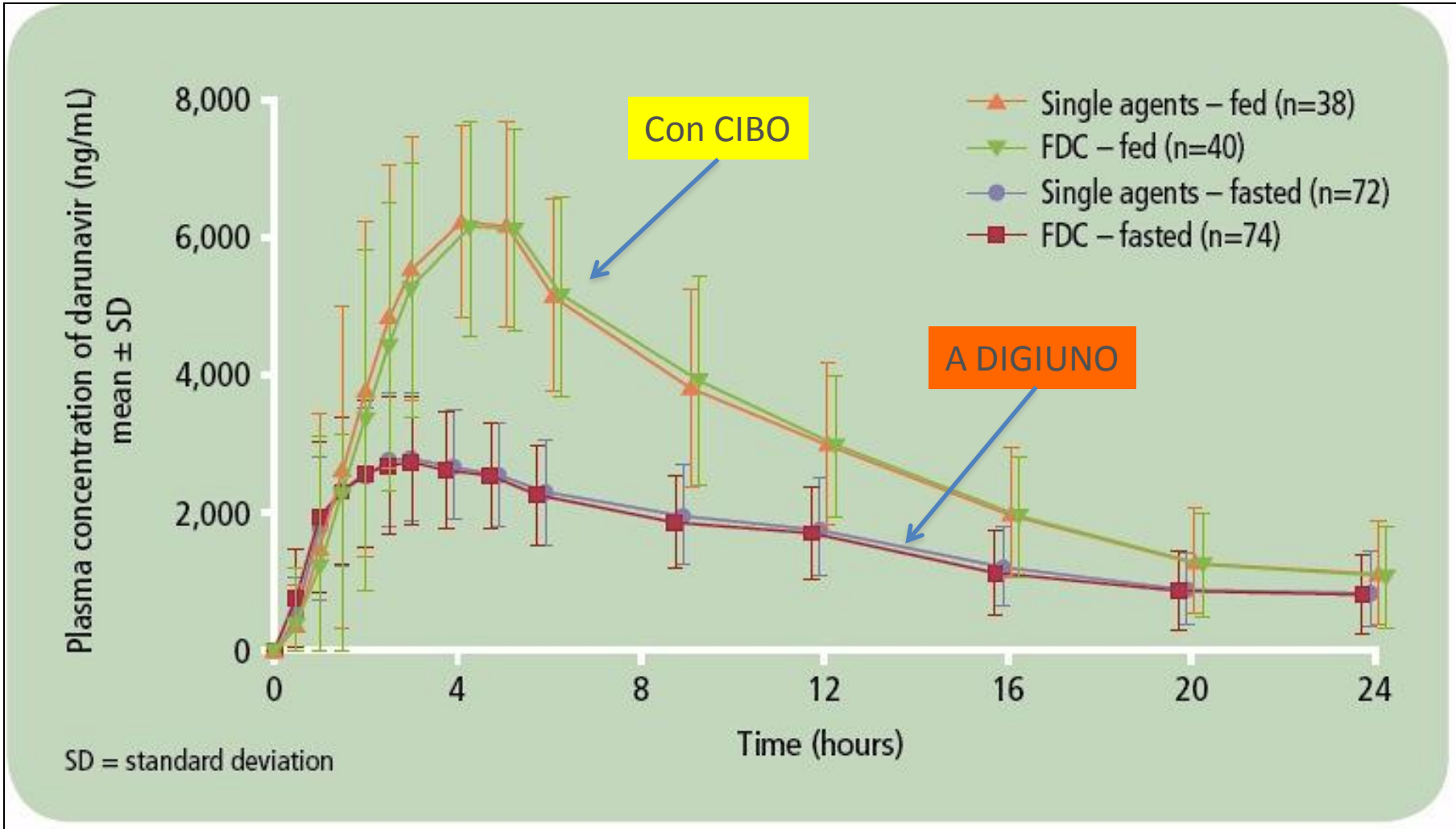
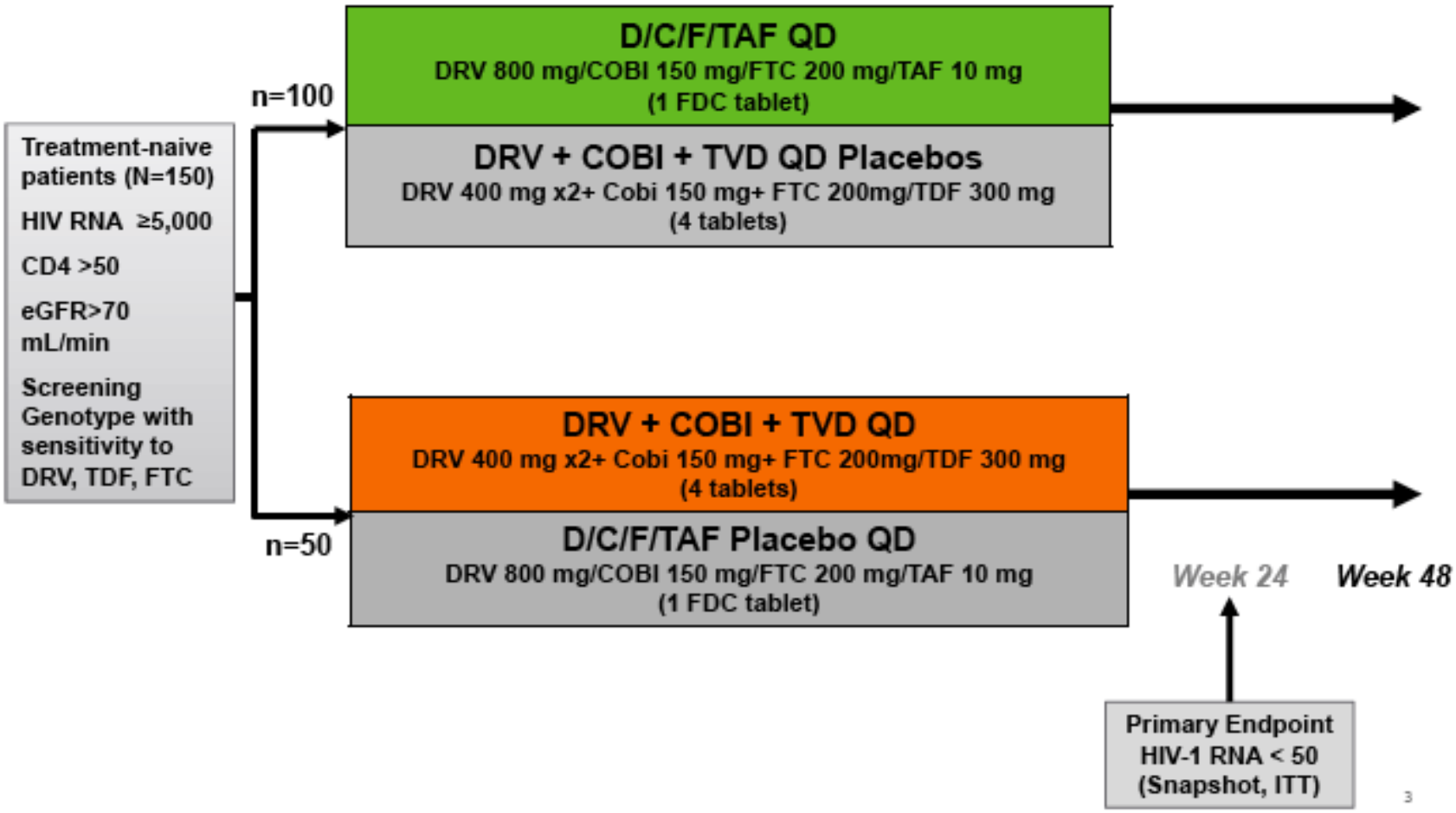
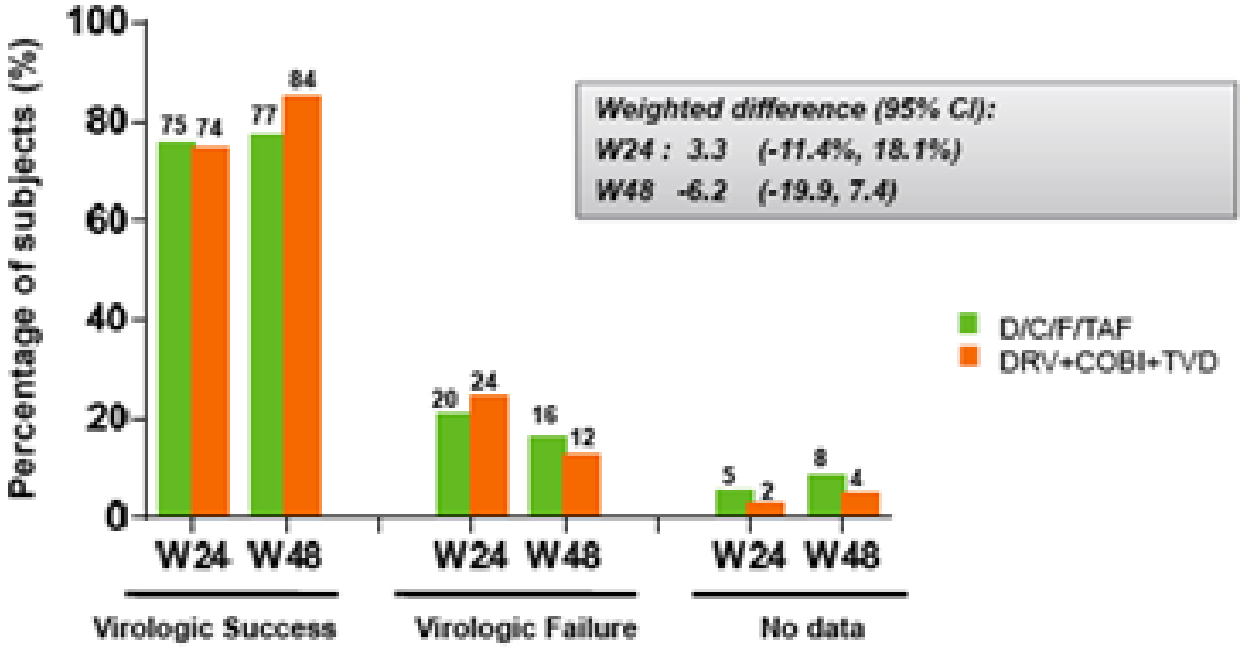


Figure 1 Darunavir plasma concentration-time curves after administration of a single dose of 800-mg darunavir with 150-mg cobicistat as either the FDC or as single agents, under fasted (Panel 1) or fed (standardised breakfast) (Panel 2) conditions. Later timepoints are deleted for clarity.

Phase 2 Study:
A Randomized, Double-Blinded, Placebo-Controlled Trial

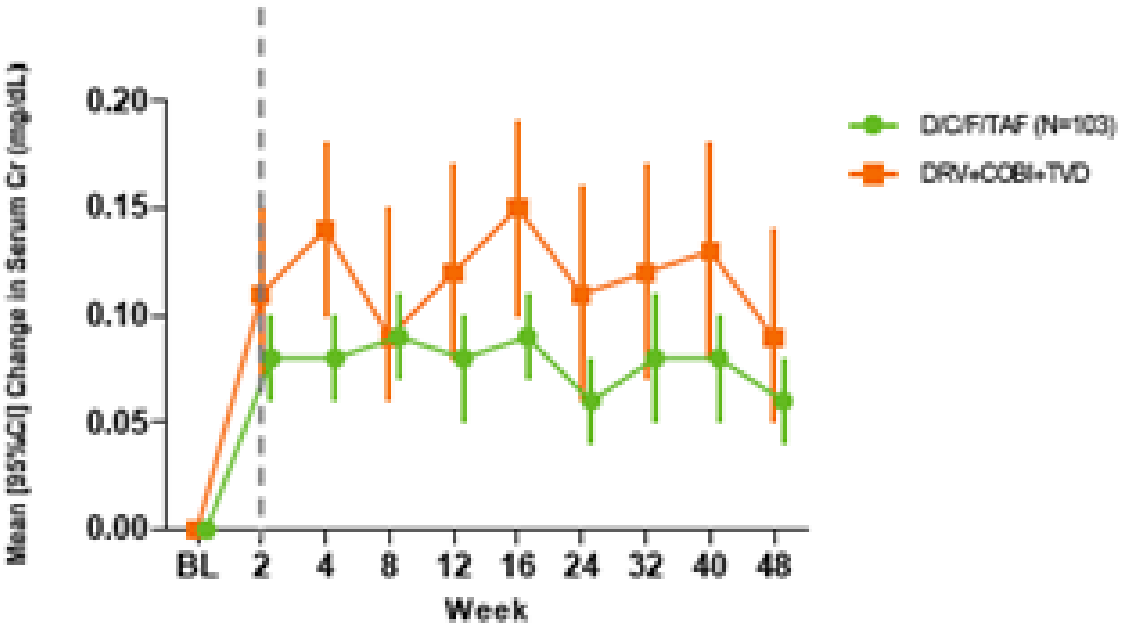


Virologic Outcomes
(HIV-1 RNA <50 c/mL at W 24,48, FDA Snapshot, ITT)



W48 Reasons for Drug Discontinuation	D/C/F/TAF 19 (18%)	DRV+ COBI+TVD 8 (16%)
Lost to Follow-up	10 (10%)	4 (8%)
Withdrew Consent	4 (4%)	2 (4%)
Investigator's Discretion	2 (2%)	0
Patient Non-Adherence	2 (2%)	0
Adverse Event	1 (1%)	2 (4%)

Creatinine Changes Over Time



Mean change in serum creatinine at Week 48

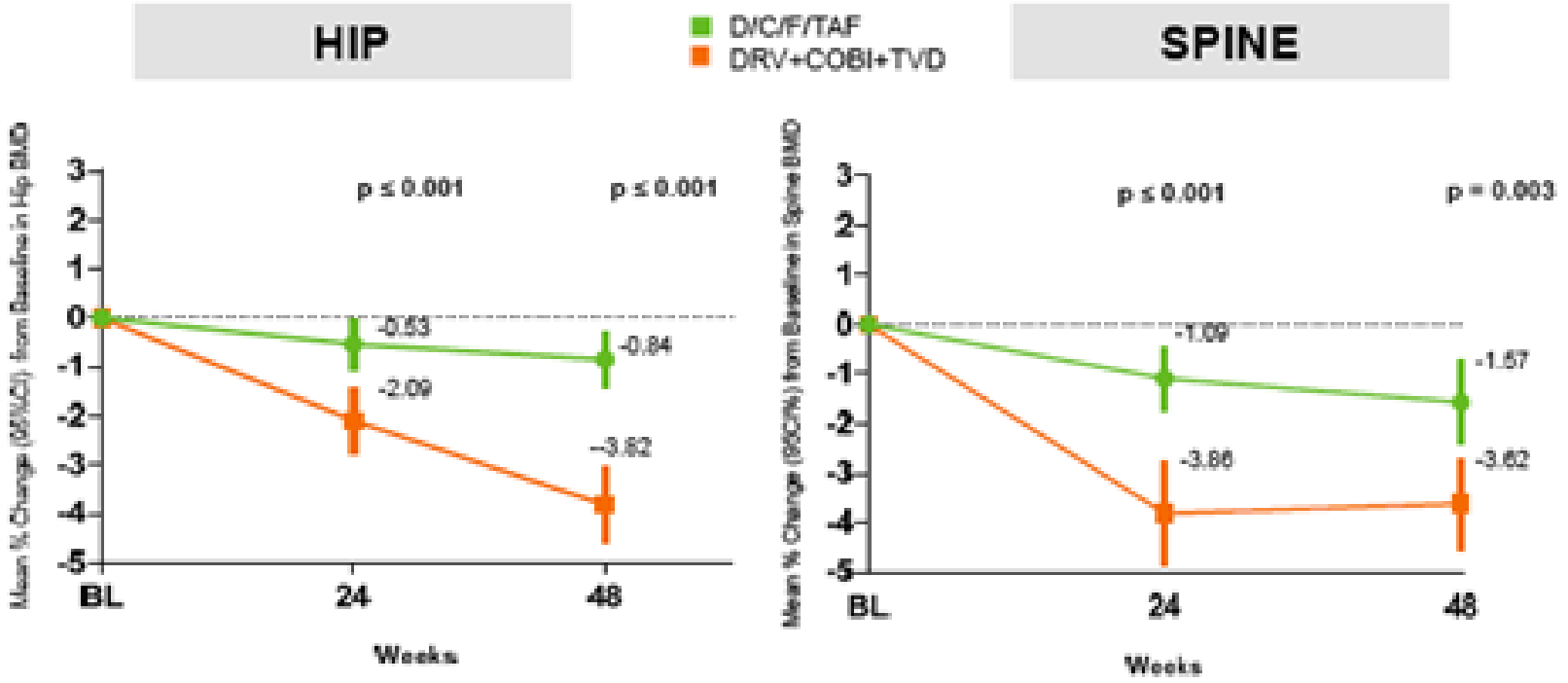
D/C/F/TAF : + 0.06 mg/dL

DRV+COBI+TVD: + 0.09 mg/dL

(p=0.053)

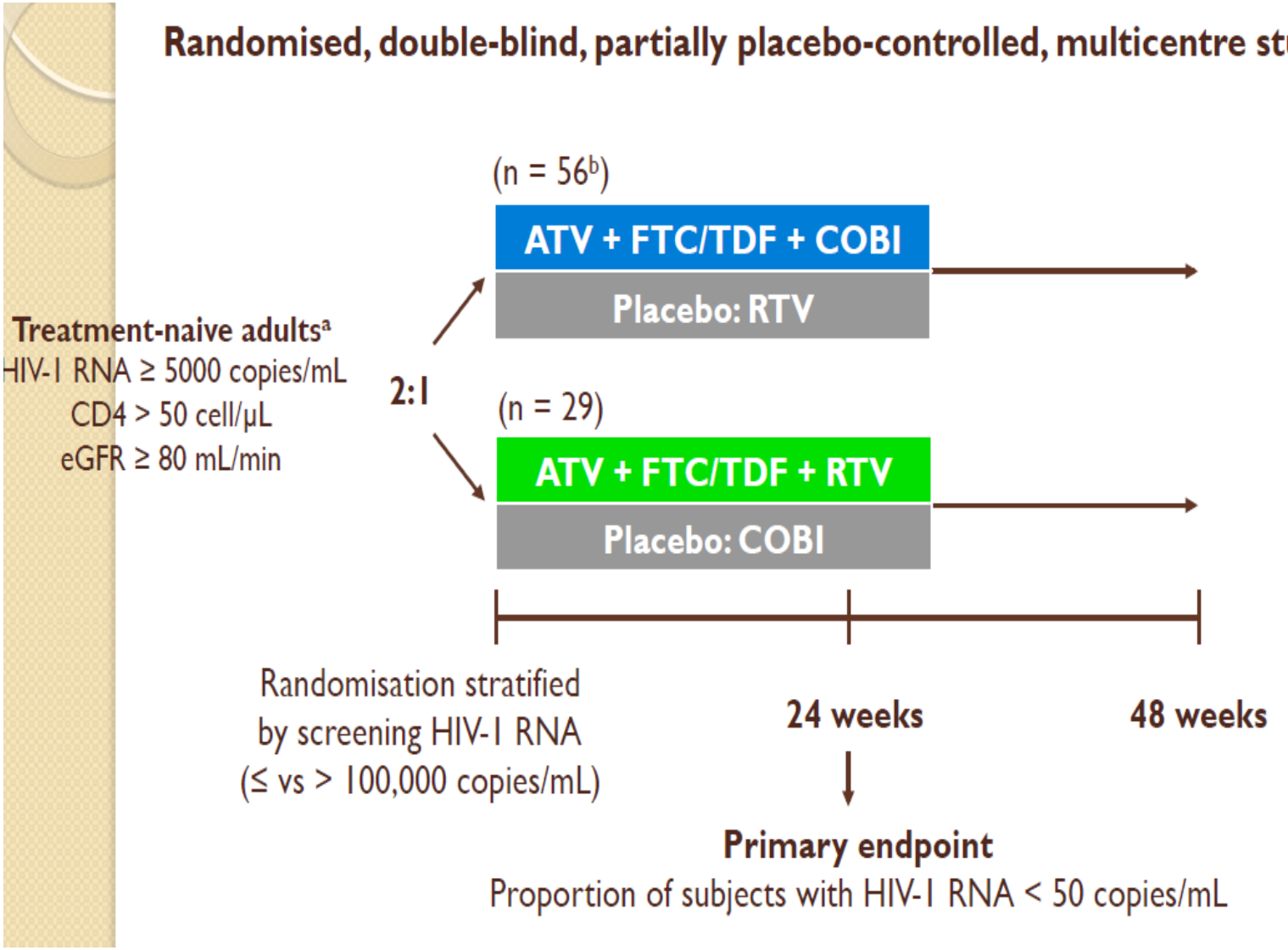
‡

Mean Percent Change in BMD (DEXA)



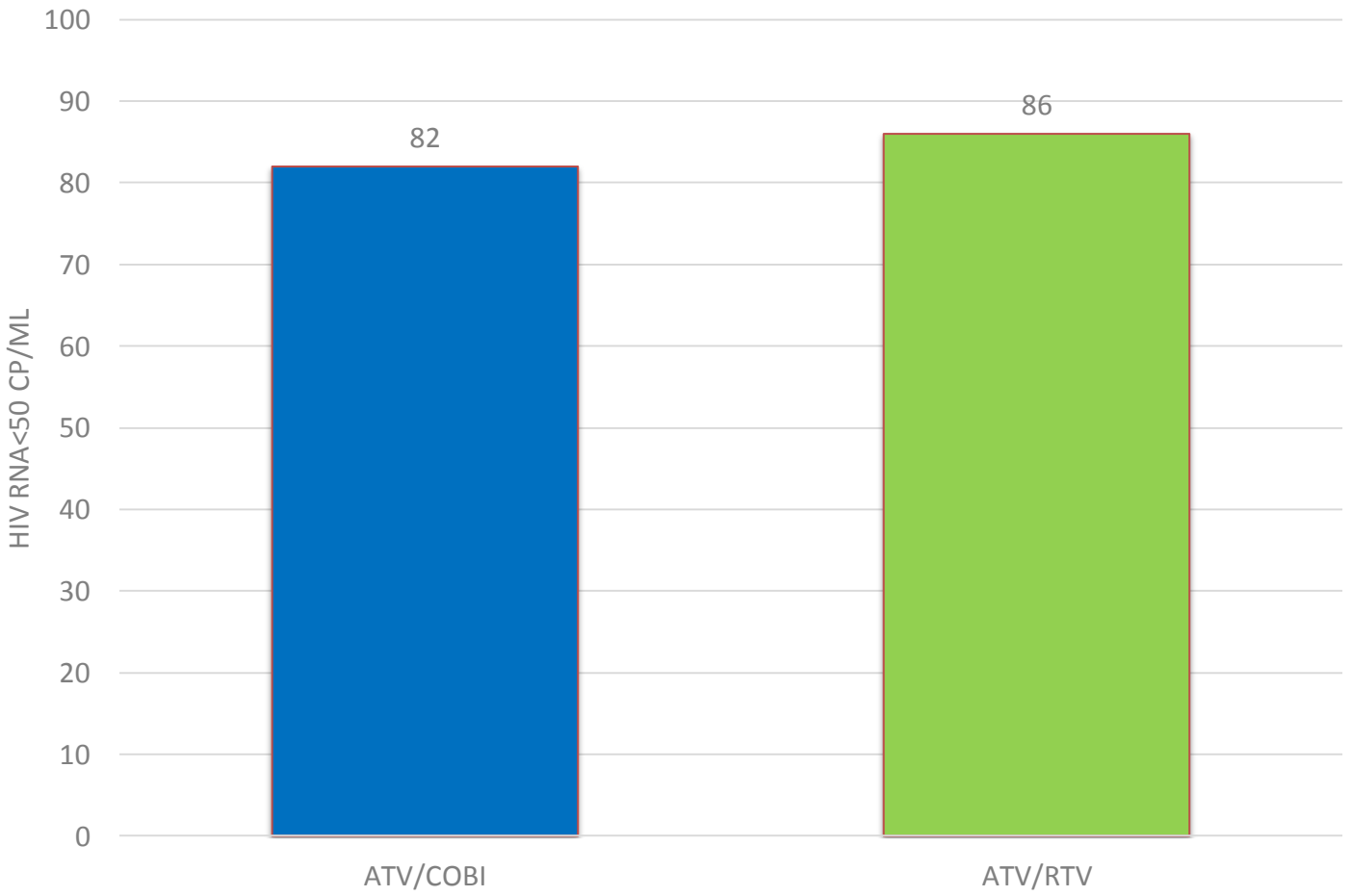
Decreases in hip and spine BMD were smaller in TAF vs. TDF group

Studio105: disegno dello studio

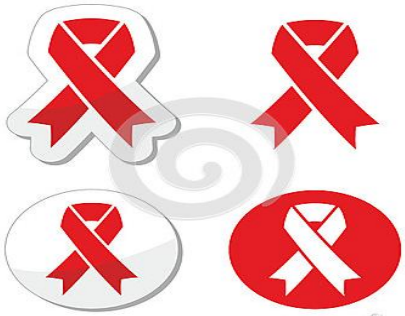


Elion R, et al; GS-US-216-0105 Study Team. Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection. AIDS. 2011 Sep 24;25(15):1881-6.

Studio105: Secondary endpoint HIV RNA<50cp/ml a 48 settimane



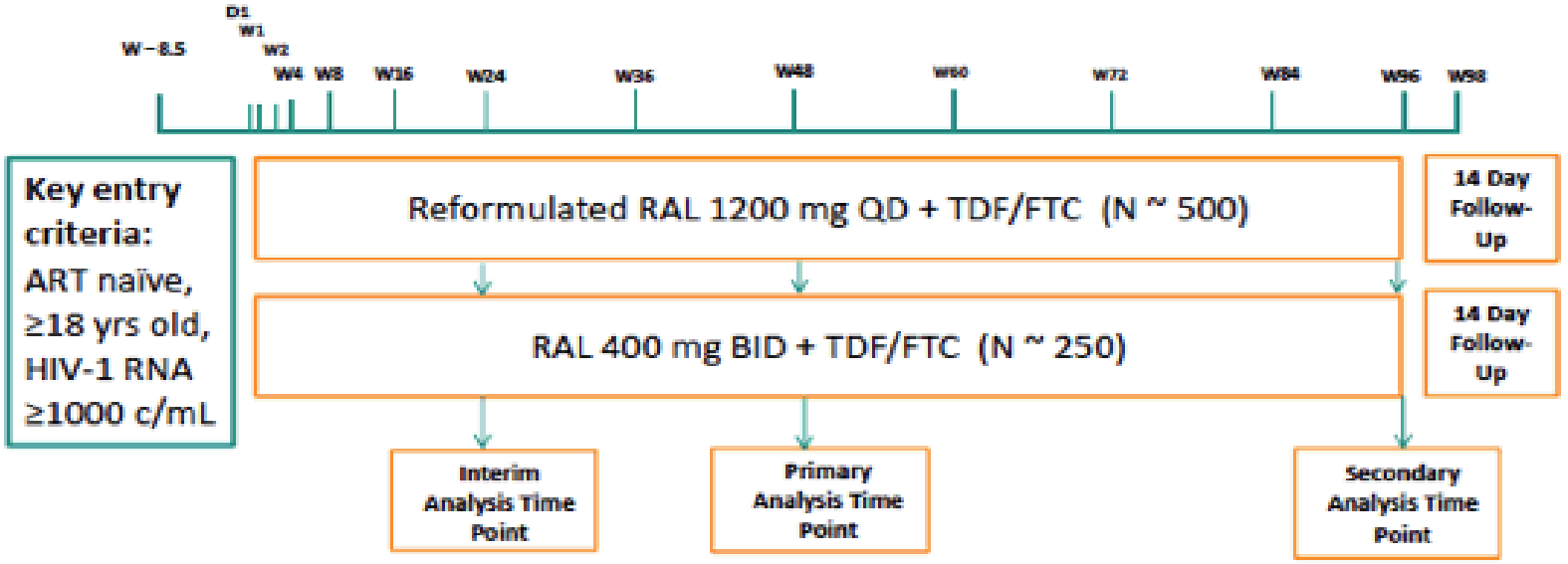
Elion R, et al; GS-US-216-0105 Study Team. Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection. AIDS. 2011 Sep 24;25(15):1881-6.



Nuova formulazione di raltegravir

ONCEMRK: Multicenter, Double-blind, Randomized Controlled Trial

Primary Hypothesis: RAL 1200 mg QD is non-inferior to RAL 400 mg BID, each in combination with TDF/FTC, as assessed by the proportion of subjects achieving HIV RNA <40 c/mL at Week 48 (non-inferiority margin of 10 percentage points).

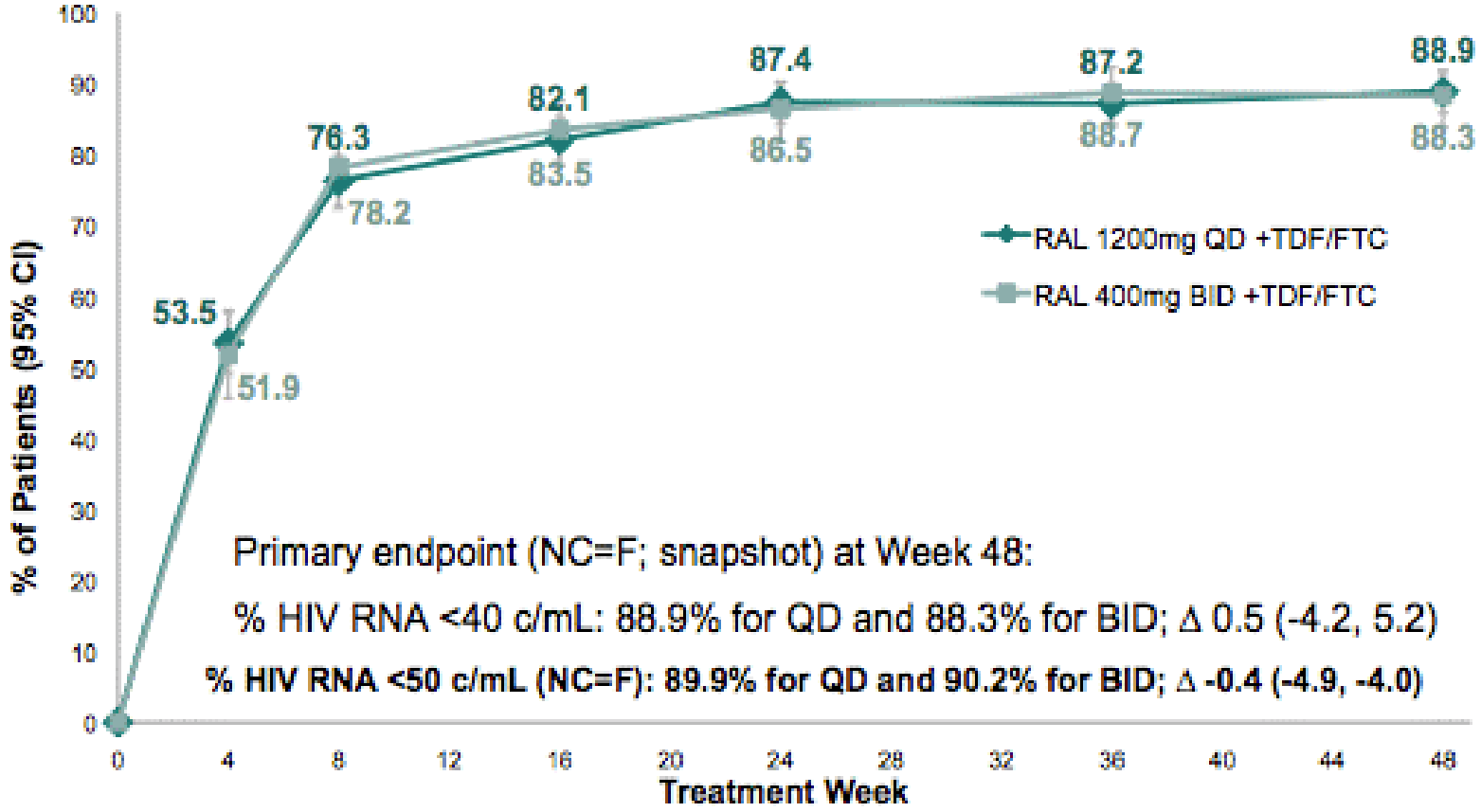


Screening Period was 60 days (~8.5 weeks) prior to randomization.

Subjects randomized in 2:1 ratio (QD:BID), stratified by screening HIV RNA (< / ≥100,000 c/mL) and hepatitis B/C co-infection.

Virologic failure was confirmed with 2 consecutive measurements of HIV RNA at least 1 week apart.

ONCEMRK: Efficacy
HIV RNA <40 copies/mL (NC=F; snapshot)



- **For subgroup with BL HIV RNA >100,000 c/mL:**
  % HIV RNA <40 c/mL (OF): 86.7% for QD and 83.8% for BID; Δ 2.9 (-6.5, 14.1)
- CD4 (cells/mm^3) increase (OF): 232 for QD and 234 for BID; Δ -2 (-31, 27)

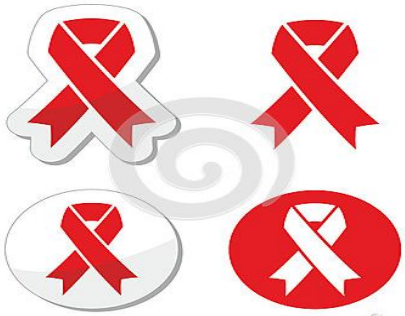
Cahn P et al. AIDS 2016 Abs FRAB0103LB

ONCEMRK: Clinical Adverse Event Summary

Parameter	RAL 1200 mg QD (N=531) (%)	RAL 400 mg BID (N=266) (%)	Difference in % (QD – BID) (95% CI)
Adverse Events (AE)	82.7	86.8	-4.2 (-9.2, 1.3)
Drug-Related (DR)	24.5	25.6	-1.1 (-7.6, 5.1)
Serious AE	5.8	9.4	-3.6 (-8.0, 0.2)
Drug-Related	0.2	0.8	-0.6 (-2.5, 0.4)
Discon. study therapy due to AE	0.8	2.3	-1.5 (-4.1, 0.1)
Due to DR AE	0.0	0.8	-0.8 (-2.7, -0.0)
Due to Serious	0.6	0.8	-0.2 (-2.2, 1.0)
Due to Serious DR AE	0.0	0.0	0.0 (-1.4, 0.7)
Deaths*	0.4	0.4	0.0 (-1.7, 1.0)

* 2 deaths in 1200 mg QD arm: immunoblastic lymphoma (onset day 36) and tuberculosis (onset day 7); 1 death in 400 mg BID arm: AIDS (multiple opportunistic infections, onset day 17).

Cahn P et al. AIDS 2016 Abs FRAB0103LB



Vecchie molecole nuove combinazioni

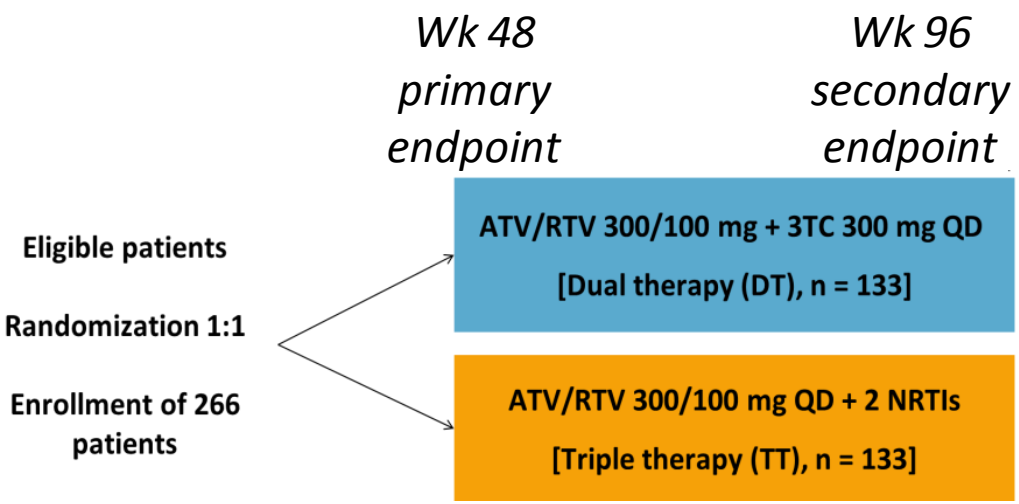
‡

Simplification to Atazanavir/ritonavir + Lamivudine versus maintaining atazanavir/ritonavir + 2NRTIs in virologically suppressed HIV-infected patients: 96-weeks data of the ATLAS-M Trial

001/IHQ/14-12//1224x October 2015

METHODS: Study Design, Inclusion Criteria, Endpoints

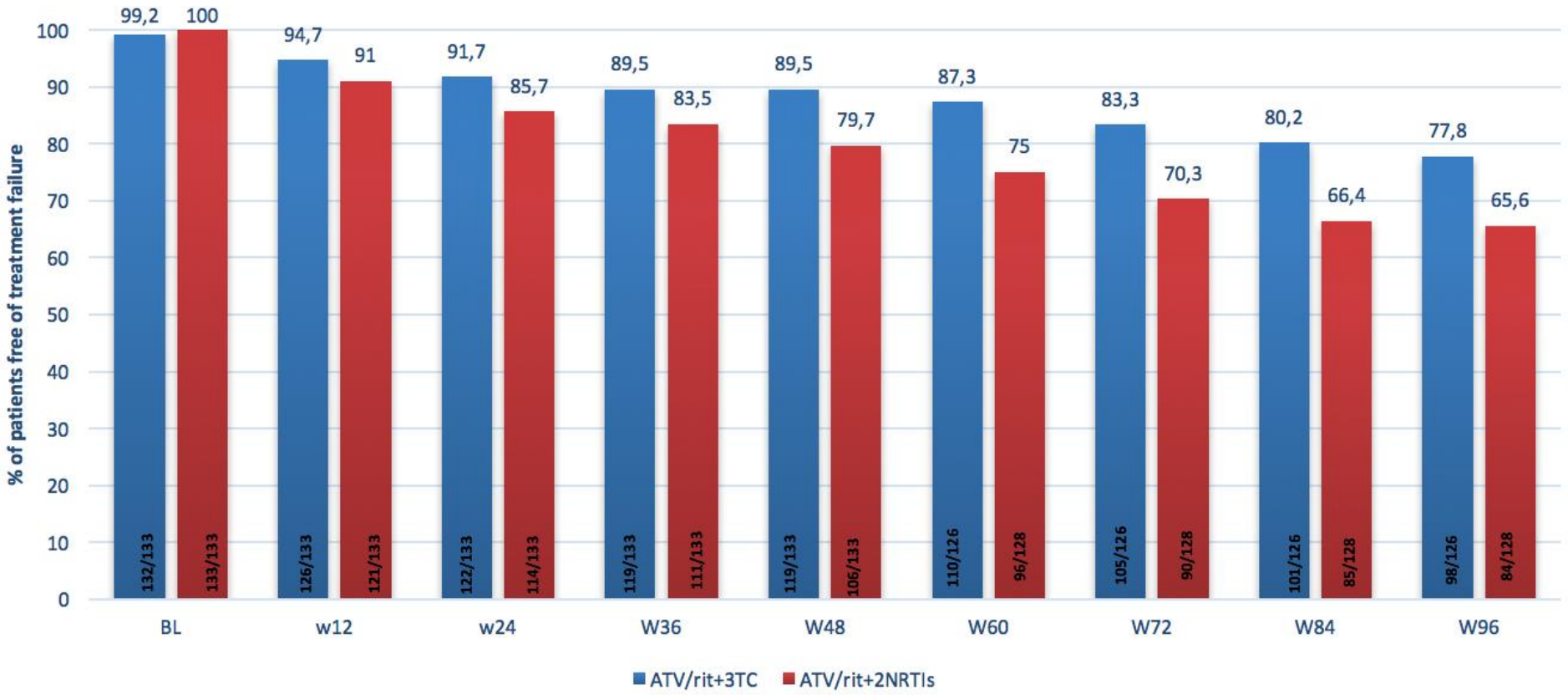
- Objective: to show 48-weeks non-inferior efficacy (margin of -12%) of switch to ATV/r+3TC vs maintaining ATV/r+2NRTIs.
- Design: phase IV, multicenter, open-label, RCT.
- Inclusion criteria: HIV+ on ATV/r+2NRTIs ≥3 months, HIV-RNA <50 cps/mL and CD4 >200 cells/µL ≥6 months.
- Exclusion criteria: previous virological failure, ATV or 3TC resistance, previous mono/dual ART, HBsAg+, pregnancy, PPI.
- Primary endpoint: proportion of patients free from treatment failure at 48 weeks at ITT (switch=failure) analysis.
- Secondary endpoint: proportion of patients free of treatment failure at 96 weeks (ITT analysis, switch = failure)



Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)

Patients free of treatment failure (ITT S=F)

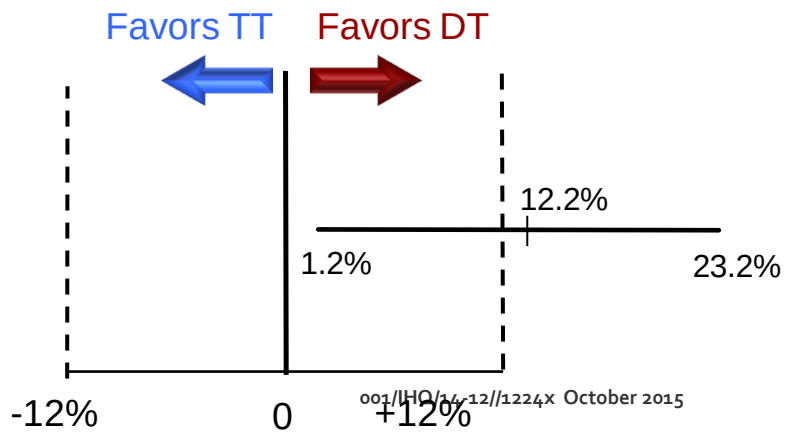
‡



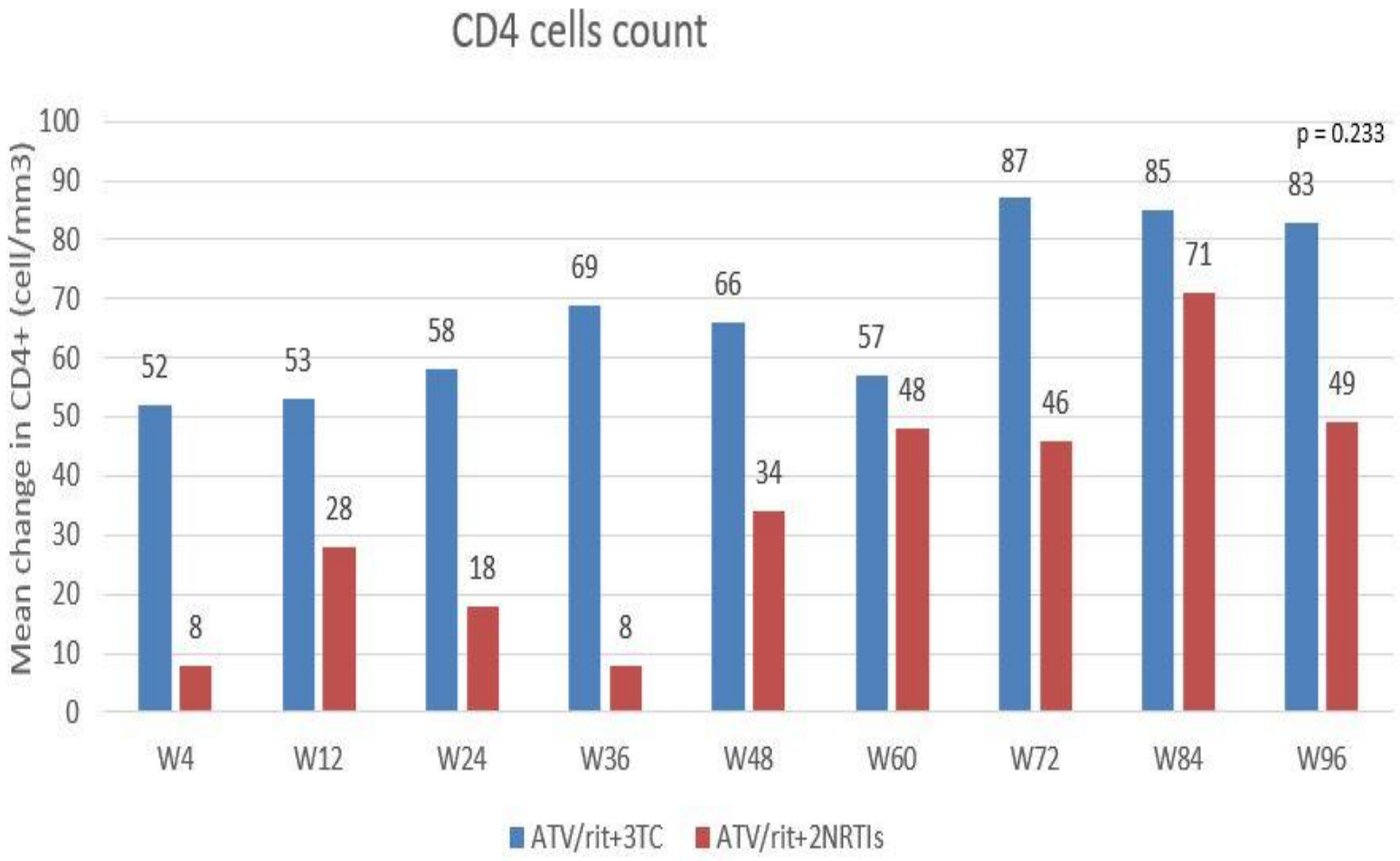
96 weeks free of TF:

DT 77.8% (95% CI 70.5-85.1)

TT 65.6% (95% CI 57.4-73.8)

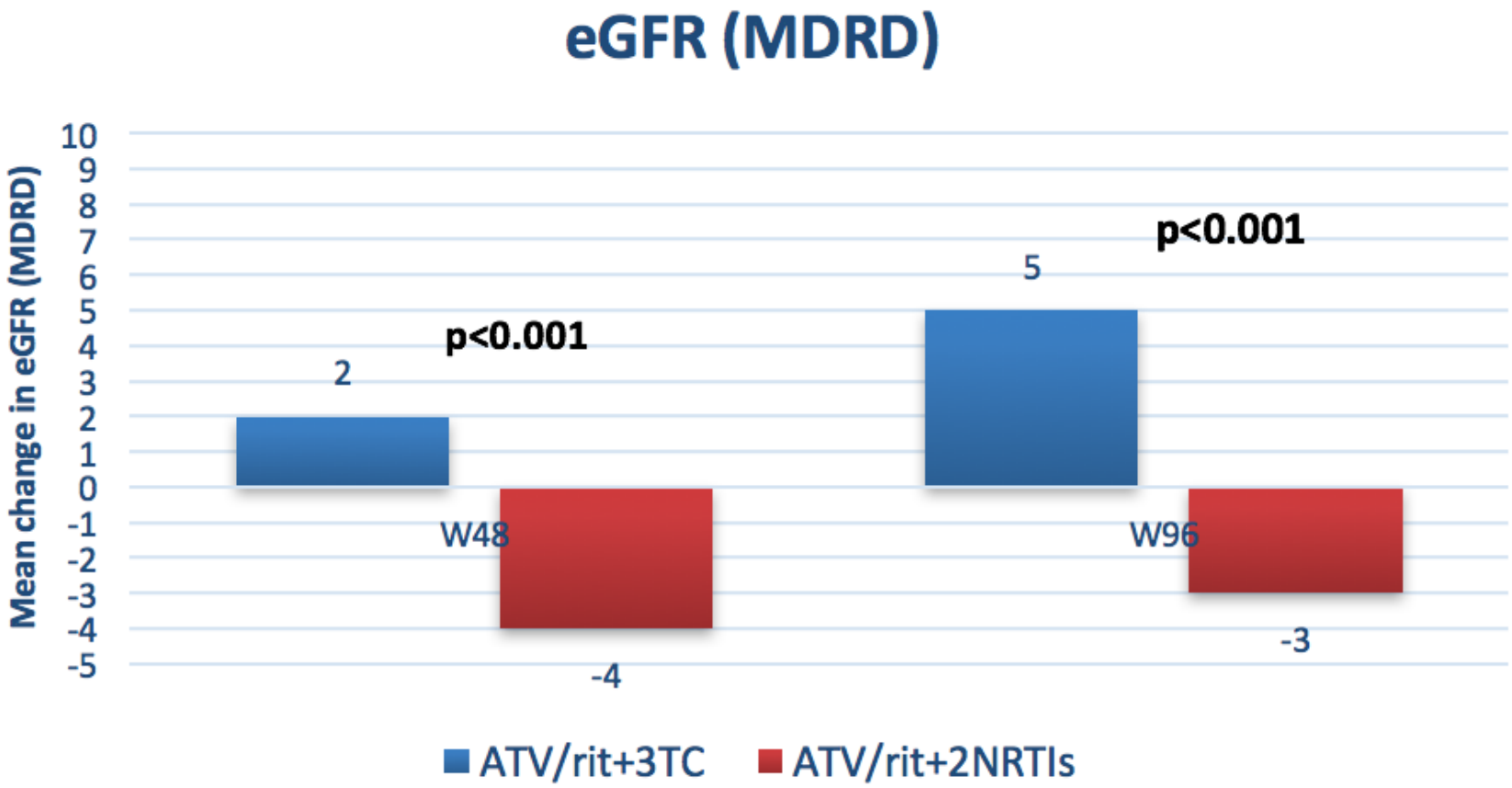


Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)



Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)

Evolution of renal function

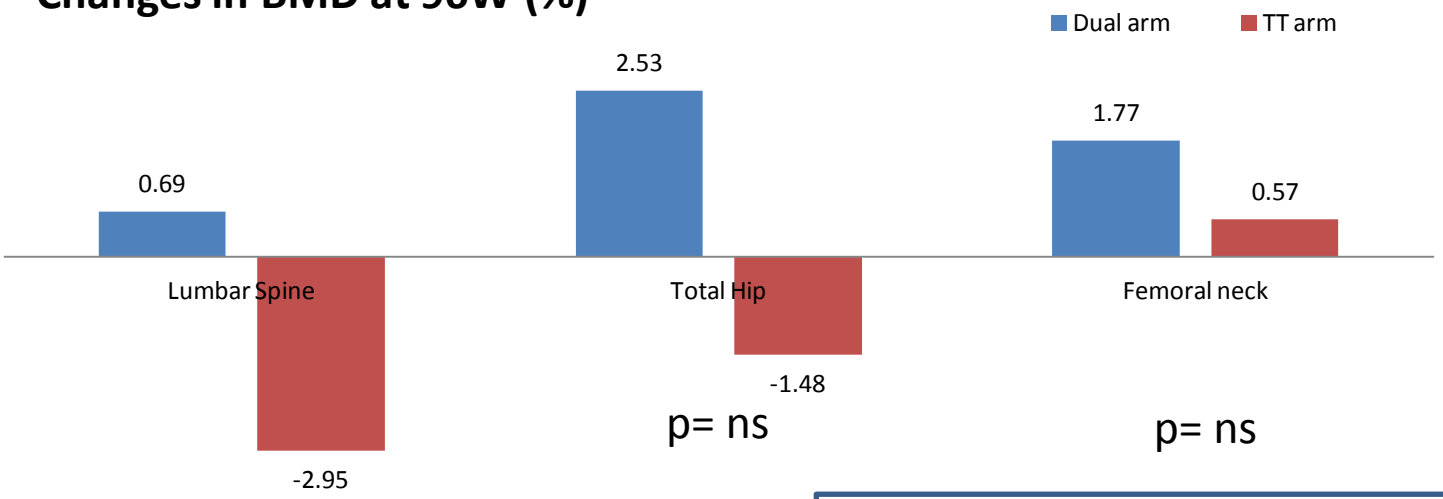


Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)

Bone outcome at 96 weeks

‡

Changes in BMD at 96W (%)



n=73
DT arm: 41
TT arm: 32

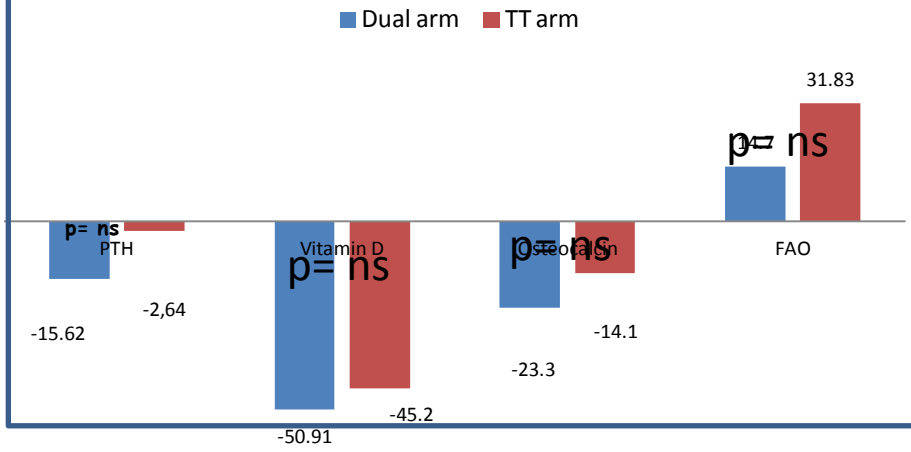
p= ns

p= ns

p=
0.02

We also analyzed body mass changes in distribution but we did not detected any differences within and between arms at 96 weeks

Bone turnover biomarkers (%)

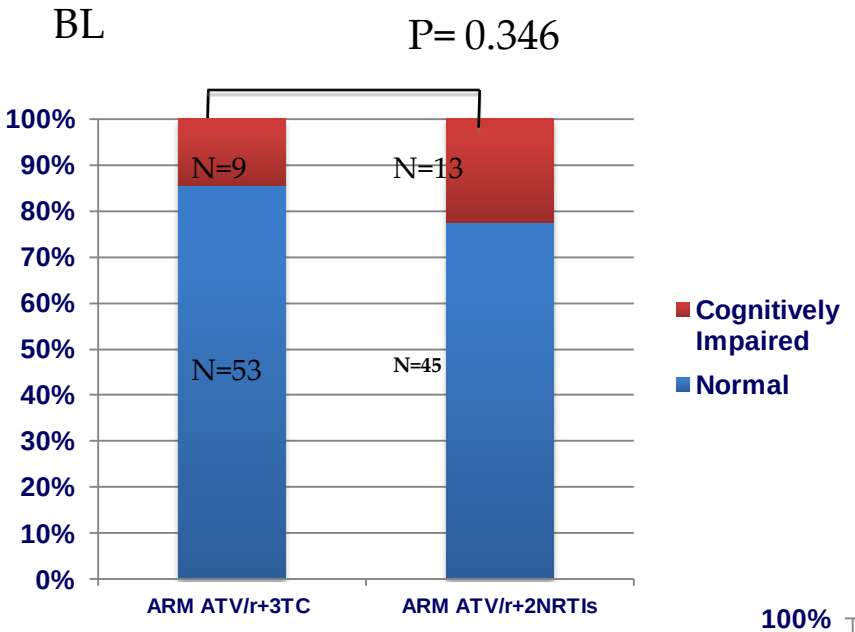


Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)

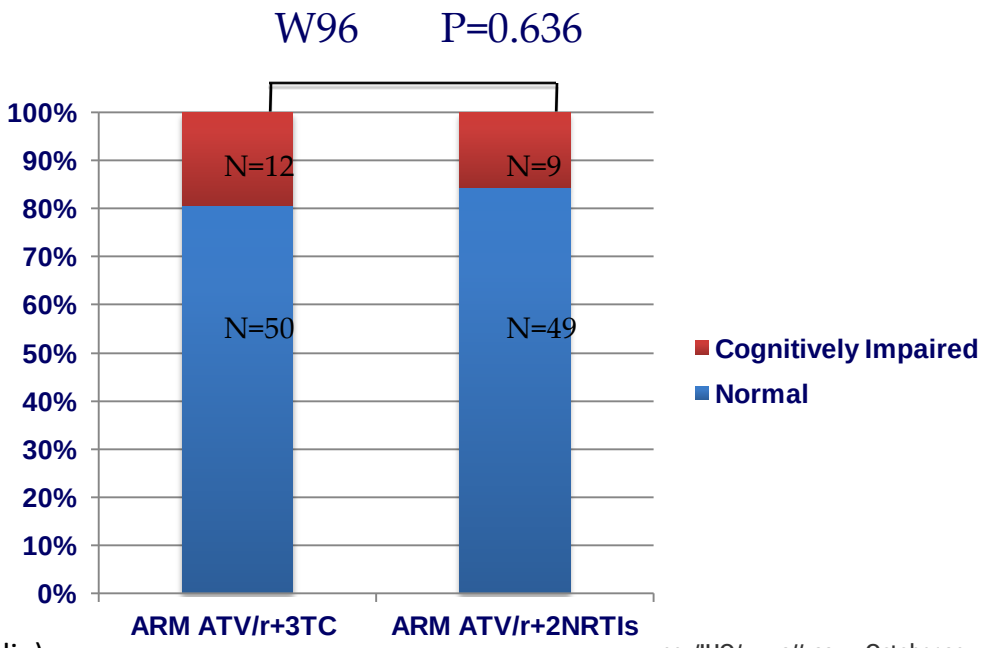
UNIVERSITÀ CATTOLICA del Sacro Cuore

NEUROCOGNITIVE SUB-STUDY (WEEK 96)

PREVALENCE OF HAND



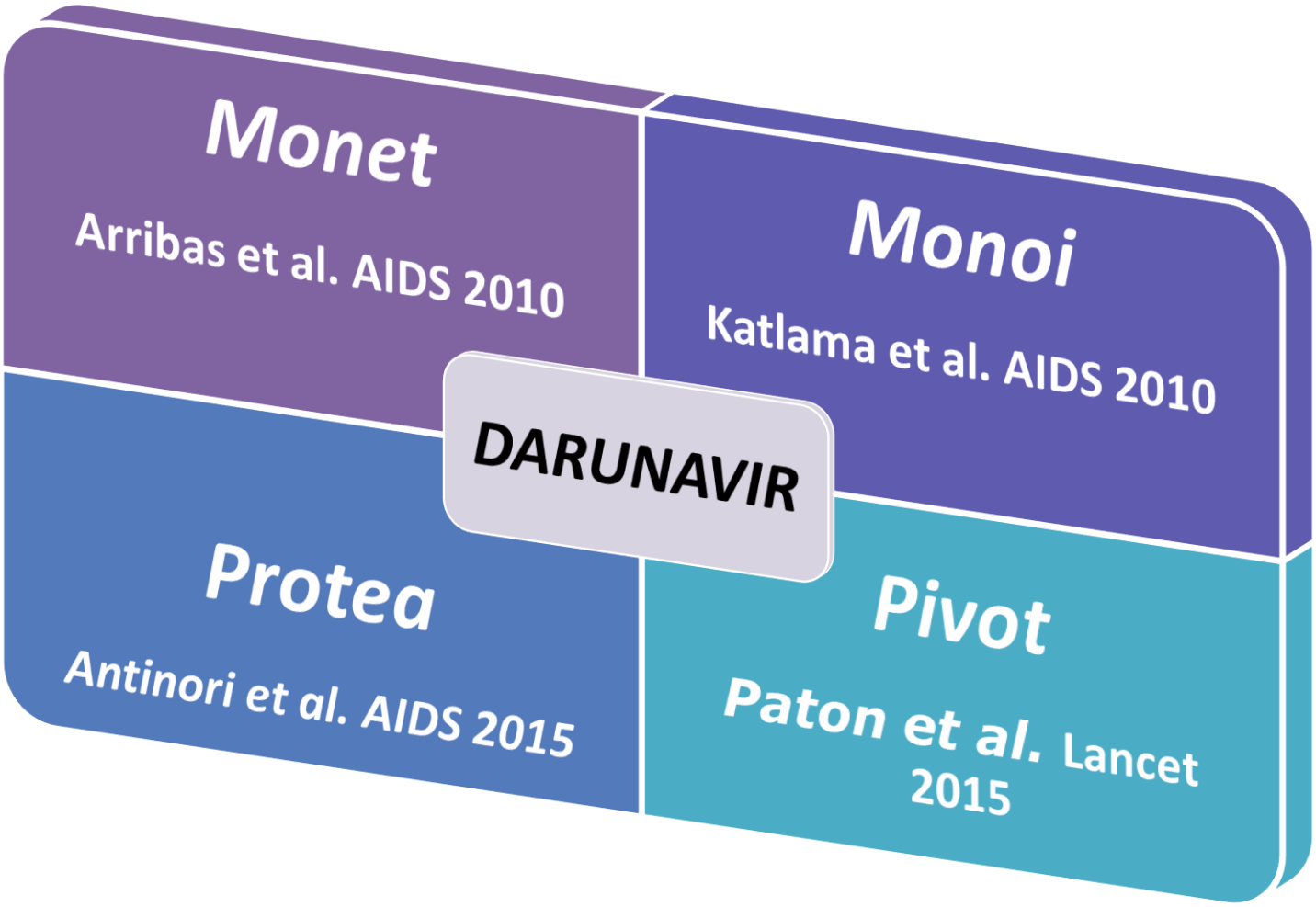
All pts showed an Asymptomatic Neurocognitive Impairment (ANI)



Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)

Darunavir Monotherapy

‡



Mono and Dual Antiretroviral Suppressive Strategies: Real Life Experience in Three Hospitals in Paris (COREVIH Ile-de-France-Centre)

Valantin et al Poster PE 8/80
15th European AIDS Conference,2015.

Objectives To evaluate the profile of suppressive antiretroviral strategies of ART used in 2014 in 3 hospitals of COREVIH Ile-de-France-Centre.

Inclusion Criteria All HIV-infected patients with a suppressed HIV-1 plasma viral load (pVL< 50 copies/ml) in 2014 entered this observational aiming at describing the strategies that include ARV mono-therapies or dual-therapies.

	Monotherapy n=343 (4%)	**Dual therapy n=832 (9%)**	**Triple therapy n=7559 (83%)**
Male / female	251 (73%) / 92 (27%)	570 (68%) / 262 (32%)	5420 (72%)/2139 (28%)
Age (median) [IQR]	51 [45-57]*	52 [46-59]*	48[40-54]
CD4/mm^3 (median) [IQR]	642 [488-843]	621 [458-844]	627 [470-826]
CD4 nadir (median) [IQR]	231 [147-319]	199 [88-309]	237 [124-353]
Previous AIDS-defining events	62 (18%)	215 (26%)*	1503 (20%)

Mono and Dual Antiretroviral Suppressive Strategies: Real Life Experience in Three Hospitals in Paris (COREVIH Ile-de-France-Centre)

	Monotherapy n=343 (4%)	Dual therapy n=832 (9%)	Triple therapy n=7559 (83%)
ARV strategies	DRV/r 213 (63%) LPV/r 79 (23%) DTG 29 (8%) ATV/r 17 (5%) FPV/r 3 (1%)	NNRTI+INI 237 (29%) INI+IP/r 181 (22%) NNRTI+IP/r 101 (12%) NRTI+IP/r 93% (11%) 2NRTI 91 (11%) Others 129 (15%)	2NRTI+NNRTI 3342 (44%) 2NRTI+IP/r 2040 (27%) 2NRTI+INI 1411 (19%) 2NRTI+ non boostedIP 313 (4%) NNRTI+INI+(IP/rouNRTIouC CR5I) 174 (2%) Others 279 (4%)
Duration of the current strategy (months)median	32 [10-58]	18 [8-46]	26 [12-58]
Duration of prior cART (years) median	16 [10-18]	18 [10-20]*	10 [5-17]
Initiation / switch	4 (1%) / 346 (99%)	8 (1%) / 821 (99%)	
Main reasons of the discontinuation of the previous line	Toxicity 98 (30%) Simplification 161 (50%) Failure 21 (7%)	Toxicity 349 (46%) Simplification 155 (20%) Failure 97 (13%)	

* p<0,001 mono or dual therapy vs triple therapy

Adapted from Valantin et al Poster PE 8/80

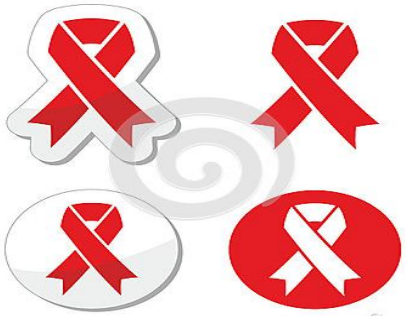
15th European AIDS Conference, Barcelona 2015.

Raltegravir/Etravirina

‡

- **Katlama *et al.*** : studio retrospettivo che ha dimostrato che uno switch con duplice terapia a base di RAL 400 / ETR 200 BID era in grado di mantenere la soppressione virologica nei pazienti HIV-1, stabilmenti soppressi in HAART : all'analisi intent- to-treat , l'efficacia a 6 mesi di follow - up è stata del 94,4 % (n = 17/18 , 95 % CI 74.2 , 99%) e il 83,3 % (n = 15/18 , 95 % CI 60.7 , 94,1 %) a 12 mesi . Nell'analisi per protocol , l'efficacia a 12 mesi era 100 % (n = 15/15 , 95 % CI 80.6 , 100 %). Non è stata registrata alcuna interruzione del trattamento correlata alla tollerabilità

- **Monteiro *et al.:*** studio prospettico di coorte, in cui 25 pazienti con soppressione virologica, con problemi di tollerabilità, problemi di sicurezza a causa di comorbidità o rischio di interazioni farmacologiche provenienti da regimi a base di PI e NRTI, venivano sostituiti a RAL 400 / ETR 200 BID: a 48 settimane l'efficacia virologica era pari all' 84% (95% IC 65,3% - 93,6%), mediante analisi intent-to-treat ed al 91,3% (95% IC 73,2% -97,6%) nell'analisi per-protocol; inoltre è stato registrano un miglioramento dei parametri lipidici, un riduzione del LTCD8 ed un aumento del rapporto CD4/CD8.



Triumeq: quali vantaggi

‡

Abacavir/dolutegravir/lamivudine in HIV-1 infection: a summary

Fixed-dose combination of an integrase strand transfer inhibitor (dolutegravir) and two nucleoside reverse transcriptase inhibitors (abacavir and lamivudine)

Once-daily, single-tablet regimen that is potentially more convenient than multiple-tablet regimens

Superior efficacy when compared with efavirenz/tenofovir disoproxil fumarate (tenofovir DF)/emtricitabine, driven by nonvirological endpoints

Generally well tolerated, with a more favourable tolerability profile than efavirenz/tenofovir DF/emtricitabine

High genetic barrier to resistance

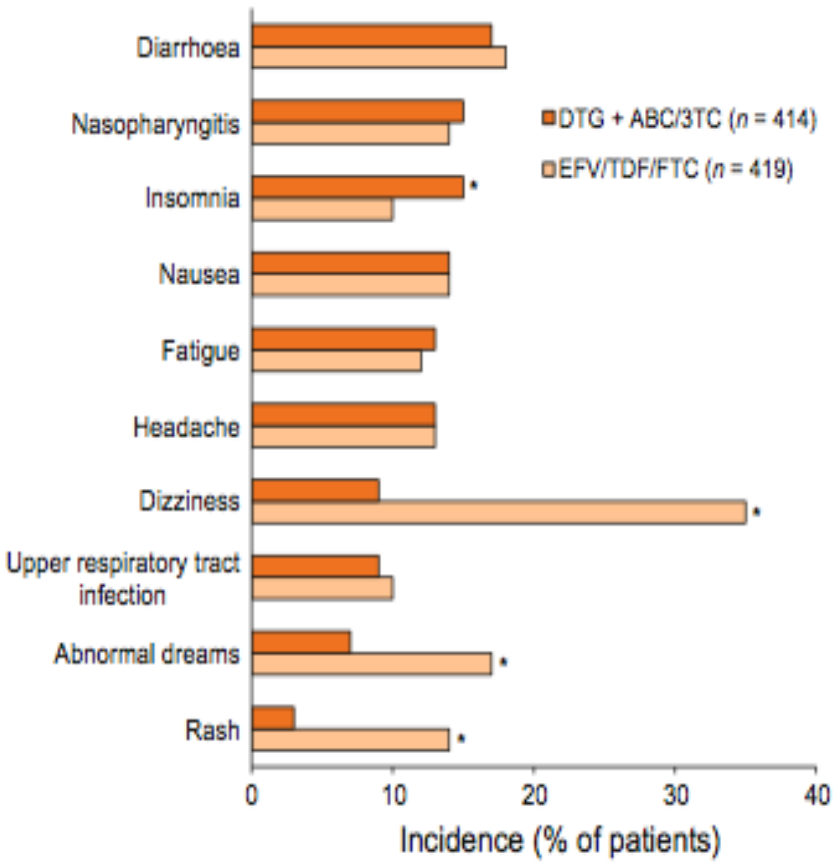


Fig. 1 Treatment-emergent adverse events with a ≥10 % incidence in the SINGLE trial [19]. *3TC* lamivudine, *ABC* abacavir, *DTG* dolutegravir, *EFV* efavirenz, *FTC* emtricitabine, *TDF* tenofovir disoproxil fumarate. * indicates relative risk 95 % confidence interval was exclusive of 1.0, indicating significant between-group difference

Greig S, Drugs 2015

0012-6667/14-12/1124x October 2015

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SINGLE STUDY

Proportion <50 c/mL (95% CI) and CD4 Change from Baseline

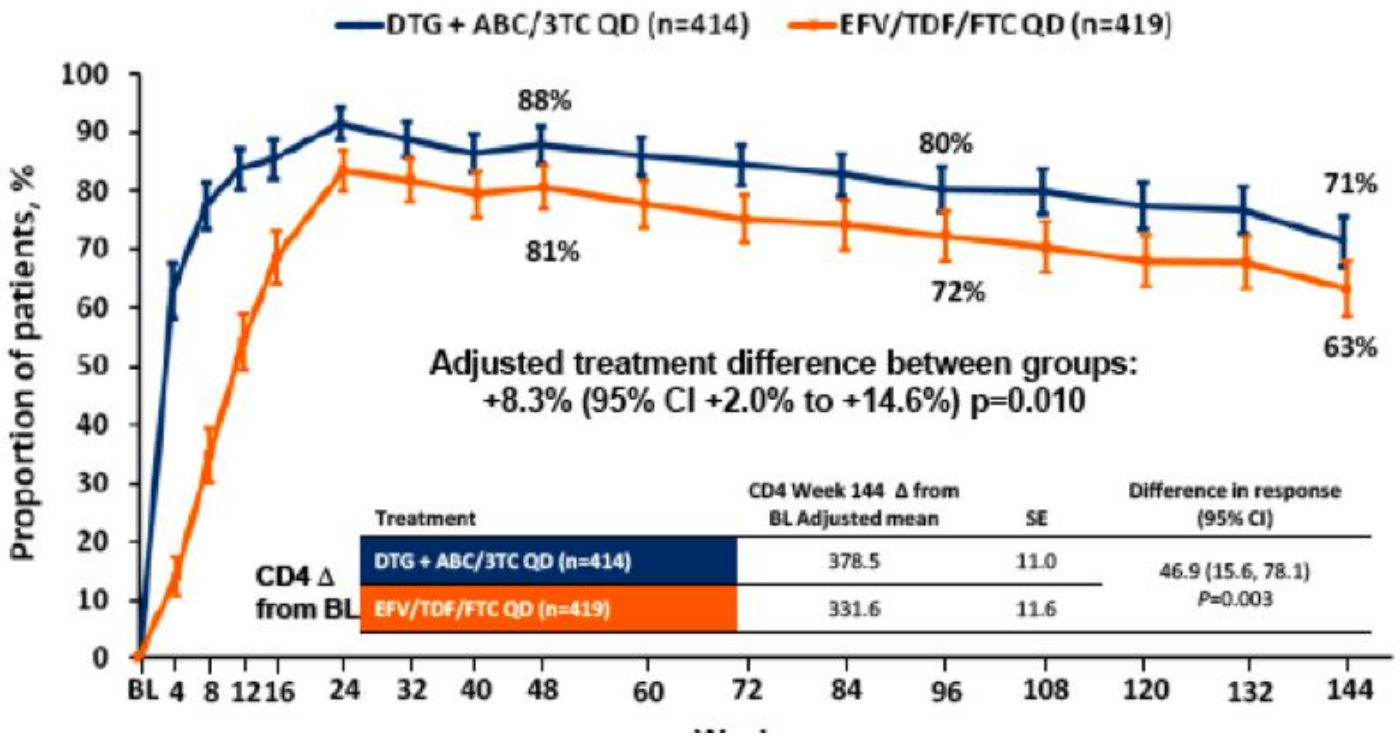

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Table 1 Efficacy of dolutegravir plus abacavir/lamuvidine in the treatment of antiretroviral therapy-naive adults with HIV-1 infection. Results from the SINGLE trial at weeks 48 [19], 96 [20] and 144 [47]; some data are from abstracts and a poster [20, 47]

Parameter	Regimen[a]	Week 48	Week 96	Week 144
Plasma HIV-1 RNA <50 copies/mL (% of pts)[b]	DTG + ABC/3TC	88*	80*	71*
	EFV/TDF/FTC	81	72	63
	Difference (95 % CI)	7 (2–12)	8.0 (2.3–13.8)	8.3 (2.0–14.6)
Median time to virological suppression (days)[c]	DTG + ABC/3TC	28**		
	EFV/TDF/FTC	84		
	Hazard ratio (95 % CI)	2.32 (2.00–2.68)		
CD4+ cell count adjusted mean change from baseline (median baseline) [cells/μL]	DTG + ABC/3TC	267 (334.5)**	325 (334.5)*	378 (334.5)*
	EFV/TDF/FTC	208 (339.0)	281 (339.0)	332 (339.0)
	Difference (95 % CI)	59 (33–84)	44.0 (14.3–73.6)	47 (16–78)
Virological failure (% of pts)[d]	DTG + ABC/3TC	4	6	9
	EFV/TDF/FTC	4	6	8

Greig S, Drug 2015

SINGLE : resistance a 144 weeks

	DTG 50 mg + ABC/3TC QD (N=414)			EFV/TDF/FTC QD (N=419)		
	Week 48	Week 96	Week 144	Week 48	Week 96	Week 144
Patients with PDVF*, n (%)	18 (4)	25 (6)	39 (9)	17 (4)	25 (6)	33 (8)
NRTI treatment-emergent major mutations	0	0	0	1	1	1
NNRTI treatment-emergent major mutations	0	0	0	4	6	6
INI-resistant treatment-emergent major mutations	0	0	0	0	0	0

*PDVF was defined as two consecutive plasma HIV-RNA values of ≥50 c/mL between Weeks 24 and 48.

Adapted from Walmsley SL, *et al. N Engl J Med* 2013;369:1807–1818 (Appendix); 2. Adapted from Walmsley SL, *et al.* CROI 2014; poster 543; 3. Adapted from Pappa K, *et al.* ICAAC 2014; abstract H-647a2.

HIV/AIDS MAJOR ARTICLE

ING116070: A Study of the Pharmacokinetics and Antiviral Activity of Dolutegravir in Cerebrospinal Fluid in HIV-1–Infected, Antiretroviral Therapy–Naive Subjects

Scott L. Letendre,[1] Anthony M. Mills,[2] Karen T. Tashima,[3] Deborah A. Thomas,[4] Sherene S. Min,[4] Shuguang Chen,[4] Ivy H. Song,[4] and Stephen C. Piscitelli[4]; on behalf of the extended ING116070 study team

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Background. Dolutegravir (DTG), a once-daily, human immunodeficiency virus type 1 (HIV-1) integrase inhibitor, was evaluated for distribution and antiviral activity in cerebrospinal fluid (CSF).

Methods. ING116070 is an ongoing, single-arm, open-label, multicenter study in antiretroviral therapy–naive, HIV-1–infected adults. Subjects received DTG (50 mg) plus abacavir/lamivudine (600/300 mg) once daily. The CSF and plasma (total and unbound) DTG concentrations were measured at weeks 2 and 16. The HIV-1 RNA levels were measured in CSF at baseline and weeks 2 and 16 and in plasma at baseline and weeks 2, 4, 8, 12, and 16.

Results. Thirteen white men enrolled in the study; 2 withdrew prematurely, 1 because of a non–drug-related serious adverse event (pharyngitis) and 1 because of lack of treatment efficacy. The median DTG concentrations in CSF were 18 ng/mL (range, 4–23 ng/mL) at week 2 and 13 ng/mL (4–18 ng/mL) at week 16. Ratios of DTG CSF to total plasma concentration were similar to the unbound fraction of DTG in plasma. Median changes from baseline in CSF (n = 11) and plasma (n = 12) HIV-1 RNA were −3.42 and −3.04 $\log_{10}$ copies/mL, respectively. Nine of 11 subjects (82%) had plasma and CSF HIV-1 RNA levels <50 copies/mL and 10 of 11 (91%) had CSF HIV-1 RNA levels <2 copies/mL at week 16.

Conclusions. The DTG concentrations in CSF were similar to unbound plasma concentrations and exceeded the in vitro 50% inhibitory concentration for wild-type HIV (0.2 ng/mL), suggesting that DTG achieves therapeutic concentrations in the central nervous system. The HIV-1 RNA reductions were similar in CSF and plasma.

Clinical Trials Registration. NCT01499199.

ARIAL : study design

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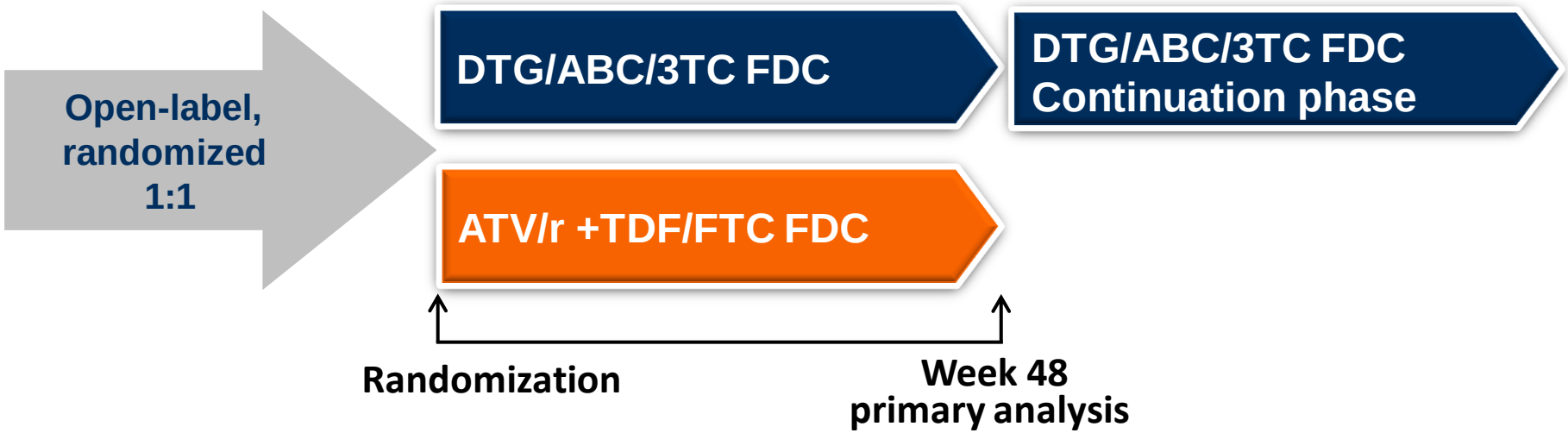
Open-label randomised non-inferiority phase 3b study



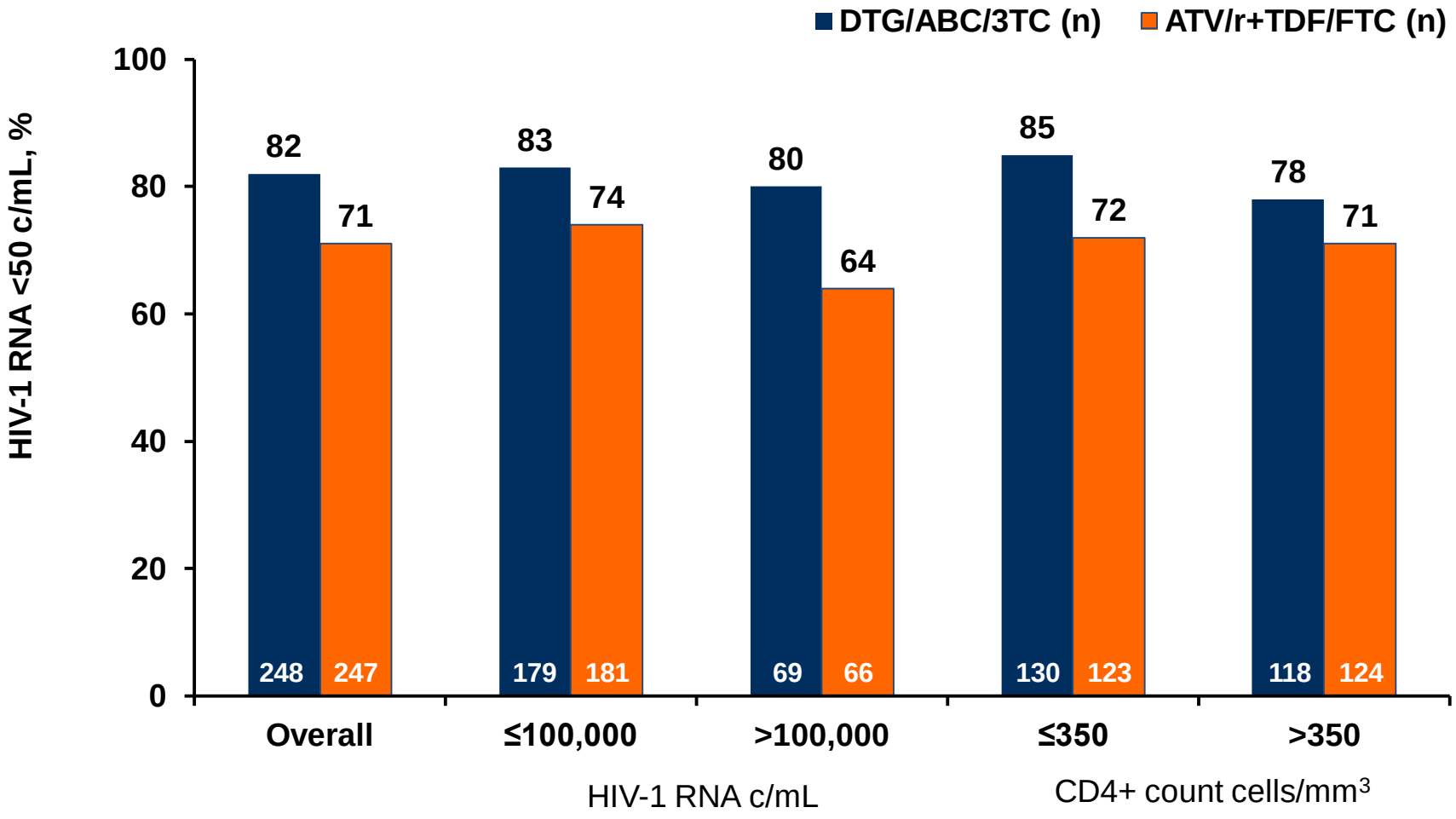
- **Key eligibility criteria:** women, ART-naive, HLA-B*5701 negative, HIV-1 RNA >500 c/mL, hepatitis B negative
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), CD4+ count (≤ or >350 cells/mm^3)
- Women who became pregnant were withdrawn and, if possible, offered entry into a DTG/ABC/3TC pregnancy study
- **Primary endpoint:** proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (-12% non-inferiority margin)

ART, antiretroviral therapy; FDA, US Food and Drug Administration; FDC, fixed-dose combination; HLA, human leukocyte antigen.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Snapshot Outcomes by Baseline Randomization Strata at Week 48: ITT-E

‡



ITT-E, intent-to-treat exposed.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Treatment Emergent Mutations in Patients with Confirmed Virologic Withdrawal

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- The resistance analysis was performed on subjects meeting confirmed virologic withdrawal (confirmed ≥400 c/mL on or after Week 24)

Resistance Analysis	DTG/ABC/3TC (n=6)	ATV/r +TDF/FTC (n=4)
INSTI	0	0
NRTI	0*	1
M184V	0	1
PI	0	0

*Two subjects receiving DTG/ABC/3TC had either K219K/Q (TAM) or E138E/G at CVW with no reduced susceptibility to DTG/ABC/3TC. K219K/Q is not selected for by ABC or 3TC nor does it affect their fold change

- No subject receiving DTG/ABC/3TC developed INSTI or ABC/3TC resistance-associated mutations

INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Summary of Psychiatric AEs

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Event	DTG/ABC/3TC FDC N=248 n (%)	ATV/r+ TDF/FTC FDC N=247 n (%)
Any event	**35 (14)**	**35 (14)**
Insomnia	10 (4)	9 (4)
Anxiety	5 (2)	7(3)
Depression	5 (2)	7 (3)
Suicidal ideation	4 (2)	3 (1)
Depressed mood	3 (1)	4 (2)
Abnormal dreams	2 (<1)	0
Panic attack	2 (<1)	2 (<1)
Agitation	1 (<1)	0
Bipolar disorder	1 (<1)	0
Elevated mood	1 (<1)	0
Mood altered	1 (<1)	2 (<1)
Mood swings	1 (<1)	0
Nightmare	1 (<1)	2 (<1)
Sleep disorder	1 (<1)	2 (<1)

Event	DTG/ABC/3TC FDC N=248 n (%)	ATV/r+ TDF/FTC FDC N=247 n (%)
Acute psychosis	0	1 (<1)
Affect lability	0	1 (<1)
Anxiety disorder	0	1 (<1)
Confusional state	0	1 (<1)
Hallucination, visual	0	1 (<1)
Intentional self-injury	0	1 (<1)
Irritability	0	1 (<1)
Mania	0	1 (<1)
Panic disorder	0	1 (<1)
Stress	0	1 (<1)

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

STRIVING

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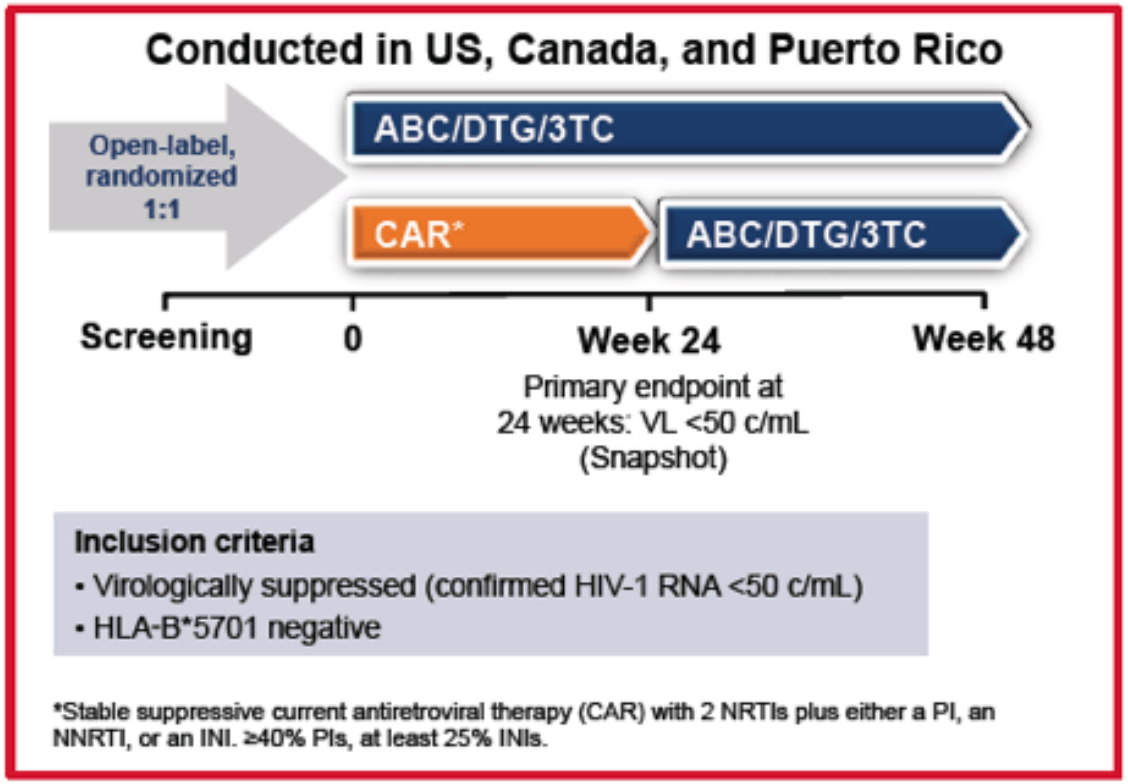
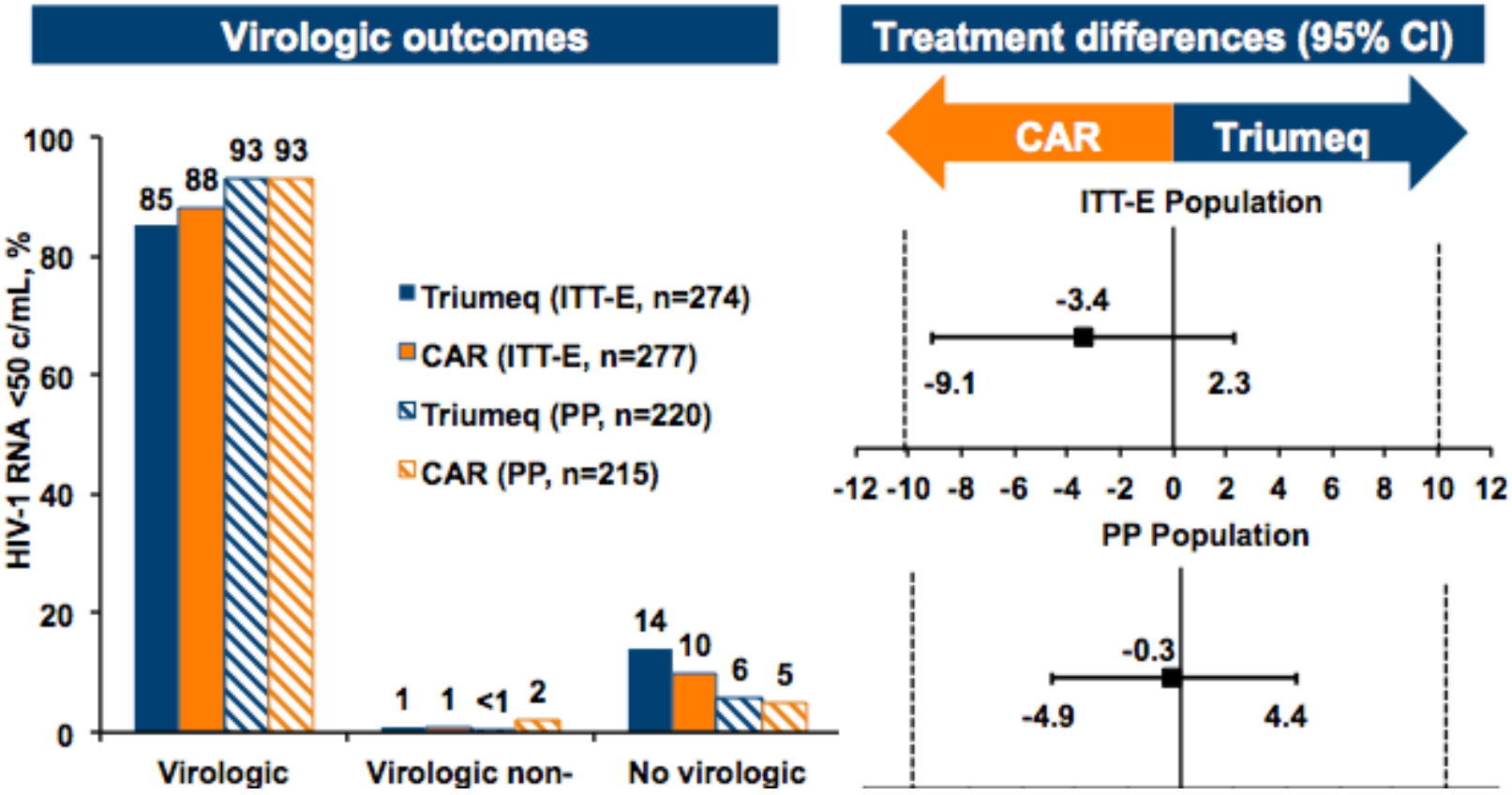
Study Design and Methods

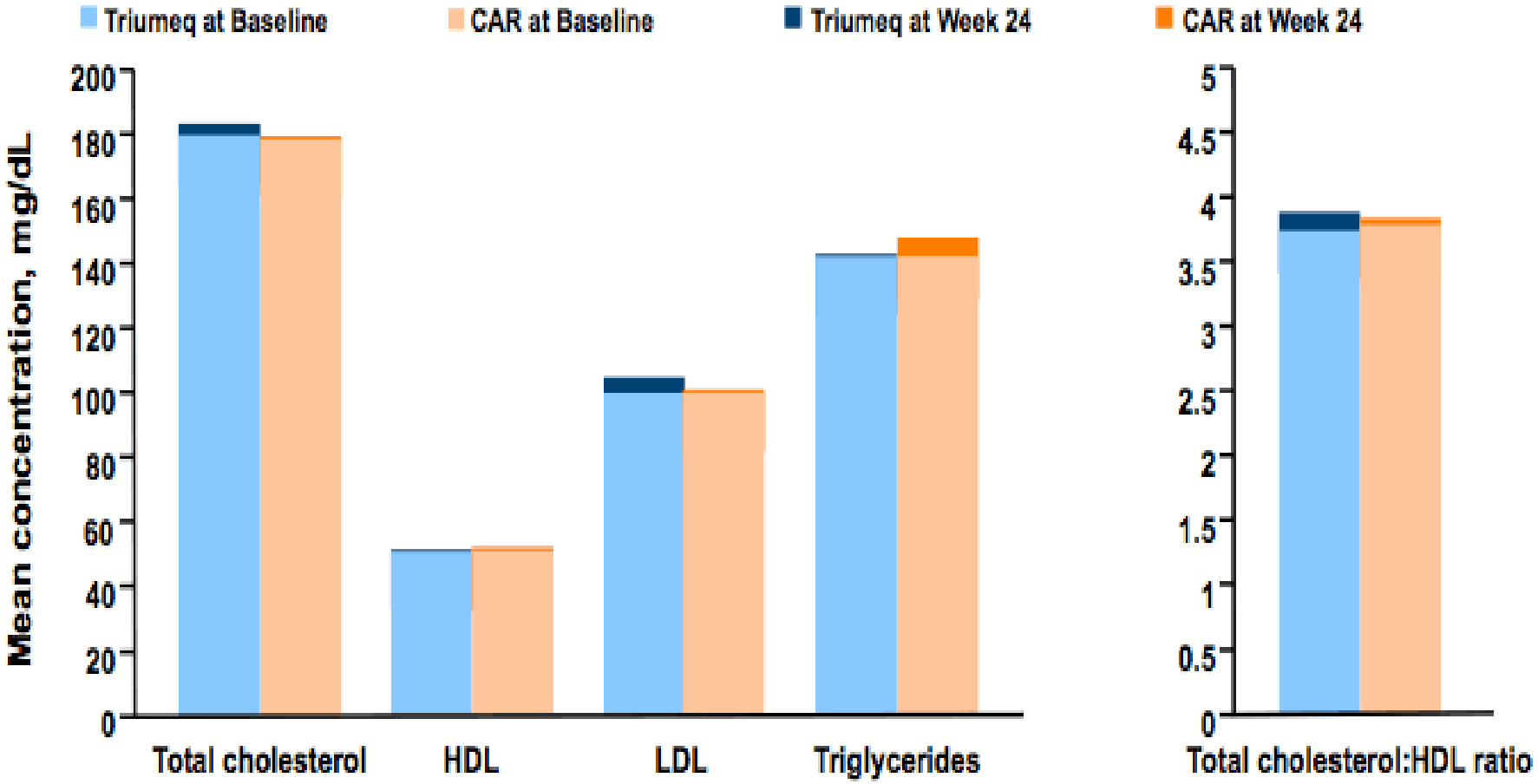
Figure 1. STRIIVING Study Design



ITT-E and PP Populations

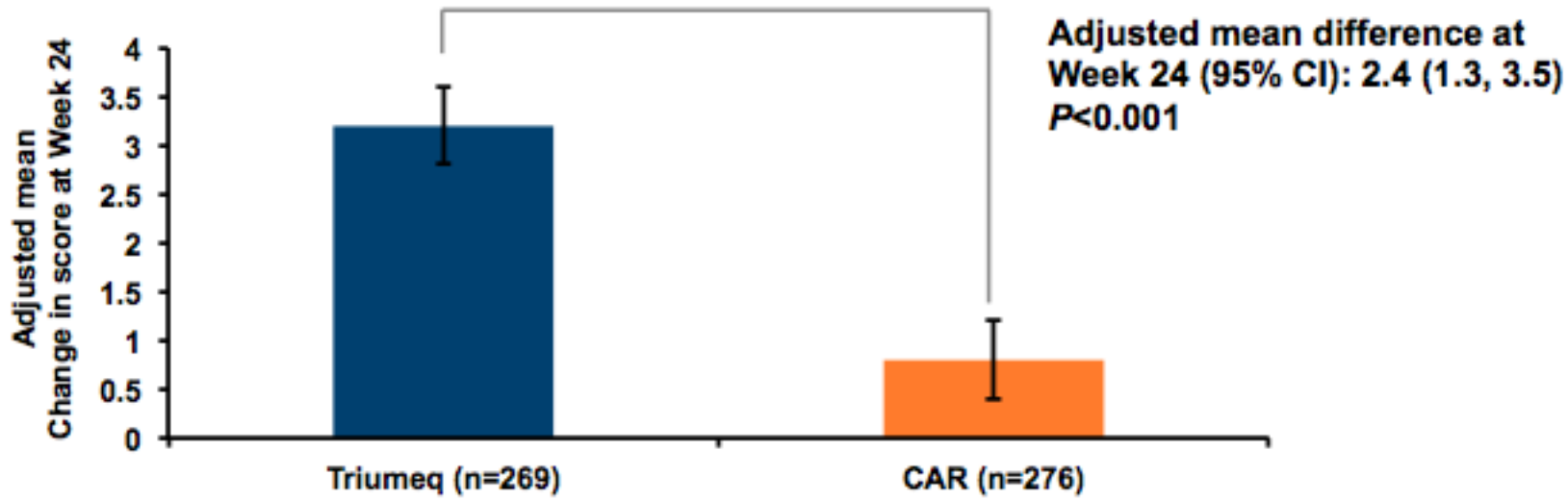


Change From Baseline in Fasting Lipids



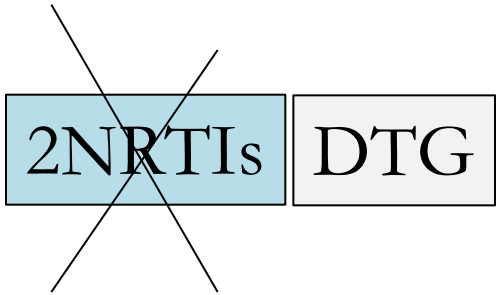
Total cholesterol		HDL		LDL		Triglycerides		Total cholesterol:HDL ratio	
Triumeq	CAR	Triumeq	CAR	Triumeq	CAR	Triumeq	CAR	Triumeq	CAR

Treatment Satisfaction–Total Score



- At baseline, overall treatment satisfaction scores were similar between groups.
- HIV TSQ total scores increased in both groups, with a statistically significant difference favoring Triumeq.

Dolutegravir senza backbone



Rationale:

1. Antiviral potency
2. No mutations at failure
3. Good backbone protection

NO randomized studies

	Mono-therapy	Dual therapy
Naive		DTG+3TC
Switch	DTG	DTG+3TC
		DTG+RPV
Salvage		DTG+RPV

PI/r?

TAF?

PADDLE: Dolutegravir (50mg) + Lamivudine (300mg) dual therapy in naive patients (week 48)

Open-label, single-arm, phase IV exploratory trial

Inclusion criteria

- ART **naïve,** adults >18 years
- HIV-1 RNA > 5000 to 100,000 copies/mL at screening
- CD4+ cell count ≥ 200 cells/mm3
- HBsAg negative

- baseline VL: 24,000 c/ml
- baseline CD4: count 400 cells/mm3
- (4 with baseline vl > 10^5)

Stopping rules!

Virologic suppression in **18 of 20 (90%)** patients at week 48

• **1 patient** virologic failure (baseline HIV-1 RNA : 106,320 copies/mL). At week 36 HIV-1 RNA 99 copies/mL and discontinued study. Patient resuppressed HIV-1 RNA by week 60 without change in ART.
Genotypic resistance analysis: no mutations in reverse transcriptase (Protease and integrase regions did not amplify)

• **1 patient** stop (week 24 and 36) due to severe AE.
Patient victim of suicide due to traumatic life event (not related to study medication)
Last HIV-1 RNA at Week 24 < 50 copies/ml

•Median CD4+ increase at week 48: **267** cells/mm³
• 8 AEs possibly related to dolutegravir seen among 6 patients through week 48 (**All AEs reported in first week**)

Cahn P et al. AIDS Conference 2016; Abs FRAB0104LB

Dolutegravir monotherapy in naive patients with HIV RNA <100,000 copies/mL.

‡

In patients refusing NRTIs…..

TABLE 1. Baseline Characteristics of the Patients, HIV RNA Level (at baseline), Number of CD4 Cells (at baseline), HIV RNA Level* After Four Week of Dolutegravir and at Last Visit, Number of CD4 Lymphocytes at Last Control, and Months on Dolutegravir Monotherapy

Patient Number	Age/Gender/Sexual Orientation	CDC Stage	CD4/μL at Baseline	HIV RNA Copies/mL at Baseline	HIV RNA at Last Visit	HIV RNA Copies/mL After 4 Week of Dolutegravir	CD4/μL at Last Visit	Months on Dolutegravir
1	40/F/hetero	A2	248	20,400	Not detectable	Not detectable	600	10
2	36/M/homo	A2	335	18,400	<20	Not detectable	471	9
3	38/F/hetero	A2	356	90,500	Not detectable	31	527	7
4	40/M/homo	A2	350	39,000	Not detectable	35	623	7
5	39/M/homo	A2	329	43,300	Not detectable	<20	613	7
6	44/M/homo	A2	229	17,500	<20	45	404	6
7	47/M/homo	A2	785	18,200	Not detectable	<20	879	6
8	45/M/bisexual	A2	214	16,900	Not detectable	Not detectable	309	8
9	76/M/homo	A2	345	52,000	Not detectable	<20	484	6

Lanzafame M et al. JAIDS 2016;72:e12-4.

Dolutegravir-based DUAL therapy in highly experienced HIV-1-infected patients.

‡

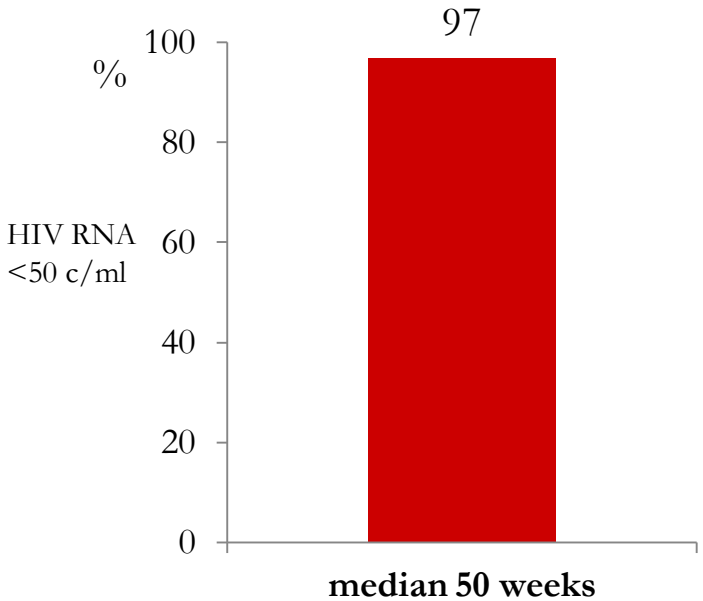
Observational study : **31 patients** with HIV RNA < 50 copies/ml (**65%** previously failed, with **26%** on RAL-based regimen)

Baseline parameters:

- median HIV diagnosis: 17 years
- virologically suppressed: for 3.7 years
- Nadir CD4: 199 cells/mm3
- median CD4 count : 702 cells/mm3
- CD4/CD8 ratio: 0.8
- HIV DNA : 2.9 log /10^6 PBMC

Dual regimen (5 pts with 50mg bid):

- RPV: 11
- ATV/r: 4
- ATV: 8
- MRV: 3
- 3TC: 3
- ABC: 1



Failing patient on DTG+MRV (non adherent)

Pt	HIV RNA at failure
1	737 copies/ml (at week 79)
DTG resistance: 72I, 121Y, 147G	

Gabavou C et al. JAC 2016;71:2359-61

15th EUROPEAN AIDS CONFERENCE
October 21–24, 2015
Barcelona, Spain

Dual therapy with DTG + 3TC maintains virologic suppression in HIV-infected HAART-treated patients: DOLULAM pilot study.

‡

27 French patients who were already on treatment and who had an undetectable viral load that was <50 copies/mL for at least a year changed ART to dolutegravir plus 3TC.

HIV treatment history: 18 years.

7 patients had already used another integrase inhibitor (raltegravir) and 8 had history of drug resistance to 3TC.

Over **24 weeks**, viral load remained less than 20 copies/mL in all participants, with one blip at 52 copies/mL.

Tolerability was also good, although 2 patients changed back to their pre-switch combination because of fatigue with dolutegravir and 3TC

Reynes J, Meftah N et Montes B. *15° AIDS Conference 2015. Abstract PE8/81.*

001/IHQ/14-12//1224x October 2015

Dolutegravir monotherapy in HIV-infected patients with suppressed viremia.

‡

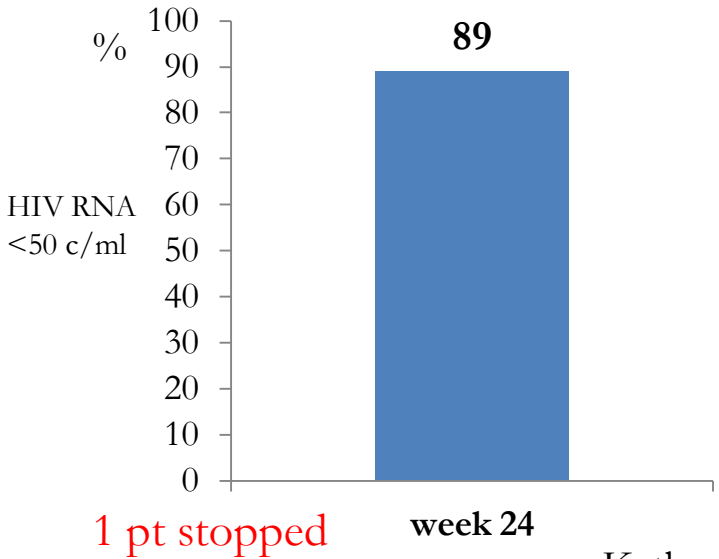
Observational study : **28 patients** with HIV RNA <50 copies/ml for at least 12 months (no history of prior IIs failure).

Baseline parameters:
median HIV diagnosis: 20 years
on ART: for 17 years
virologically suppressed : for 79 months
median CD4 count = 624 cells/

Baseline regimens:

- 3-drug regimen: 10
- dual regimen: 10
- DRV/r mono: 8

(12 exposed to IIs)



1 pt stopped

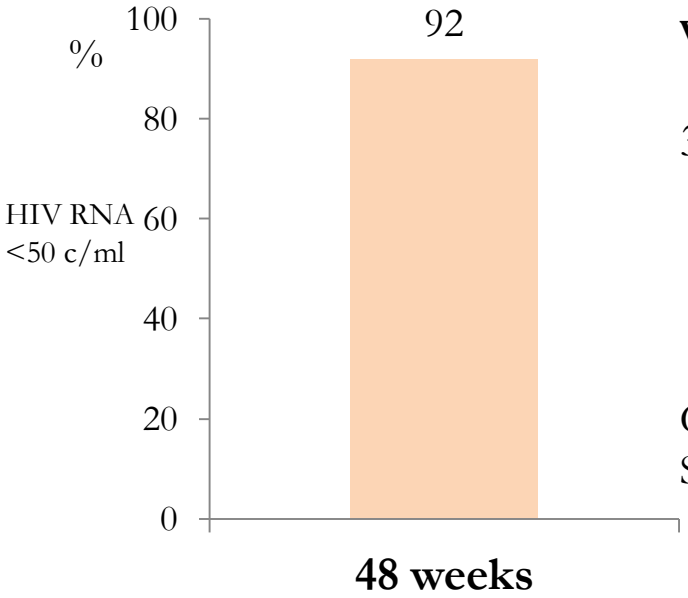
Failing patients (all with prior exposure to IIs)

	HIV RNA at failure (c/ml)	II-resistance mutations	DTG level
1	291, w24	N155H	1459
2	469, w13	L74I, E92Q	1927
3	2,220, w24	E138K, G140A, Q148R	2173

Katlama C et al. JAC 2016; 71:2646-50

Switch to Dolutegravir 50mg + Rilpivirine 25mg in patients with multiple previous ART failures. ‡

	NRTI	NNRTI	PI	INSTI
Previous exposure,* %		90		
Previous failure, %		68		
Primary resistance mutations, (%)		37		
Median number of resistance mutations, n		2.0		



Weeek 48 HIV RNA was < 50 c/ml in 92% (35/38)

3 patients discontinued study by week 48:

1. Gastrointestinal toxicity
2. Drug–drug interaction with omeprazole
3. Physician's decision

CD4 count was stable

Stable renal function (by CKD-EPI eGFR, mL/min/1.73 m2)

Diaz A et al. AIDS Confer 2016, Abs TUPDB0106.

Triumeq: quali Svantaggi

Psychiatric Adverse Events From the DTG ART-Naive Phase III/IIIb Clinical Trials

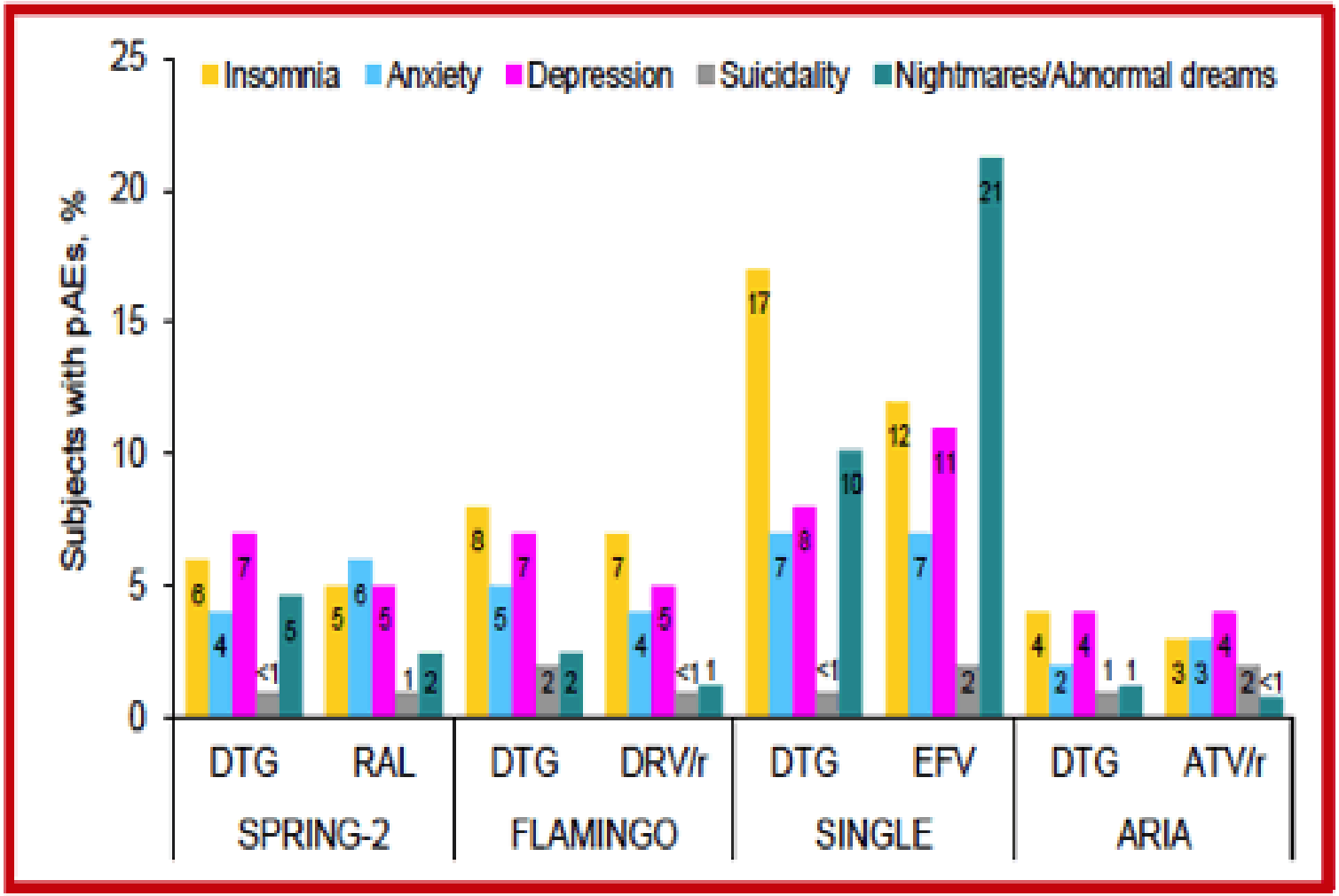
Reported by Jules Levin
HIV Glasgow Oct 23-26 2016

Romina Quercia,1Jeremy Roberts,2Andrew Murungi,1Lloyd Curtis,3Nassrin Payvandi,1Justin Koteff,4Michael Aboud1
1ViiV Healthcare, Brentford, UK; 2GlaxoSmithKline, Mississauga, Ontario, Canada; 3GlaxoSmithKline, Stockley Park, UK; 4ViiV Healthcare, Research Triangle Park, NC, USA

Methods

- This analysis presents an update to data in the abstract submitted on May 20, 2016. Additional time points have been added, and a regrouping of the pAE categories was done to better reflect the data and clinical practice
- Included are phase III/IIIb clinical trials that investigated DTG 50 mg once daily in treatment-naive adults with at least 48 weeks of data as of April 2016, which includes the SPRING-2, FLAMINGO, SINGLE, and ARIA studies
- In all of these clinical trials, pAEs were captured through AE and serious AE (SAE) reporting after baseline at scheduled study visits
- Medical Dictionary for Regulatory Activities (MedDRA) preferred terms used to code pAEs in clinical trials were examined, and company safety physicians grouped related terms into 4 main pAE categories
  - Insomnia (insomnia, initial insomnia, terminal insomnia, and middle insomnia)
  - Anxiety (anxiety and anxiety disorder)
  - Depression (depression, major depression, depressed mood, depressive symptom, and bipolar disorder)
  - Suicidality (suicide attempt, suicidal ideation, completed suicide, intentional self-injury, and self-injurious behavior)
- Nightmares/Abnormal dreams were captured as a separate category apart from the 4 main pAE categories

Figure. Percentage of Subjects With Psychiatric Adverse Events in DTG Phase III/IIIb Clinical Trials in ART-Naive Adults



pAE, psychiatric adverse event.

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INFEKTIONSMEDIZINISCHES
CENTRUM HAMBURG

Higher Rates of Neuropsychiatric Adverse Events Leading to Dolutegravir Discontinuation in Women and Older Patients

Michael SABRANSKI, Christoph WYEN, Tanya WELZ, Michael KOLB, Eva WOLF, Hans-Jürgen STELLBRINK, and Christian HOFFMANN

HIV Drug Therapy 2016, Oct 25, Glasgow

Methods

- Retrospective analysis of anonymized data for all HIV+ patients under routine clinical care in two large German HIV treatment centres
- All patients who initiated an INSTI-based therapy between January 2007 and April 2016
- Patients receiving INSTIs within RCTs, who initiated their INSTI-based ART elsewhere or had not at least one follow-up visit were excluded
- Start/stop dates and all reasons for discontinuation were extracted from the electronic database (in both centres, treating physicians routinely document the main reason for any ART discontinuation or modification)
- "Neuropsychiatric" AEs: insomnia, sleep disturbances, dizziness, nervousness, restlessness, depression, poor concentration, headache, slow thinking and otherwise unexplained pain or paraesthesia

AEs leading to INSTI discontinuation

	Dolutegravir n=985	Elvitegravir n=287	Raltegravir n=678
Renal % (n)	0.2 % (2)	3.5 % (10)	0.0 % (0)
Gastrointestinal % (n)	0.7 % (7)	2.8 % (8)	0.9 % (6)
Hepatic % (n	0.1 % (1)	0.0 % (0)	0.1 % (1)
Skin % (n)	0.3 % (3)	0.7 % (2)	0.1 % (1)
Other % (n)	0.5 % (5)	1.4 % (4)	0.9 % (6)
Neuropsychiatric % (n)	5.0 % (49)	1.0 % (3)	2.1 % (14)
Neuropsychiatric Adverse Events*			
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

Conclusions

- In this large cohort, the discontinuation rate of DTG due to neuropsychiatric AEs was almost 6% within 12 months.
- This rate was higher than that reported in randomized clinical trials (see abstract #210) and higher than for RAL or EVG/c.
- Women, older patients and patients who simultaneously initiated abacavir had a 2-3 fold higher risk of DTG discontinuation due to neuropsychiatric AEs.
- AEs were reversible and not severe.
- As DTG is likely to remain among the preferred antiretroviral options for HIV + patients, it is vital that post-marketing surveillance and further research be done to learn more about mechanisms for potential neurotoxicity.

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Pharmacokinetics of Dolutegravir When Administered With Mineral Supplements in Healthy Adult Subjects

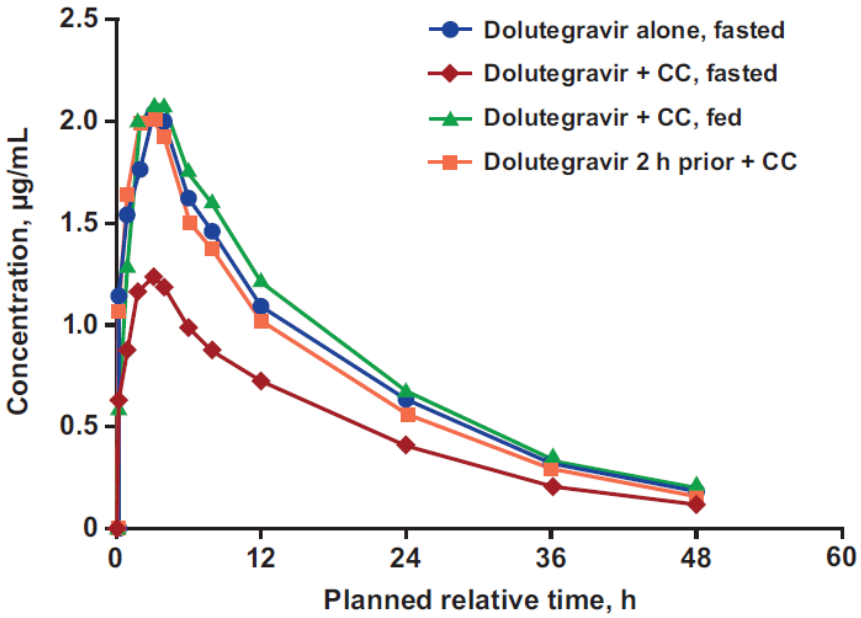


Figure 1. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without calcium carbonate (CC) (1,200 mg, single dose).

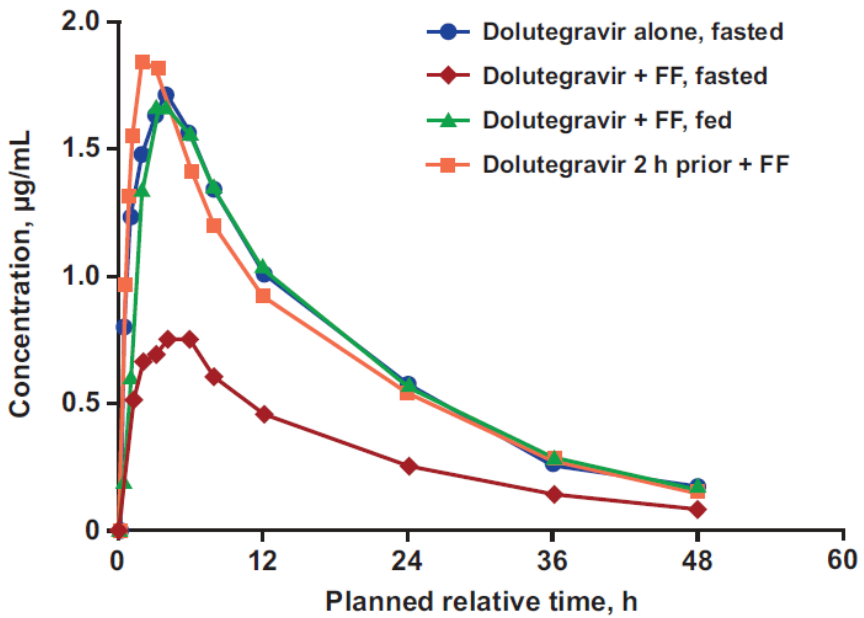


Figure 2. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without ferrous fumarate (FF) (324 mg, single dose).

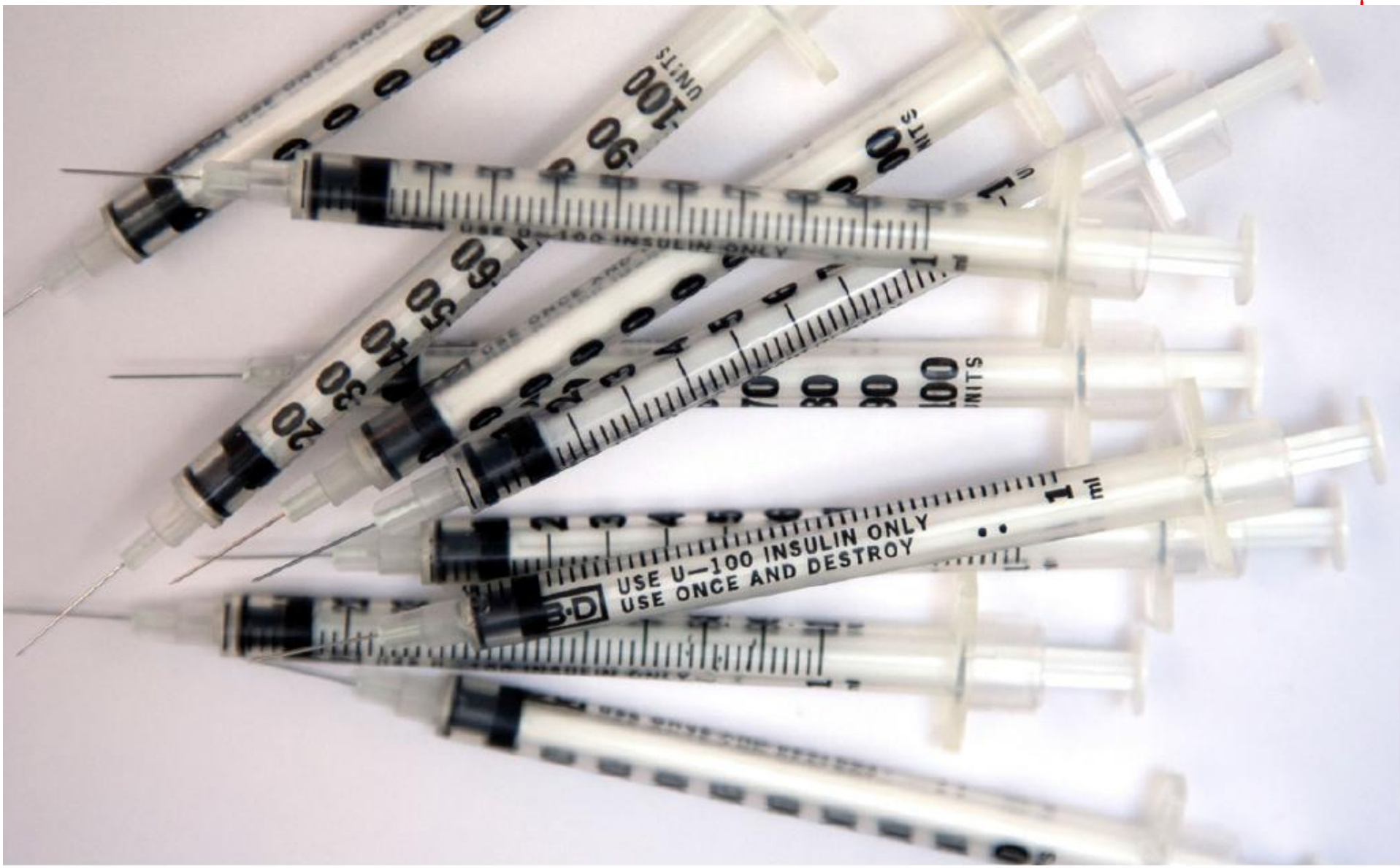
40% reduction in AUC

55% reduction in AUC

Chelation of integrase inhibitors with divalent cations (magnesium, calcium, iron, aluminium)

Song et al. J Clin Pharmacol 2015

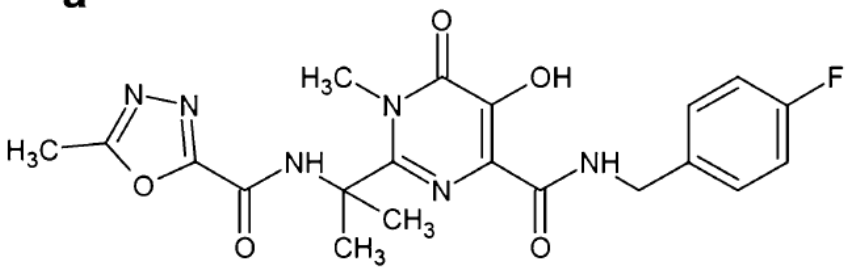
CABOTEGRAVIR:
UNA POSSIBILITA' DI TERAPIA LONG-ACTING



Sticking it to HIV: Long-acting injections could help promote adherence.

Nat Medicine 2014

a



RALTEGRAVIR

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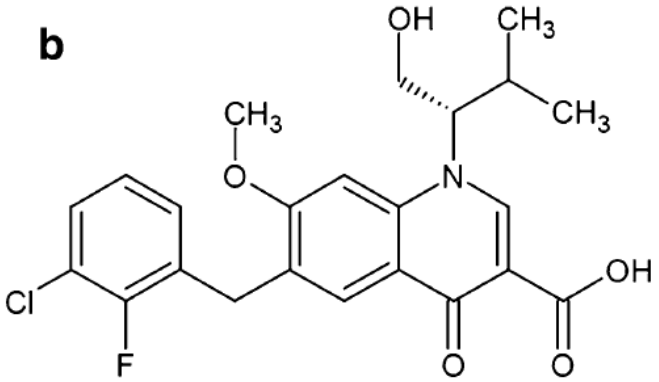
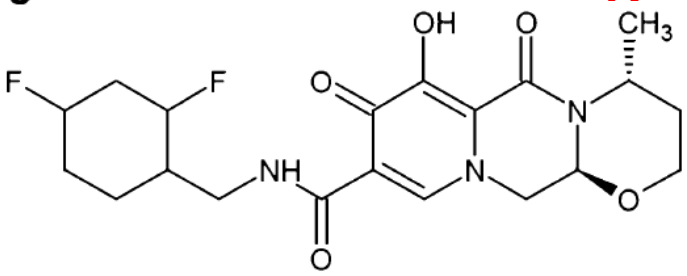


ELVITEGRAVIR

c



DOLUTEGRAVIR

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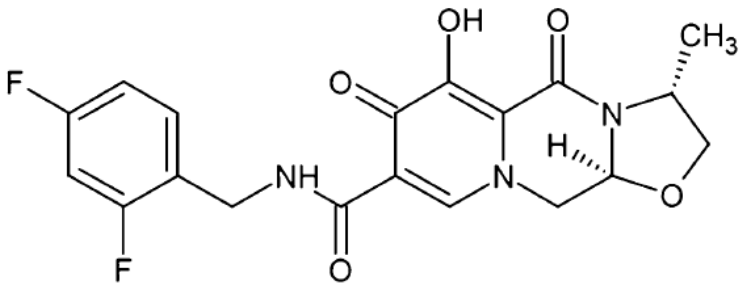
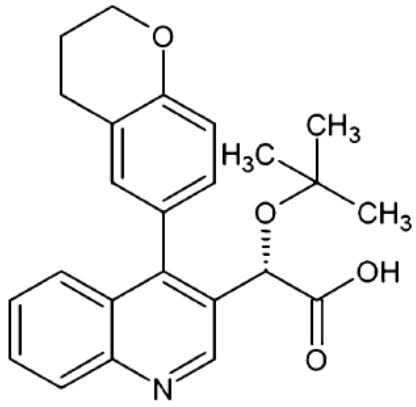


CABOTEGRAVIR

e



Karmon, SL. Drugs 2013

Factors affecting long-acting absorption

- Sex (male and female)
- Body mass index (BMI)
- Body fat distribution
- Muscle mass
- Injection technique
- Physical activity

Distribution to tissue of cabotegravir long-acting

‡

- Protection has been demonstrated in rectal and vaginal SHIV challenge experiments, suggesting adequate drug concentration are achieved.
- Penetration of cabotegravir long-acting to vaginal, cervical, and rectal tissue was assessed following a single dose in healthy adults.
- The tissue-to-plasma ratios noted in humans were comparable with those observed in non-human primate models for PreP

TABLE 3. Summary of 744 Tissue Concentrations by Visit and Overall Tissue:Plasma Ratios by Tissue Type*

	400 mg IM Unsplit (Cohort 8) (n = 4/Visit)			400 mg IM Split (2 × 200 mg IM, Cohort 9) (n = 4/Visit)		
Tissue Type	Week 2 (µg/g)	Week 8 (µg/g)	Overall Tissue:Plasma	Week 4	Week 12	Overall Tissue:Plasma
Cervical	0.081 (NQ-0.17)	0.096 (0.06–0.19)	0.20 (0.0–0.40)	0.177 (0.07–0.50)	0.133 (NQ-0.21)†	0.16 (0.0–0.4)
Vaginal	0.121 (NQ-0.18)	0.184 (0.09–0.44)	0.28 (0.0–0.7)	0.155 (NQ-0.90)	0.181 (NQ-0.35)	0.19 (0.0–0.7)
Rectal	NQ (NQ-0.10)	NQ (NQ-0.05)	0.00 (0.0–0.1)	0.079 (NQ-0.20)	0.063 (NQ-0.08)	0.08 (0.0–0.2)

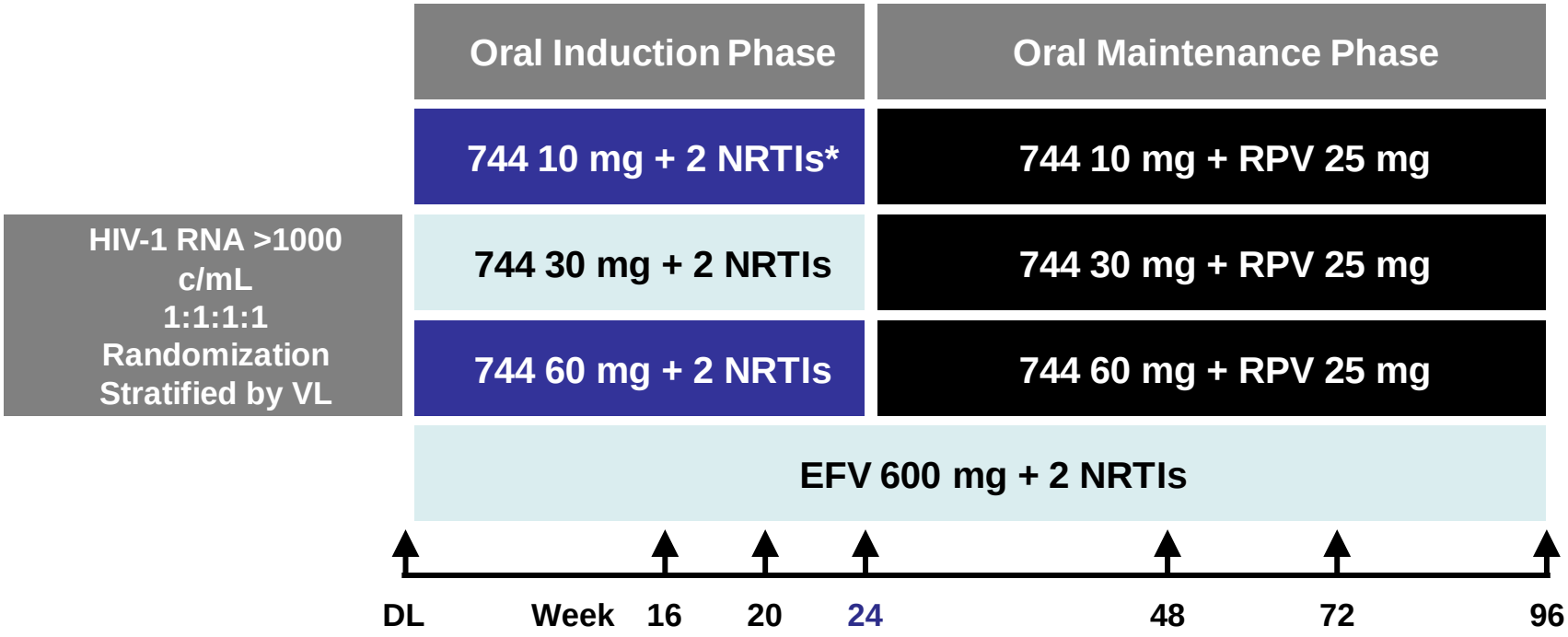
*Median (range).
†n = 3.
NQ, nonquantifiable concentration measured as below the lower limit of quantitation (50 µg/g).

Spreen SL. JAIDS 2014

Latte 96 week: cabotegravir and rilpvirine as two-drug oral maintenance therapy

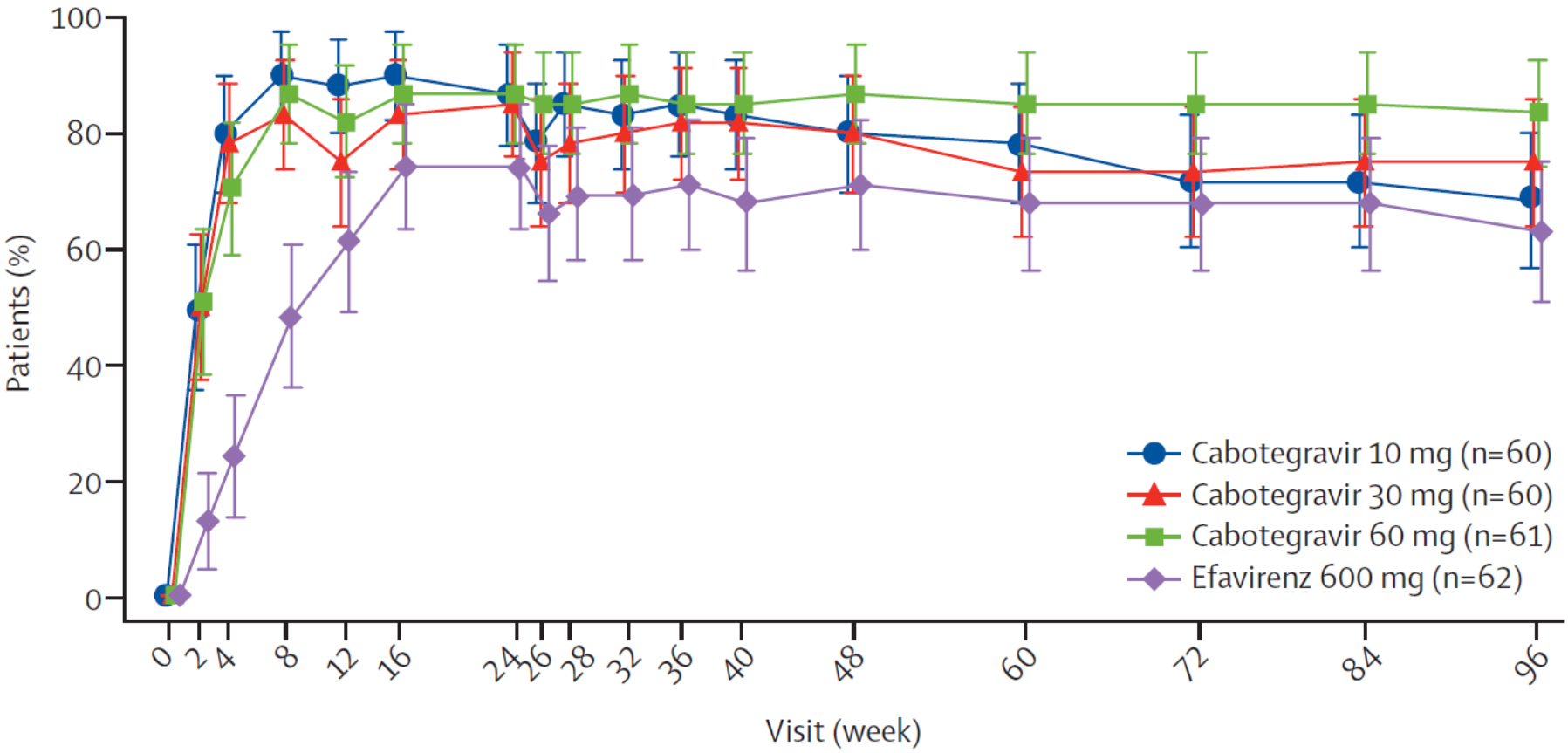
‡

- Phase IIb, randomized, multicenter, partially blind, dose-ranging study
- Patients on 744 + NRTI: If week 20 VL <50 c/mL – simplify to 744/RPV at week 24
- Following Week 96, subjects on the CAB arms transition into the Open-Label Phase. Subjects on the EFV arm are withdrawn from the study at Week 96.



Margolis DA. Lancet Infect Dis 2015

Latte 96 week: virological results



Proportion of patients with HIV-RNA concentration of less than 50 copies per ml by visit in the intention-to-treat-exposed population

Margolis DA. Lancet Infect Dis 2015

Latte 96 week: adverse events

	Cabotegravir 10 mg* (n=60)	Cabotegravir 30 mg* (n=60)	Cabotegravir 60 mg* (n=61)	Cabotegravir total* (n=181)	Efavirenz 600 mg (n=62)
Total adverse events (≥10% incidence in any treatment group)					
Any event	56 (93%)	55 (92%)	60 (98%)	171 (94%)	60 (97%)
Dizziness	7 (12%)	7 (12%)	3 (5%)	17 (9%)	18 (29%)
Upper respiratory tract infection	11 (18%)	17 (28%)	16 (26%)	44 (24%)	12 (19%)
Diarrhoea	14 (23%)	14 (23%)	15 (25%)	43 (24%)	12 (19%)
Abnormal dreams	1 (2%)	5 (8%)	6 (10%)	12 (7%)	15 (24%)
Insomnia	5 (8%)	7 (12%)	11 (18%)	23 (13%)	15 (24%)
Nausea	14 (23%)	12 (20%)	16 (26%)	42 (23%)	13 (21%)
Headache	13 (22%)	13 (22%)	14 (23%)	40 (22%)	7 (11%)
Fatigue	8 (13%)	8 (13%)	8 (13%)	24 (13%)	11 (18%)
Nasopharyngitis	11 (18%)	6 (10%)	8 (13%)	25 (14%)	6 (10%)
Cough	8 (13%)	6 (10%)	5 (8%)	19 (10%)	8 (13%)
Rash	4 (7%)	7 (12%)	5 (8%)	16 (9%)	8 (13%)
Back pain	7 (12%)	5 (8%)	6 (10%)	18 (10%)	6 (10%)
Bronchitis	5 (8%)	7 (12%)	6 (10%)	18 (10%)	4 (6%)
Depression	5 (8%)	6 (10%)	4 (7%)	15 (8%)	4 (6%)
Syphilis	8 (13%)	3 (5%)	4 (7%)	15 (8%)	4 (6%)
Vomiting	3 (5%)	7 (12%)	4 (7%)	14 (8%)	3 (5%)
Abdominal pain	6 (10%)	4 (7%)	4 (7%)	14 (8%)	1 (2%)
Sinusitis	4 (7%)	2 (3%)	6 (10%)	12 (7%)	4 (6%)
Oropharyngeal pain	3 (5%)	6 (10%)	3 (5%)	12 (7%)	2 (3%)
Gastroenteritis	7 (12%)	0	2 (3%)	9 (5%)	1 (2%)

ber 2015

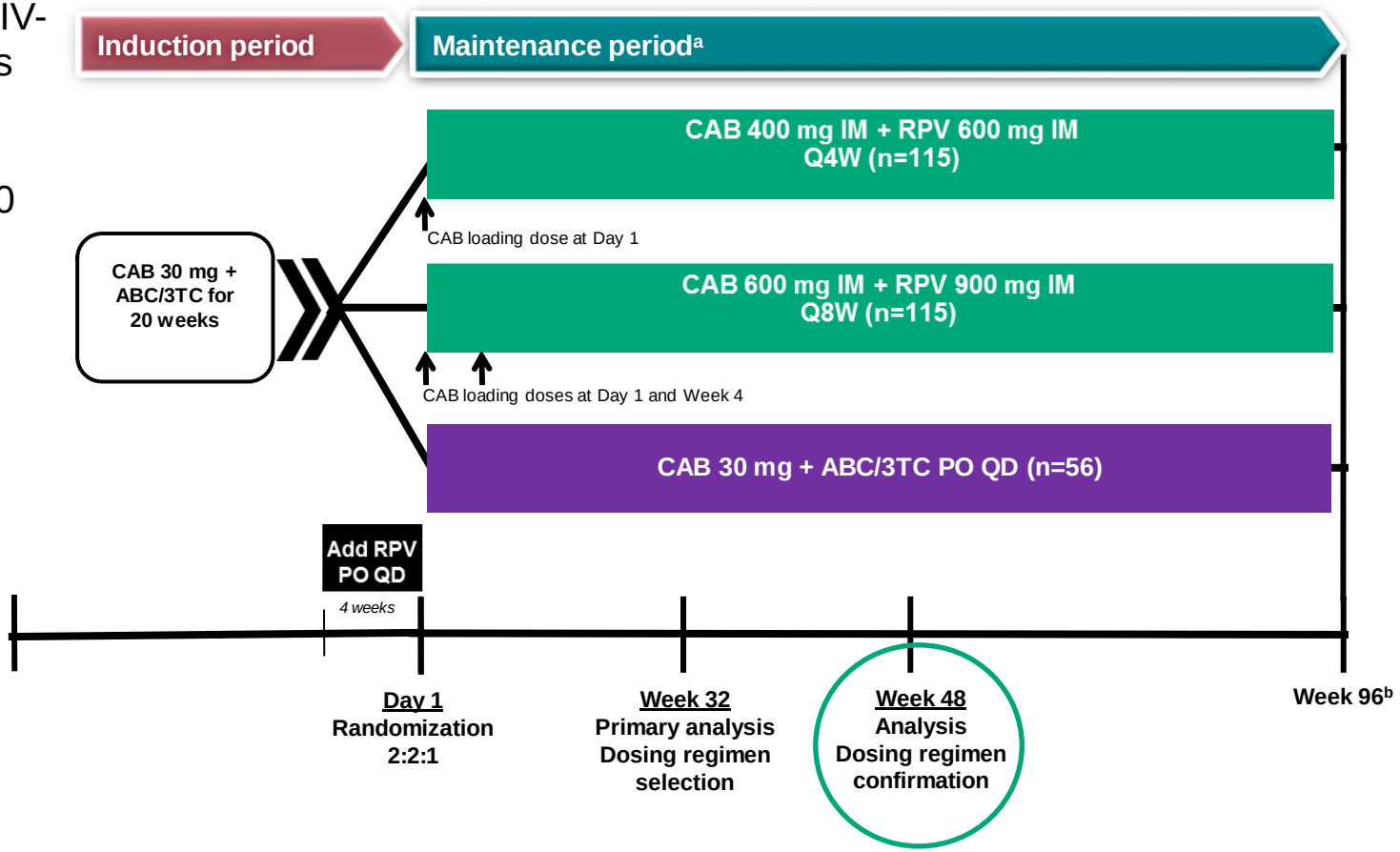
Margolis DA. Lancet Infect Dis 2015

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

‡

- Multicenter, open-label phase IIb study
  - **Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32**

ART-naive HIV-infected pts with CD4+ cell count > 200 cells/mm^3 (N = 309)



Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Snapshot Outcomes: HIV-1 RNA <50 c/mL at Week 48 (ITT-ME)

‡

Week 48 outcome	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Virologic success	**106 (92%)**	**105 (91%)**	**50 (89%)**
Virologic non-response	**8 (7%)**	**1 (<1%)**	**1 (2%)**
Data in window not <50 c/mL[a]	6 (5%)	1 (<1%)	0
Discontinued for lack of efficacy	1 (<1%)	0	1 (2%)
Discontinued for other reason while not <50 c/mL	1 (<1%)[b]	0	0
No virologic data in window	**1 (<1%)**	**9 (8%)**	**5 (9%)**
Discontinued due to adverse event or death[c]	0	6 (5%)	2 (4%)
Discontinued for other reasons[d]	1 (<1%)	3 (3%)	3 (5%)

[a]Week 48 HIV-1 RNA Q8W: 50 c/mL, 57 c/mL, 97 c/mL, 110 c/mL, 135 c/mL, 463/205 c/mL; Q4W: 59 c/mL; Q8W: 5 of 6 remain in the study, 4 of 6 have HIV-1 RNA <50 c/mL at all subsequent visits through W80. [b]Withdrew consent: intolerability of injections. [c]Q4W: hepatitis C, rash, depression, psychosis, epilepsy, and Churg-Strauss vasculitis; oral CAB: hepatitis C, DILI. [d]Q8W: ISR; Q4W: pregnancy, prohibited medication, relocation; oral CAB: lost to follow-up, relocation, withdrew consent (wanted injections rather than oral tablets).

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Protocol-Defined Virologic Failure (PDVF): Genotype

‡

Maintenance period[a]	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Subjects with PDVF	2 (1%)[b]	0	1 (2%)
INI-r mutations	1[c]	0	0
NRTI-r mutations	0	0	0
NNRTI-r mutations	1[c]	0	0

- NNRTI—**K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); INI—**Q148R** (FC CAB=5.1; Dolutegravir=1.38)[c]
- No additional PDVFs beyond W48 on any arm (all subjects through W72)[d]

PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 $\log_{10}$ c/mL increase from nadir HIV-1 RNA value ≥200 c/mL. [a]One additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence. [b]One PDVF at Week 4: no detectable RPV at Week 4 and Week 8, suggesting maladministration. [c]One PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL). [d]Contains data beyond W48.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Experiences with long-acting injectable ART: a qualitative study among people living with HIV participating in a phase II study of cabotegravir + rilpivirine (LATTE-2) in the US and Spain

Qualitatively explore perspectives and experiences with LAI ART among LATTE-2 trial participants and clinical care providers

- How do patients experience the injections?
- How do patients experience coming to clinic?
- How does LAI ART compare to daily oral?
- Who are the “right” patients for LAI ART?
- How and where to best deliver LAI ART?

INJECTION EXPERIENCES

Majority of participants reported some level of side effects

- Mostly soreness and minor bruising at site for 1-2 days
- Some managed these effects with Ibuprofen/Acetaminophen
- Minority of participants reported more intense reactions
- Hardness at injection site, fever, impaired mobility issues

Broad agreement that side effects were "worth it"

- *"One day is nothing…it's as if you have a day with a headache. You take Ibuprofen and that's it. You put up with it. It's temporary"*. (Spain, Male trial participant)
- *"It might be painful, but it's better than pills"*. (US, Male trial participant)

INJECTION EXPERIENCES

‡

❖**Convenience**

-Perceived as simple and easy to integrate into one's daily life

❖**Greater confidentiality, privacy**

-Seen as more "discrete", with less opportunity for discrimination

Psycho-social, emotional benefits

-For some, LAI ART provided relief from the unwanted daily reminder of HIV associated with pills

"It seems to me that it's much better because you simply ***don't have to worry about anything****. If you go on a trip, you don't have to bring your pills or take anything at all along. You follow your '****normal life****'. You come once a month. You get the shot and it's over. You don't have to be thinking everyday …oh I forgot to take the pill. Or …when did I take it last... You just don't worry about anything. In reality,* ***taking the pill everyday keeps it present [HIV****]…and the shot is just once a month…you remember it when you come in and the rest of the time you* ***can basically forget it"****.* (Spain, Male trial participant

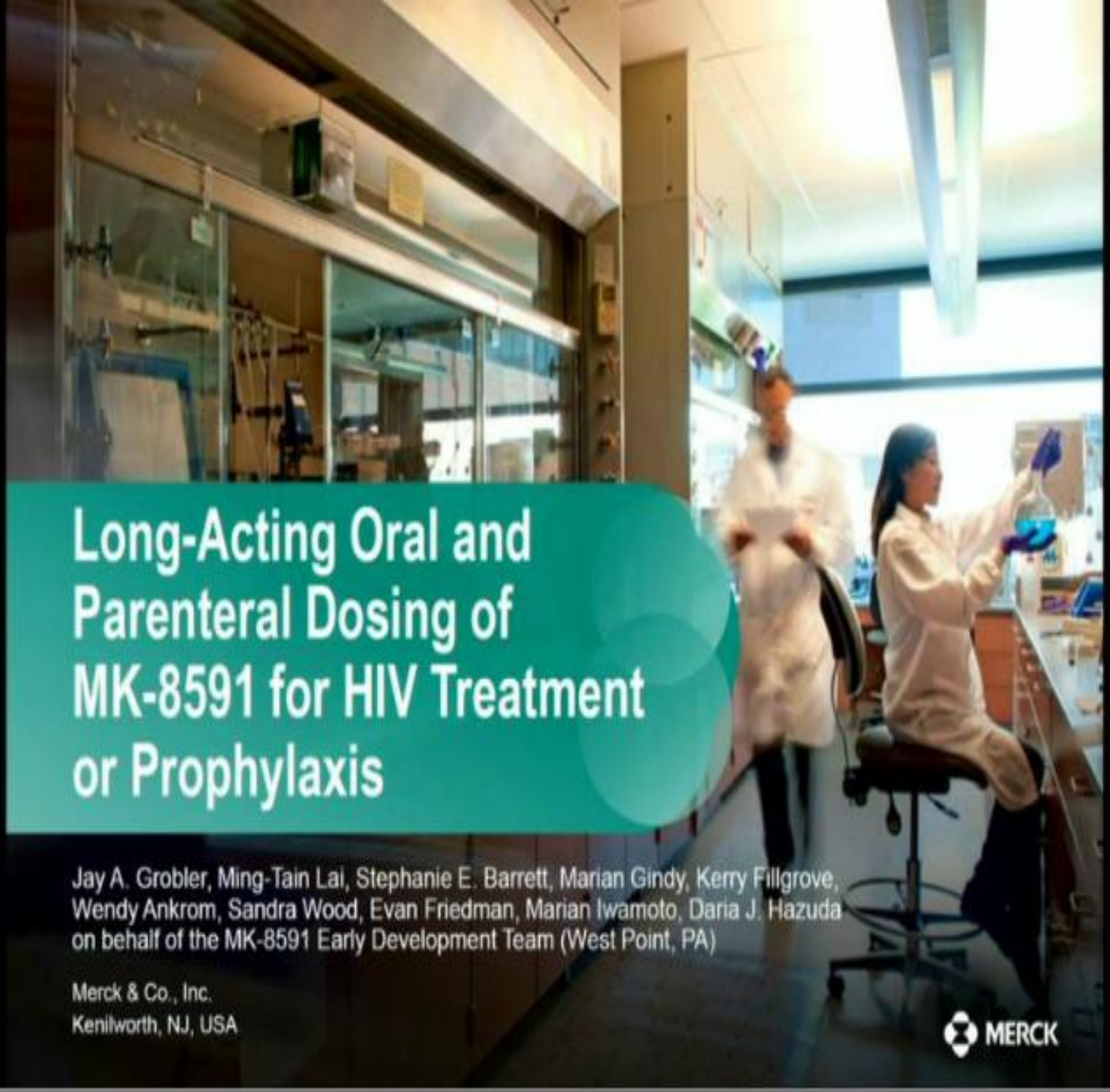
COMPARISON: LAI vs. ORAL ART

‡

In addition to being more convenient, participants reported feeling:

Less Stigma:
"It's less and less stigmatized with the injection*,*
because I don't feel like I'm reminding myself of [HIV]…
with the injection you go through days and weeks…two months not having to worry about that, so it's less stigmatized". (US, Male trial participant)

Less Pressure:
"I love it because I don't have to take a daily medication,
so that's just one less thing on my plate that I have to worry about…
I definitely feel there's less pressure*. I like the injection because it's not a daily, in my face, I have to do this".* (US, Female trial participant)



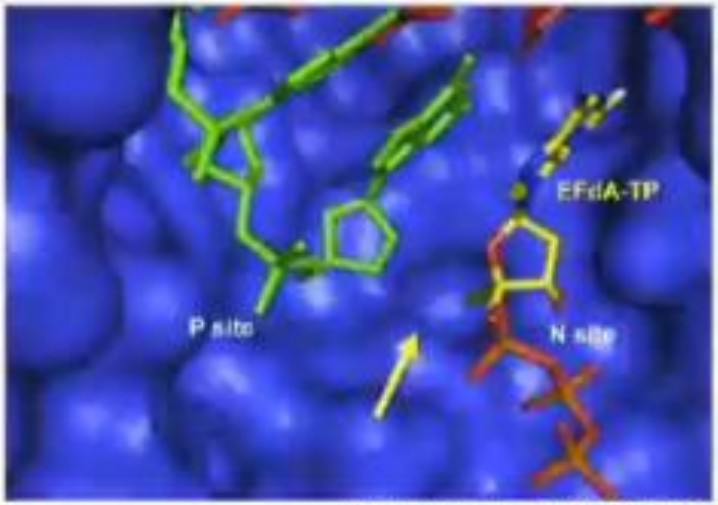
Long-Acting Oral and Parenteral Dosing of MK-8591 for HIV Treatment or Prophylaxis

Jay A. Grobler, Ming-Tain Lai, Stephanie E. Barrett, Marian Gindy, Kerry Fillgrove, Wendy Ankrom, Sandra Wood, Evan Friedman, Marian Iwamoto, Daria J. Hazuda on behalf of the MK-8591 Early Development Team (West Point, PA)

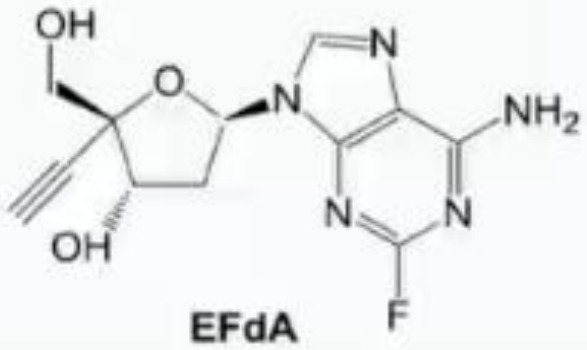
Merck & Co., Inc.
Kenilworth, NJ, USA

MERCK

MK-8591, EFdA: A Novel Nucleoside with a Unique Mechanism of Action



Michailidis et al (2009) JBC

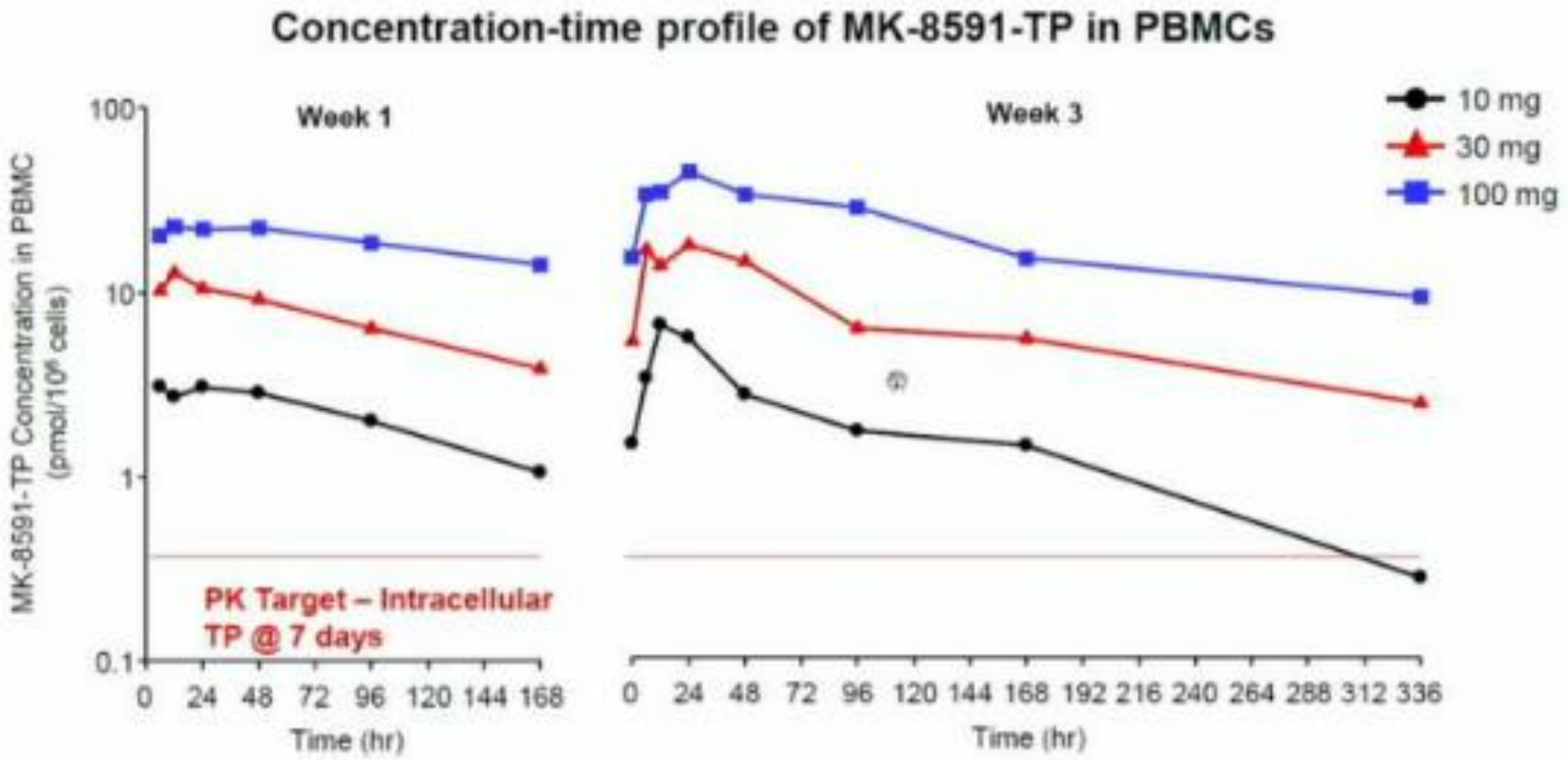


EFdA

- MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA) licensed from Yamasa
- Virologic profile and mechanism of action is extensively described in the literature (Mitsuya, Sarafianos, Parniak)
  - Non-obligate chain terminator
  - Inhibits reverse transcriptase by preventing translocation
  - Potent antiviral activity (PBMC EC_{50} = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)

MERCK

MK-8591 Human Phase 1 PK Confirms QW Potential

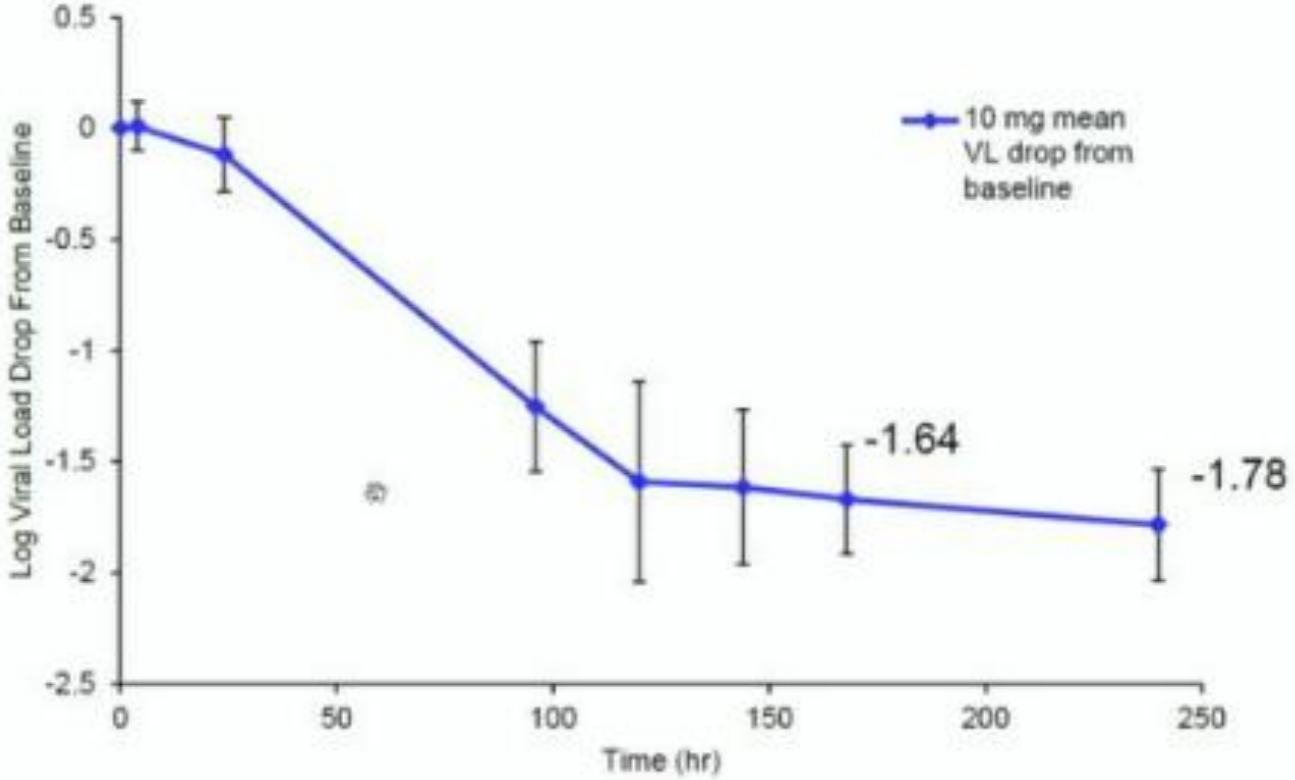


- Well tolerated in healthy adult subjects
- Intracellular MK-8591-TP C_{168hr} target concentration exceeded with 10 mg dose for > 7 days

MERCK

MK-8591 is Effective in HIV patients when Dosed Once-Weekly: Results from ongoing Ph1b study

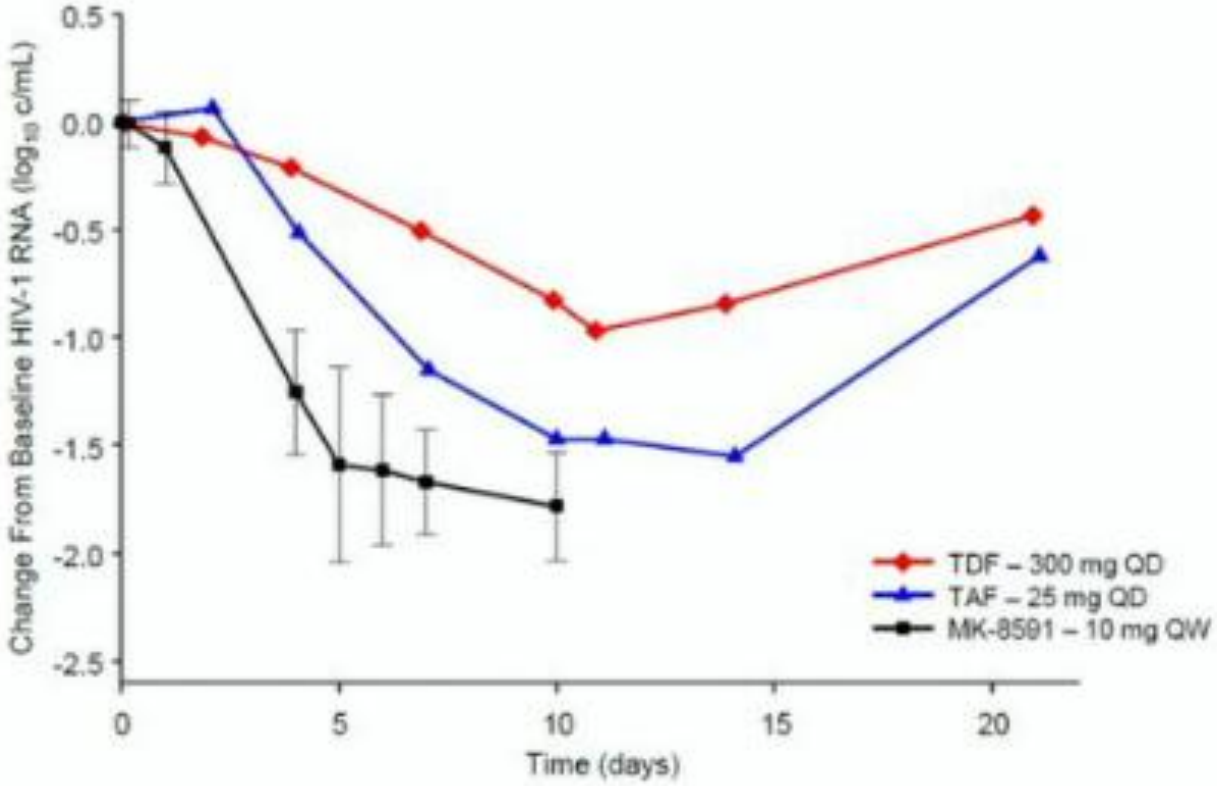
Friedman, et al., Poster 437LB



- A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10
- Intracellular MK-8591-TP $t_{1/2}$ = 103 hr
- No evidence of resistance out to Day 10

MERCK

Comparison of Single Once-Weekly Dose of MK-8591 and Once-Daily Dosing of TDF and TAF



Adapted from:
Ruane PJ, DeJesus E, Berger D, et al. *J Acquir Immune Defic Syndr*. 2013;63(4):449-455

Mean and standard deviation MK-8591 data from: PN003, Panel A (10 mg).

MERCK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