# Progress in HIV Therapy

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# Outline

- Goals and evolution of antiretroviral therapy
- The importance of resistance barrier
- The effect of M184V/I
- Drug safety and tolerability

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# Goals of HIV Therapy

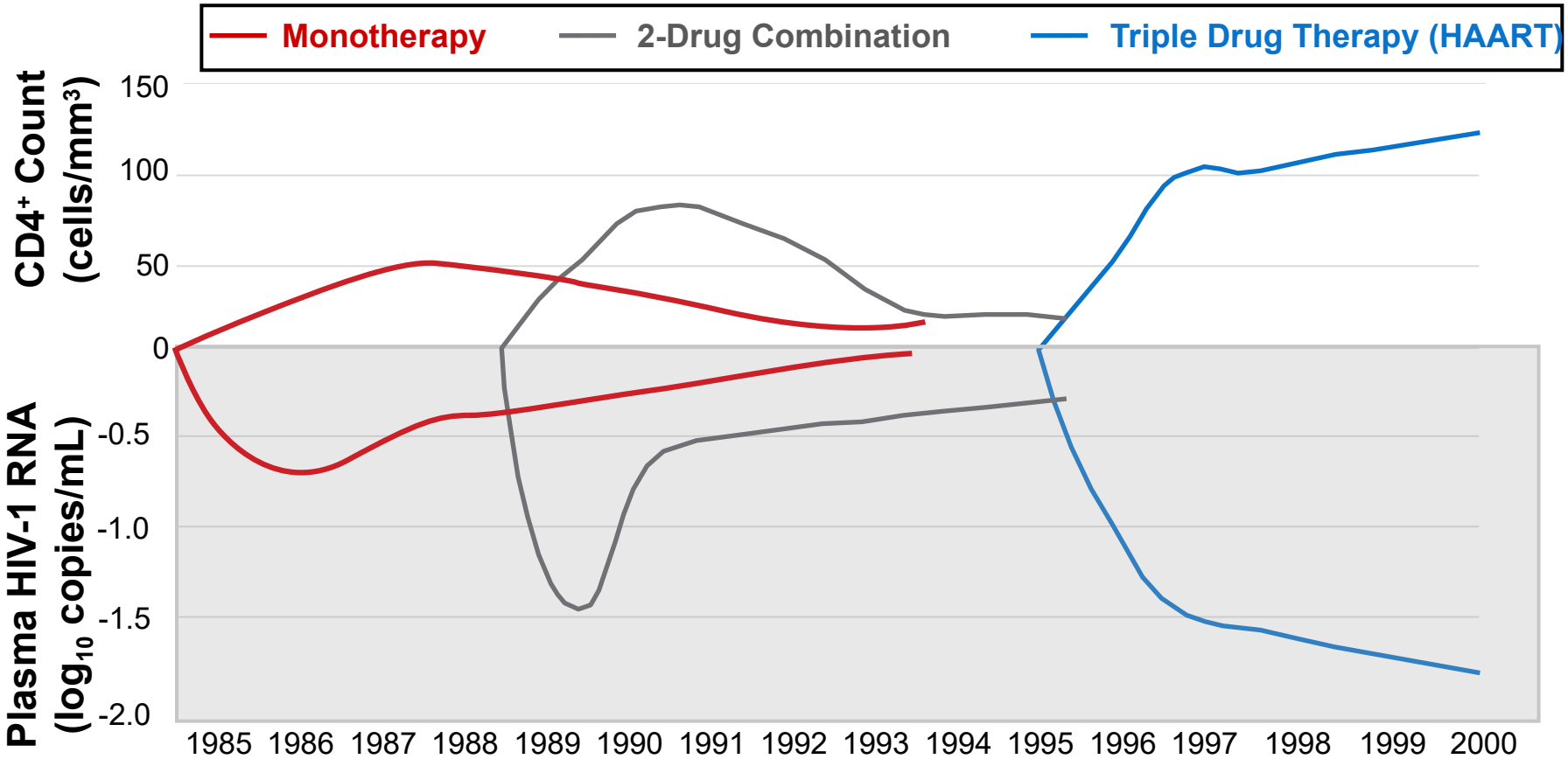
- **Indefinitely maintain suppression of plasma HIV RNA levels below the level of detection of sensitive of HIV RNA assays – FDA Guidance[1]**
- **Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 count, and confers substantial clinical benefits – DHHS Guidelines[2]**



1. DHHS & FDA CDER. *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. November* 2015. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128
2. DHHS. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 2017*. Available at: *http://aidsinfo.nih.gov/guidelines*

# Evolution of HIV Treatment

- Shift from monotherapy to triple therapy based on more durable suppression with prevention of resistance development




HAART: Highly Active Antiretroviral Therapy

Modified from Cohen CJ J Manag Care Pharm. 2006;12(7)(suppl S-b):S6-S11.

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- Barrier to resistance
- The effect of M184V/I
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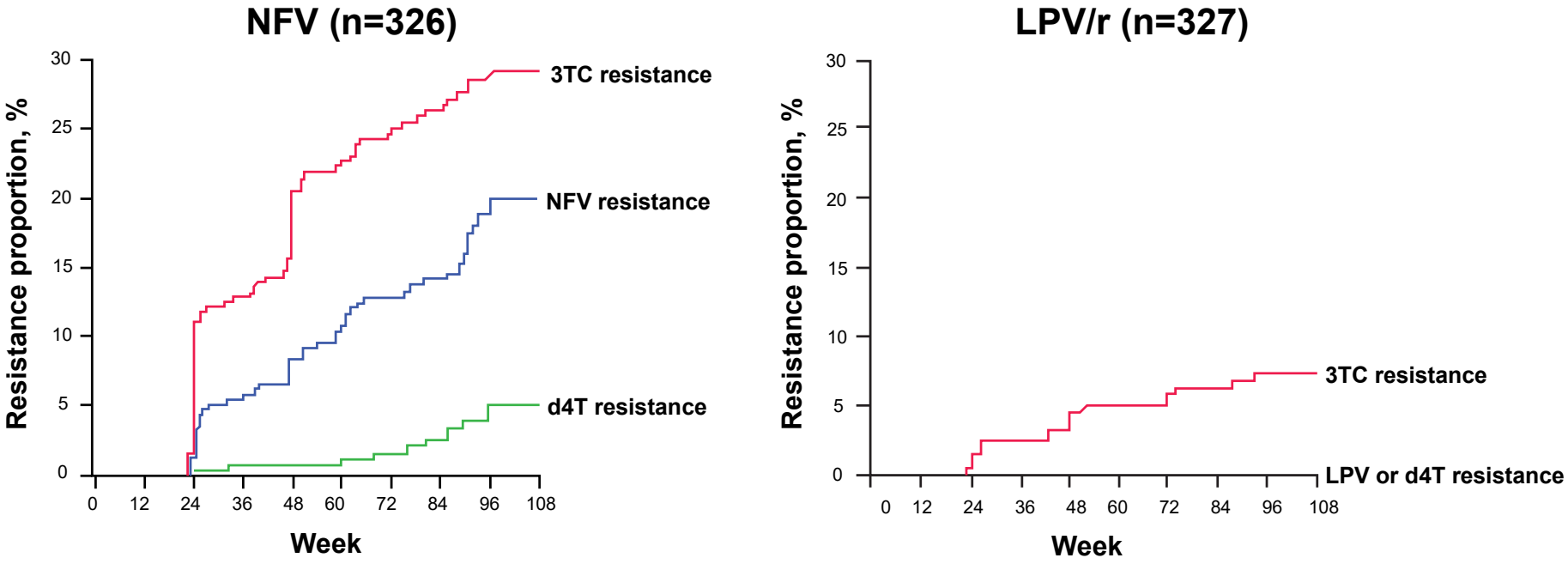
# Paradigm Shift: Preventing Resistance

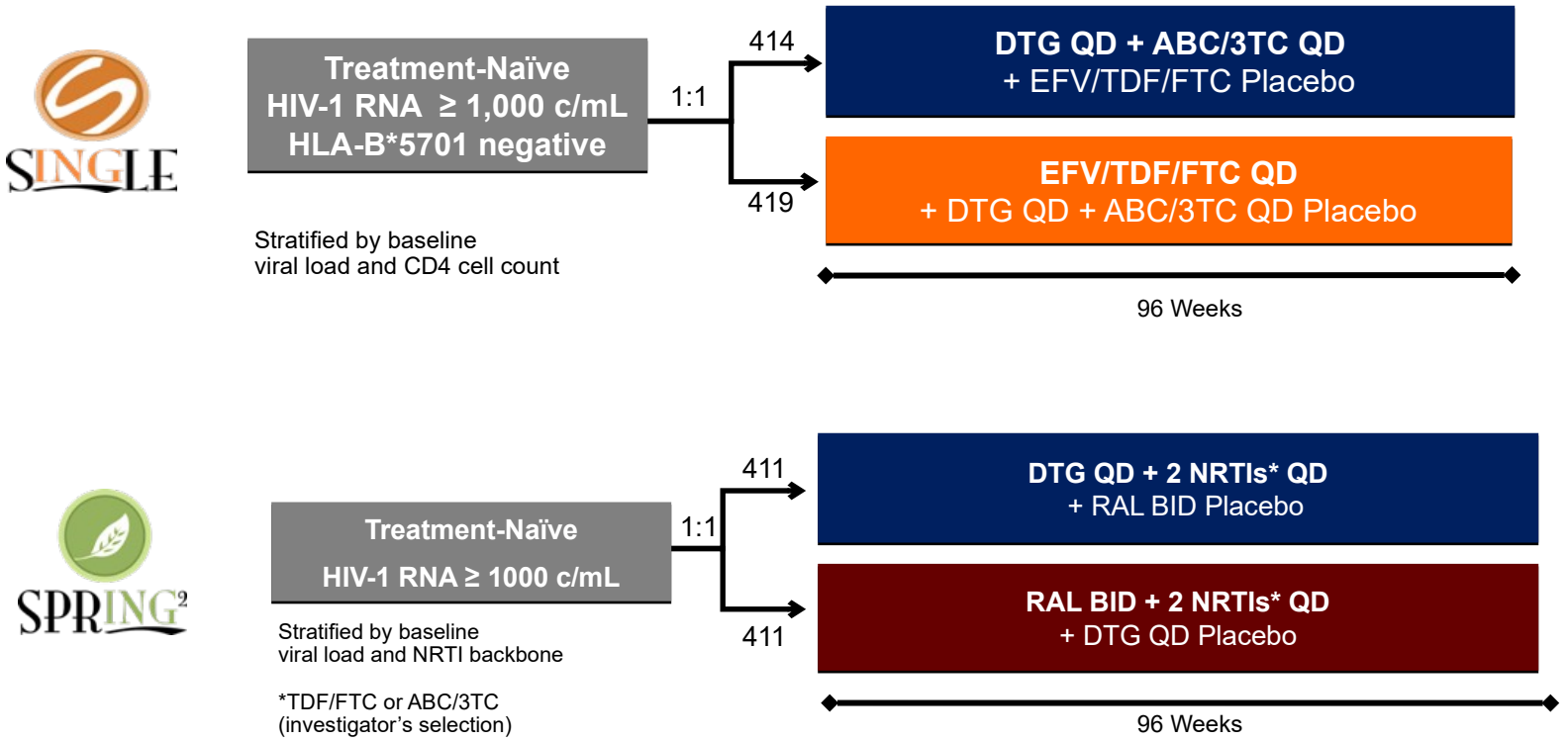
**Double-blind, randomized trial in ART-naïve HIV-infected adults comparing NFV vs LPV/r both with NRTIs of d4T + 3TC at Week 108[1]**




- **DHHS Guidelines recognize the importance of resistance barrier in justification of LPV/r's preferred status[2]**
  - 2003: trial data for virologic potency, patient tolerance, and pill burden
  - 2004: trial data for virologic potency, *barrier to virologic resistance*, patient tolerance

1. Kempf D, et al. J Infect Dis. 2004 Jan 1;189(1):51-60. DOI: 10.1086/380509
2. DHHS. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. November 2003 & October 2004*. Available at: https://aidsinfo.nih.gov/guidelines/archive/adult-and-adolescent-guidelines

# Study Design




1. Walmsley S, et al. N Engl J Med 2013. 369(19):1807-18. DOI: 10.1056/NEJMoa1215541
2. Walmsley S, et al. J Acquir Immune Defic Syndr. 2015;70(5):515-9. doi: 10.1097/QAI.0000000000000790.
3. Raffi F, et al. Lancet. 2013 Mar 2;381(9868):735-43. doi: 10.1016/S0140-6736(12)61853-4

# Resistance Consequences of Virologic Failure

| SINGLE | DTG + ABC/3TC (n=414) | EFV/TDF/FTC (n=419) |
|---|---|---|
| **Participants with PDVF, n** | **25** | **25** |
| NRTI major mutations, n | 0 | 1 |
| NNRTI major mutations, n | 0 | 6 |
| INSTI major mutations, n | 0 | 0 |

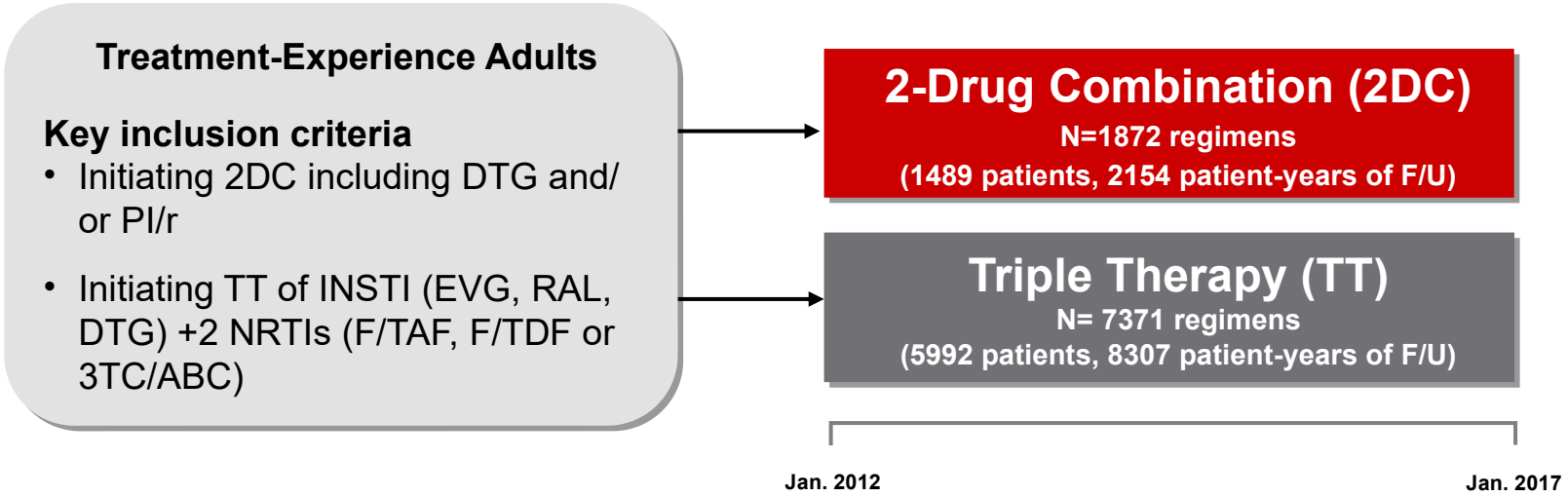
| SPRING2 | DTG QD + 2 NRTIs (n=411) | RAL BID + 2 NRTIs (n=419) |
|---|---|---|
| **Participants with PDVF, n** | **22** | **29** |
| NRTI major mutations, n | 0 | 4 |
| INSTI major mutations, n | 0 | 1 |

**No integrase mutations or major RT mutations detected on DTG + 2 NRTIs through Week 96**

1. Walmsley S, et al. CROI 2014. Boston, MA. Poster#543
2. Walmsley S, et al. J Acquir Immune Defic Syndr. 2015;70(5):515-9. doi: 10.1097/QAI.0000000000000790.
3. Raffi F, et al. Lancet. 2013 Mar 2;381(9868):735-43. doi: 10.1016/S0140-6736(12)61853-4

# Study Design

**Retrospective analysis of VACH cohort - a prospective multicenter Spanish cohort**




- **Endpoints**
  - Time to non-persistency (all cause discontinuation)
    - Compared for STR vs. multi-tablet regimens since newest STR was available (May 2016)
  - Time to virological failure (based on clinician diagnosis in chart)
  - Time to adverse events leading to discontinuation
- **Methods**
  - Kaplan-Meier curves and Cox proportional hazard models

2DC: 2-drug combination; F/U, follow up; STR: single tablet regimen; TE: treatment-experienced; TT: triple therapy

Teira R, et. al. EACS 2017. Milan, Italy. PE9/33

VACH Cohort - Spain

# Clinical Experience: 2-Drug Combinations vs Triple Therapy

## Discontinuation for Any Reason

**Retrospective analysis of a large Spanish cohort (n= 9243) to compare the real-world persistence, efficacy, and toxicity of DTG and PI containing 2-Drug Combinations (2DC; n=1872) vs. INSTI containing Triple Therapy (TT; n=7371) in treatment experienced patients (2012-2016)**

| 3-Drug Regimen (n=7371) | | n (%) |
|---|---|---|
| DTG | + (ABC/3TC or TDF/FTC) | 3090 (42%) |
| EVG/c | + (TAF/FTC or TDF/FTC) | 2966 (40%) |
| **RAL** | **+ (ABC/3TC or TDF/FTC)** | **1315 (18%)** |

| 2-Drug Regimen (n=1872) | | n (%) |
|---|---|---|
| DRV or LPV | 3TC | 643 (34%) |
| DRV or LPV | RPV | 207 (11%) |
| DRV or LPV | RAL | 334 (18%) |
| DTG | DRV | 249 (13%) |
| DTG | 3TC | 146 (8%) |
| DTG | RPV | 293 (16%) |

**Risk of Discontinuation for Any Reason**

- Overall: 29% higher for 2DC vs TT
  - Adjusted HR=1.29; p<0.0001
- DTG analysis: 49% higher risk with 2DC vs TT
  - Adjusted HR=1.49; p=0.0001

* Kaplan-Meier curves and Cox proportional hazard models controlled for demographics, comorbidities, viral load, CD4, number of previous regimens, CD4 nadir and years on antiretroviral therapy – all at patient-regimen initiation

Teira R, et. al. EACS 2017. Milan, Italy. PE9/33

VACH Cohort – Spain

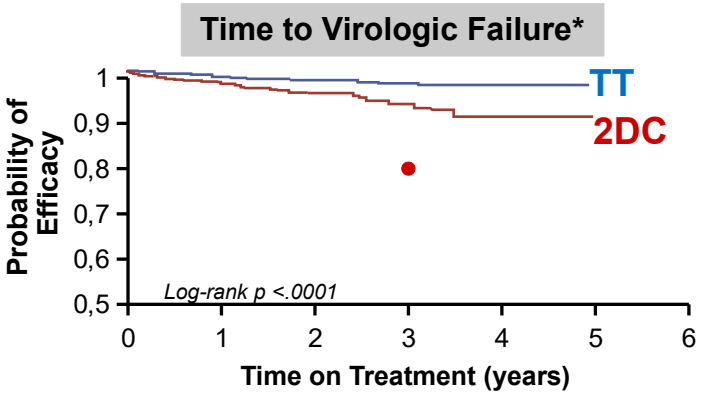
# Clinical Experience: 2-Drug Combinations vs Triple Therapy

## Virologic Failure and Toxicity

**Retrospective analysis of large cohort (n= 9243) to compare real-world persistence, efficacy, and toxicity of DTG and PI containing 2DC (n=1872) vs. INSTI TT (n=7371) in ART experienced patients (2012-2016)**

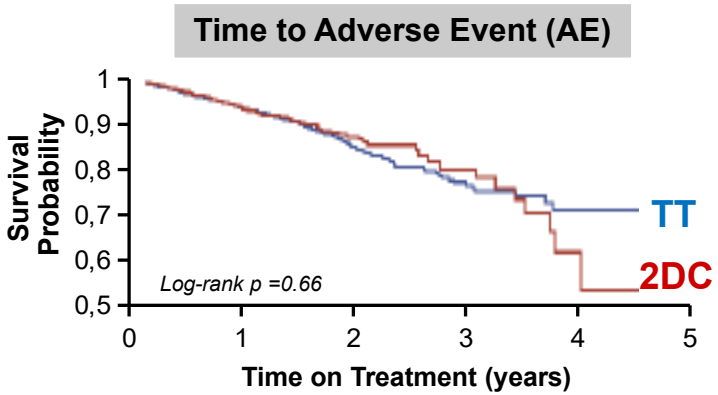
### Risk of Virologic Failure

- Significantly higher with 2DC vs TT
  - 2-fold higher overall and 3-fold higher with DTG (both p < 0.0001)




### Risk of Toxicity (Intolerance or AEs)

- No differences was observed after controlling for demographic and clinical characteristics
  - Overall (p=0.16) and DTG analyses (p=0.99)




**“In this analysis of 9262 recent patient-regimens, probability of remaining free of**

**v**

**and/or PI/r containing Dual Therapy, with no trade-offs in toxicity.”**

aHR: adusted HR; 2DC: 2-drug combinations; TT: triple therapy

Teira R, et. al. EACS 2017. Milan, Italy. PE9/33

* Kaplan-Meier curves and Cox proportional hazard models controlled for demographics, comorbidities, viral load, CD4, number of previous regimens, CD4 nadir and years on antiretroviral therapy – all at patient-regimen initiation

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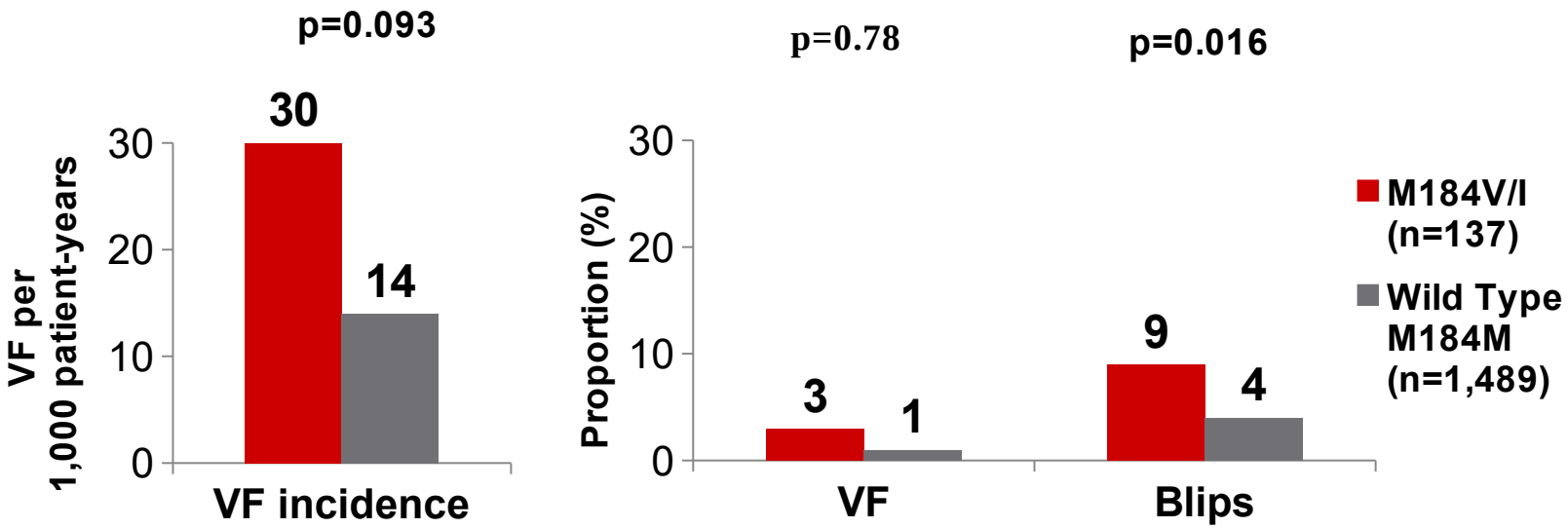
European HIV cohorts (ARCA, ICONA, ANRS CO3, ATHENA, SHCS)

# Impact of M184V/I on DTG/ABC/3TC Efficacy in Virologically Suppressed Adults

**Evaluation of effect of M184V/I in 1626 virologically suppressed adults switching to DTG/ABC/3TC with available genotype followed until first virological failure (VF) with pre-VF blips documented from 5 prospective European HIV cohorts**




- Overall, only 21 patients had protocol-defined virologic failure during the study (1.29%), which may preclude generalizability
  - VF rates and incidence were numerically higher with M184V/I (both p=NS)

Olearo F, et al. HIV Drug Therapy 2018, Glasgow, UK, Oral 214

European HIV cohorts (ARCA, ICONA, ANRS CO3, ATHENA, SHCS)

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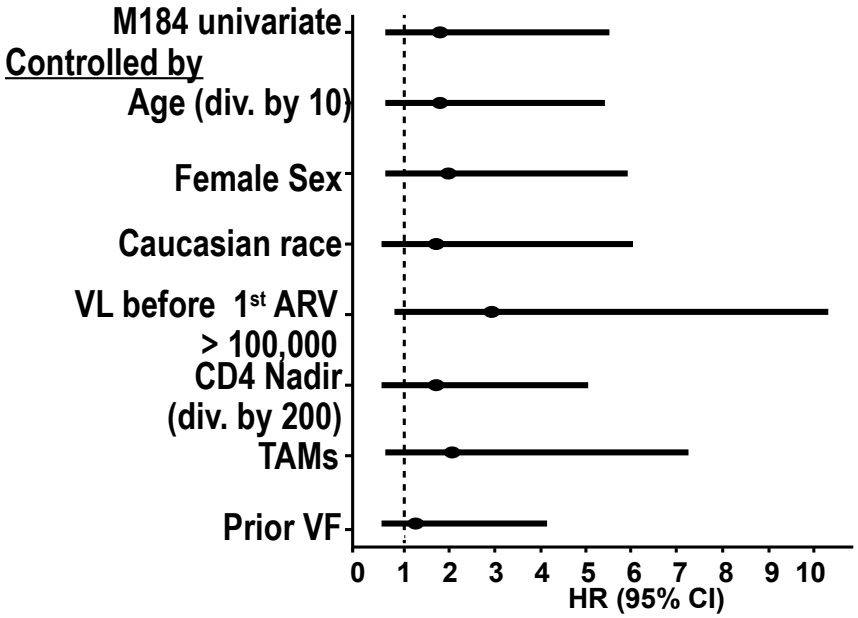
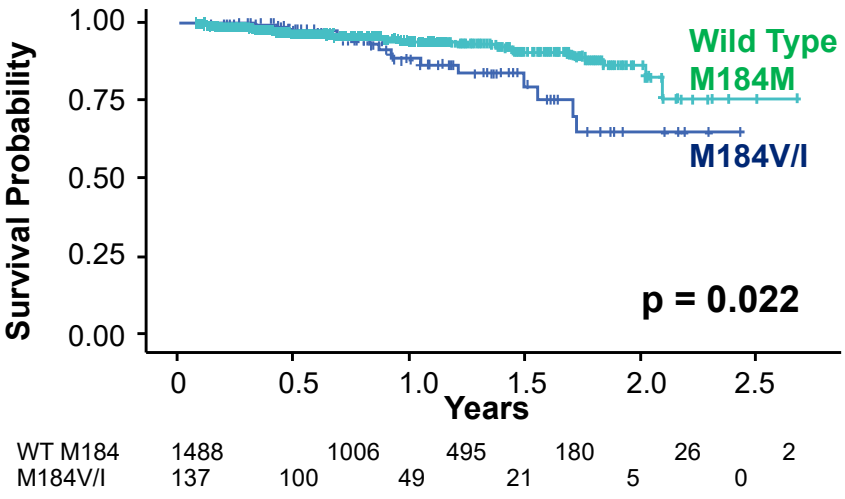
## VF Risk by M184V/I Presence




## Composite VF and Blip Analysis by M184V/I Presence



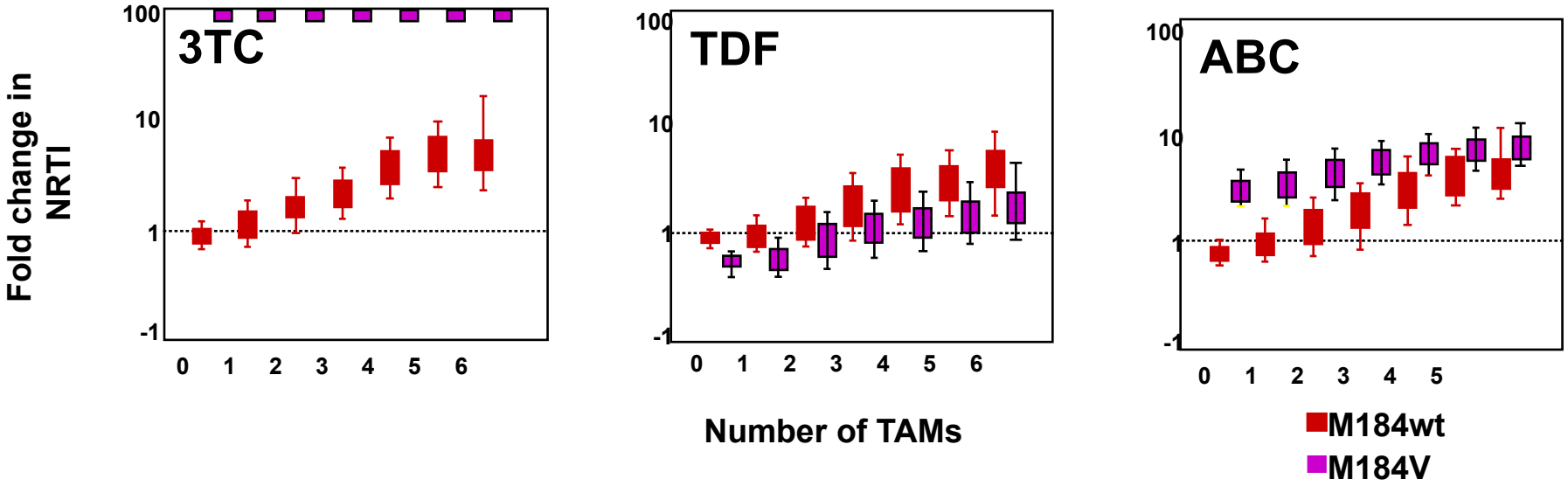

- **No significant difference in the VF risk among those with or without M184V/I**
- **Unable to exclude or confirm possibility of effect of M184V/I on VF risk**
- **Trend of increased VF risk with M184V/I**

- **The effect of M184V/I reaches statistical significance in univariate analysis (HR 1.9, CI 1.1-3.3, p=0.02) but not multivariate analysis (HR 1.6, CI 0.4-5.6, p=0.44)**

WT: wild type

Olearo F, et al. HIV Drug Therapy 2018, Glasgow, UK, Oral 214

# Impact of M184V & TAMs on 3TC, TDF and ABC Susceptibility




**TDF was more likely than ABC to retain antiviral activity in the presence of TAMs and M184V**

Whitcomb JM, et al. JID 2003; 188:992-1000

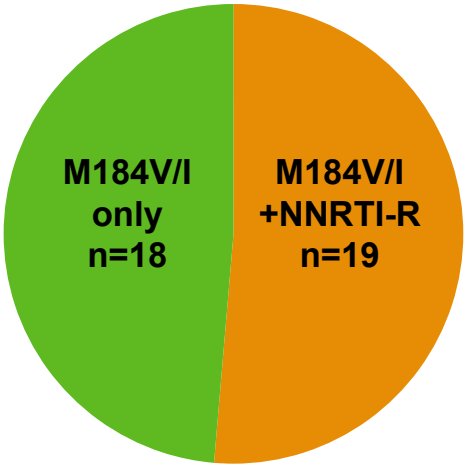
‡

# M184V/I Resistance Tests Differences

**Multicenter, open-label, single arm study of suppressed adults with M184V/I switching to E/C/F/TAF from FTC/TDF or ABC/3TC + third agent (n=37)**

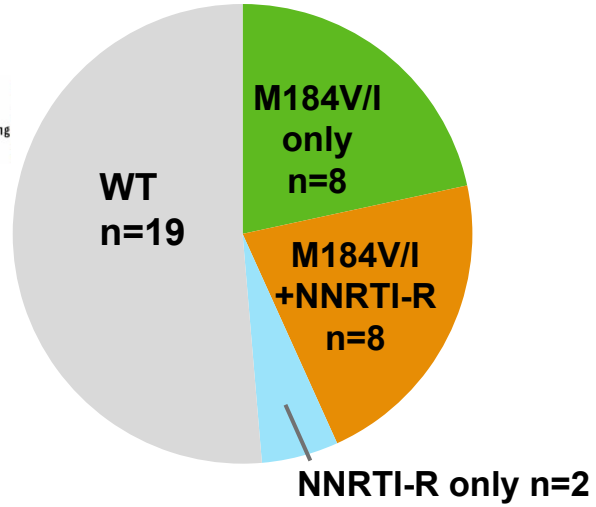
| Historical Resistance Testing[1,2,4] | Archive Resistance Testing[1,3,4] |
|---|---|
| • Viral (not integrated) genotype from HIV RNA<br>• Samples (plasma) taken at historical point when participant was viremic or newly diagnosed<br>• Minimum HIV VL required: ≥500 c/mL | • Proviral (integrated) genotype from DNA of infected PBMCs<br>• Samples (whole blood) taken at screening visit<br>• Minimum HIV VL required: none, low/undetectable VL accepted |

## Historical




## Proviral DNA

GenoSure archive® HIV-1 Next Generation DNA Sequencing Assay




**Less than 1/2 of study participants' M184V/I were detected by proviral DNA (archive) vs historical genotype resistance testing**

1. Perez-Valero I, et al. AIDS 2018. Amsterdam, Netherlands. Oral #TUAB0104.
2. Monogram Biosciences. HIV Genotypic Testing. July 2018. https://www.monogrambio.com/hiv-tests/genotypic-assays
3. Monogram Biosciences. GenoSure Archive. July 2018. https://www.monogrambio.com/hiv-tests/suppression-management/genosure-archive
4. Monogram Biosciences. HIV Ordering Procedures. July 2018. https://www.monogrambio.com/contact-support/ordering/sample-handling.

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- Goals and evolution of antiretroviral therapy
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# Study Design

**Integrated analysis of 26 Phase 2/3 Clinical Trials (N=10,330) representing exposure totaling 12,519 person-years (py) to TAF, 5947 py to TDF, and 1029 py to ABC**

**Primary outcomes (N=26 trials, 10,330 participants)**

- PRT
- Discontinuations due to renal AEs

**Secondary outcomes (N=10 trials; n=3 naïve [2362 participants], n=7 suppressed [5300 participants])**

- Treatment-emergent renal AEs*
- SCr (mg/dL)
- eGFR by Cockcroft-Gault (CrCl; mL/min)
- Treatment-emergent total proteinuria (dipstick)
- UACR
- Tubular proteinuria (urine RBP:Cr and β2M:Cr)

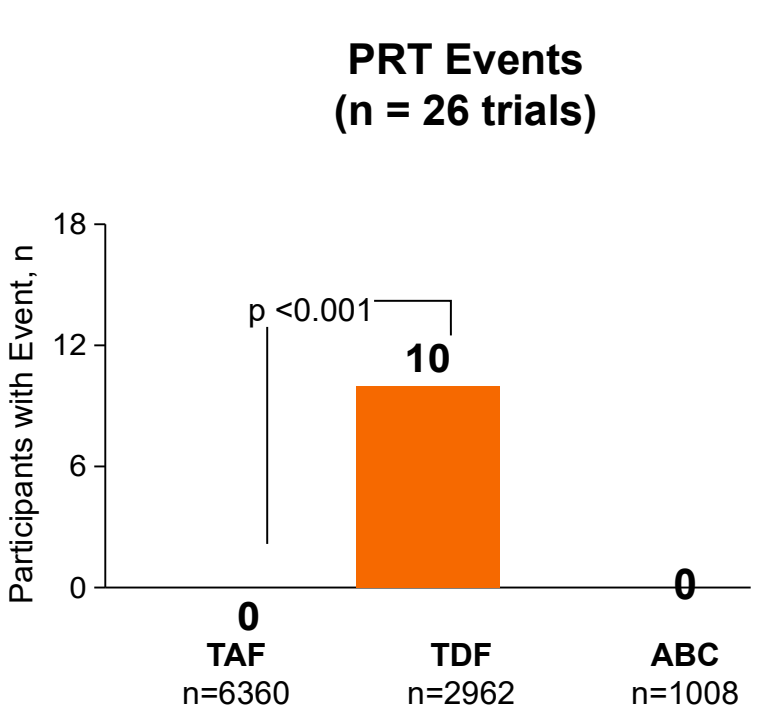
| | | TAF, n=6360 | TDF, n=2962 | ABC, n=1008 | Total , N=10,330 |
|---|---|---|---|---|---|
| Patient-years (py) of exposure | | 12,519 | 5,947 | 1,029 | 19,495 |
| Age, years | | 41 (7, 80) | 42 (18, 79) | 45 (18, 82) | 42 (7, 82) |
| Sex, n (%) | Male | 4966 (78) | 2436 (82) | 862 (86) | 8264 (80) |
| | Female | 1394 (22) | 526 (18) | 146 (15) | 2066 (20) |
| Race, n (%) | White | 3796 (60) | 1884 (64) | 687 (68) | 6367 (62) |
| | Black | 1799 (28) | 739 (25) | 267 (27) | 2805 (27) |
| | Asian | 373 (6) | 181 (6) | 25 (3) | 579 (6) |
| | Native Hawaiian or Pacific Islander | 24 (<1) | 8 (<1) | 2 (<1) | 34 (<1) |
| | American Indian or Alaska Native | 30 (1) | 19 (1) | 6 (1) | 55 (1) |
| | Other | 322 (5 ) | 126 (4) | 18 (2) | 466 (5) |
| | Not collected* | 16 (<1) | 5 (<1) | 3 (<1) | 24 (<1) |
| Ethnicity, n (%) | Hispanic or Latino | 1188 (19) | 537 (18) | 159 (16) | 1884 (18) |
| Treatment status, n (%) | Naive | 2191 (34) | 975 (33) | 315 (31) | 3481 (34) |
| | Experienced | 4169 (66) | 1987 (67) | 693 (69) | 6849 (66) |
| eGFR (CrCl), mL/min | | 108.8 (91.2, 129.6) | 107.7 (90.9, 128.4) | 108.0 (89.4, 129.7) | 108.6 (91.0, 129.3) |
| eGFR, Schwartz, mL/min/1.73 m$^2$ | | 153.3 (136.1, 170.9) | | | 153.3 (136.1, 170.9) |

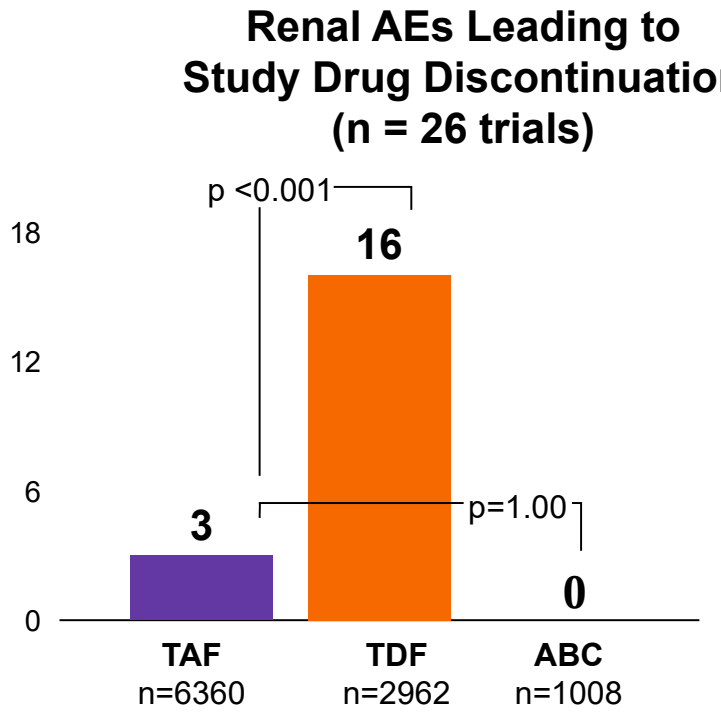
Data are median (interquartile range) or n (%), except for age, which is median (range). *Race data collection not permitted by jurisdiction.
eGFR, Schwartz, estimated glomerular filtration rate by the Schwartz formula (pediatric individuals only).

Gupta S, et al. AIDS 2018. Amsterdam, NL. Poster TUPEB113

* Renal and urinary disorders system organ class from MedDRA v18.1-19.1

# PRT and Renal AEs Leading to Discontinuation: TAF vs. TDF and ABC



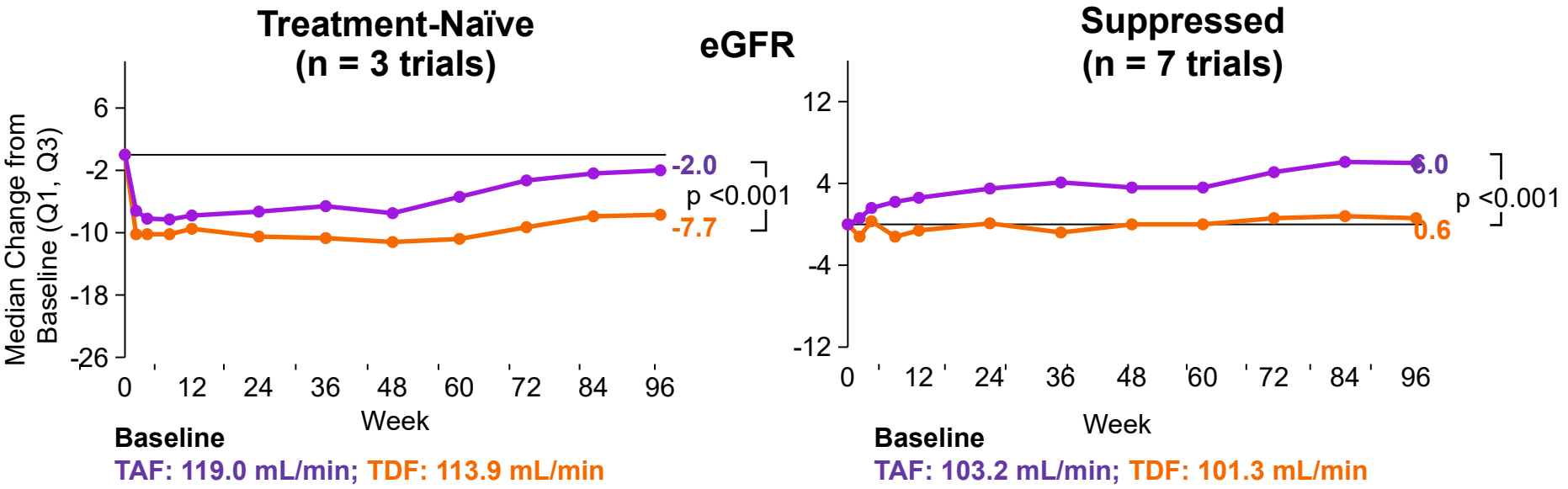

- There were no cases of PRT or Fanconi syndrome that occurred after 12,519 py of exposure to TAF vs 10 cases after 5947 py of exposure to TDF (p <0.001)
- Fewer participants discontinued for renal AEs on TAF vs TDF (3 vs 16, p <0.001)
  - The 3 events in the TAF arm included acute renal failure, interstitial nephritis, and acute kidney failure, none of which were considered related to study drug by the investigators

PRT, proximal renal tubulopathy
Differences between treatment groups compared using Fisher exact test



Gupta S, et al. AIDS 2018. Amsterdam, NL. Poster TUPEB113

# Renal Biomarkers: TAF vs. TDF




## Treatment-Emergent Proteinuria By Dipstick

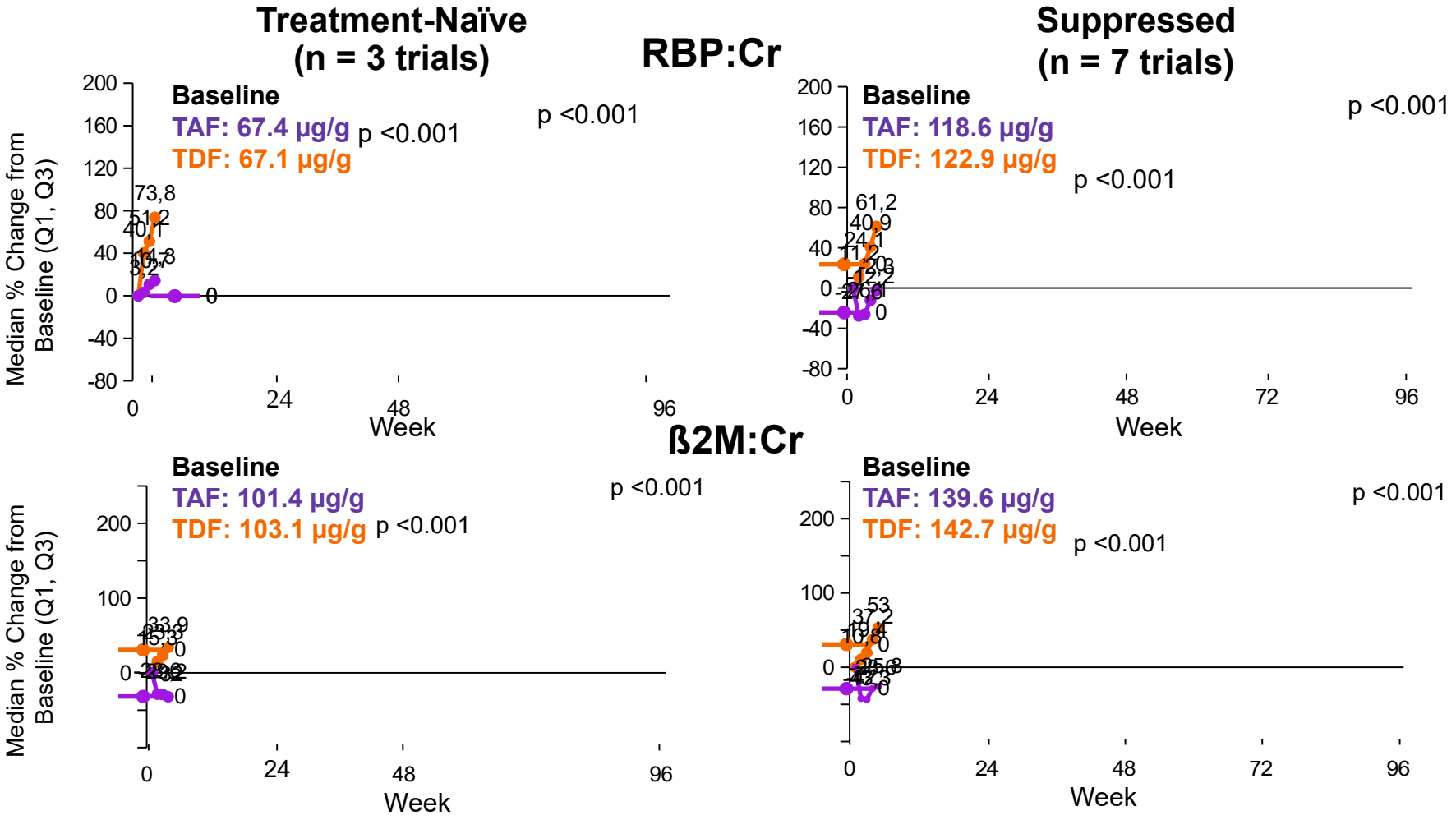
| Participants with Proteinuria, % | TAF | TDF | P-Value |
|---|---|---|---|
| Week 48 | 29% (345/1176) | 37% (319/865) | <0.001 |
| **Week 96** | 36% (307/862) | 41% (354/865) | **0.02** |

| Participants with Proteinuria, % | TAF | TDF | P-Value |
|---|---|---|---|
| Week 48 | 24% (538/2287) | 26% (460/1794) | 0.12 |
| **Week 96** | 28% (636/2287) | 31% (561/1794) | **0.02** |

**Renal biomarkers favored TAF vs. TDF in both treatment-naïve and virologically suppressed participants**

Gupta S, et al. AIDS 2018. Amsterdam, NL. Poster TUPEB113

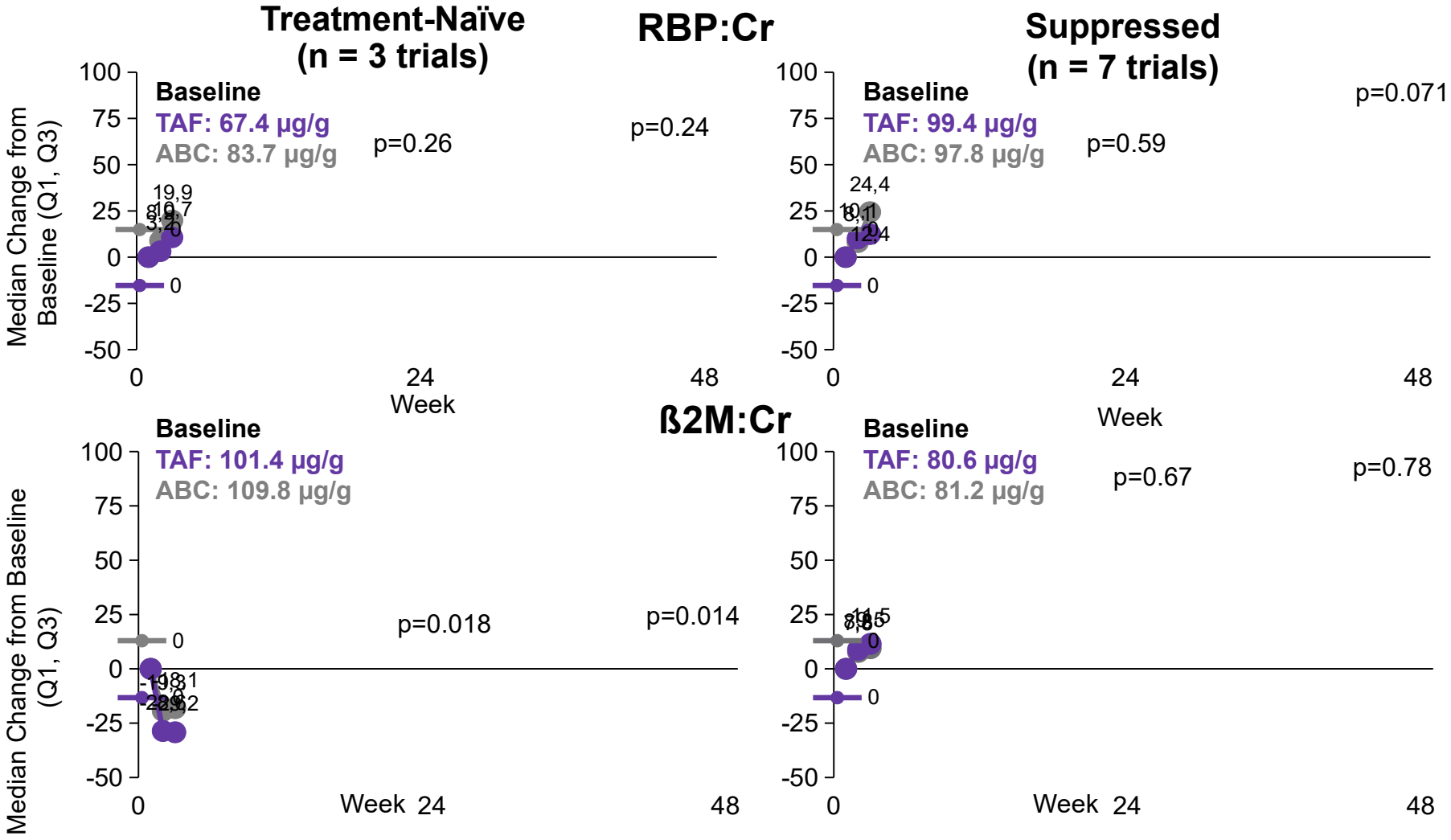
# Renal Biomarkers: TAF vs. TDF




**Renal biomarkers favoured TAF vs. TDF in both treatment-naïve and virologically suppressed participants**

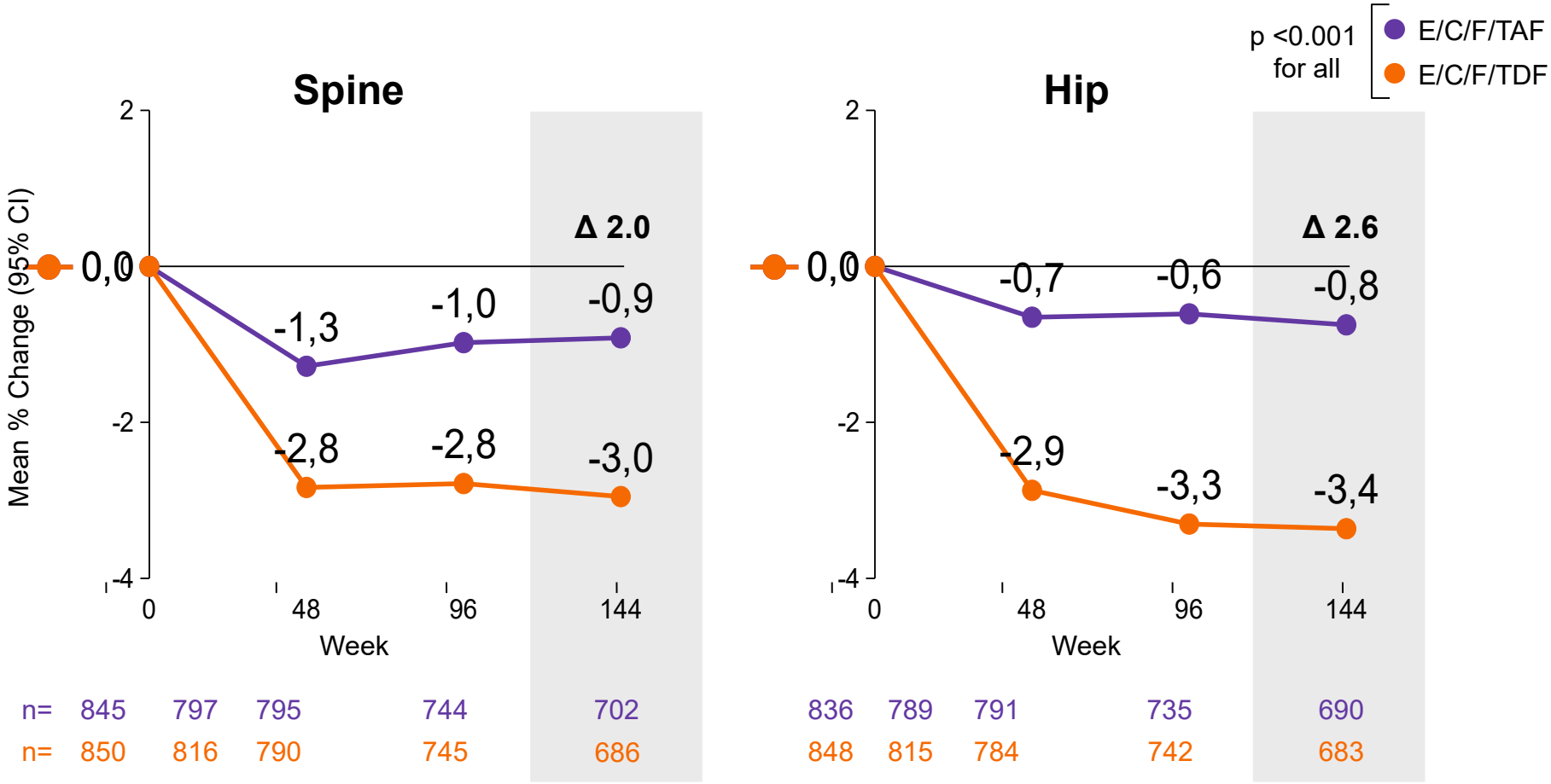
Gupta S, et al. AIDS 2018. Amsterdam, NL. Poster TUPEB113

# Renal Biomarkers: TAF vs. ABC




**Renal biomarkers were similar or more favourable for TAF vs. ABC**

# Results: Change in Spine and Hip BMD Through Week 144*

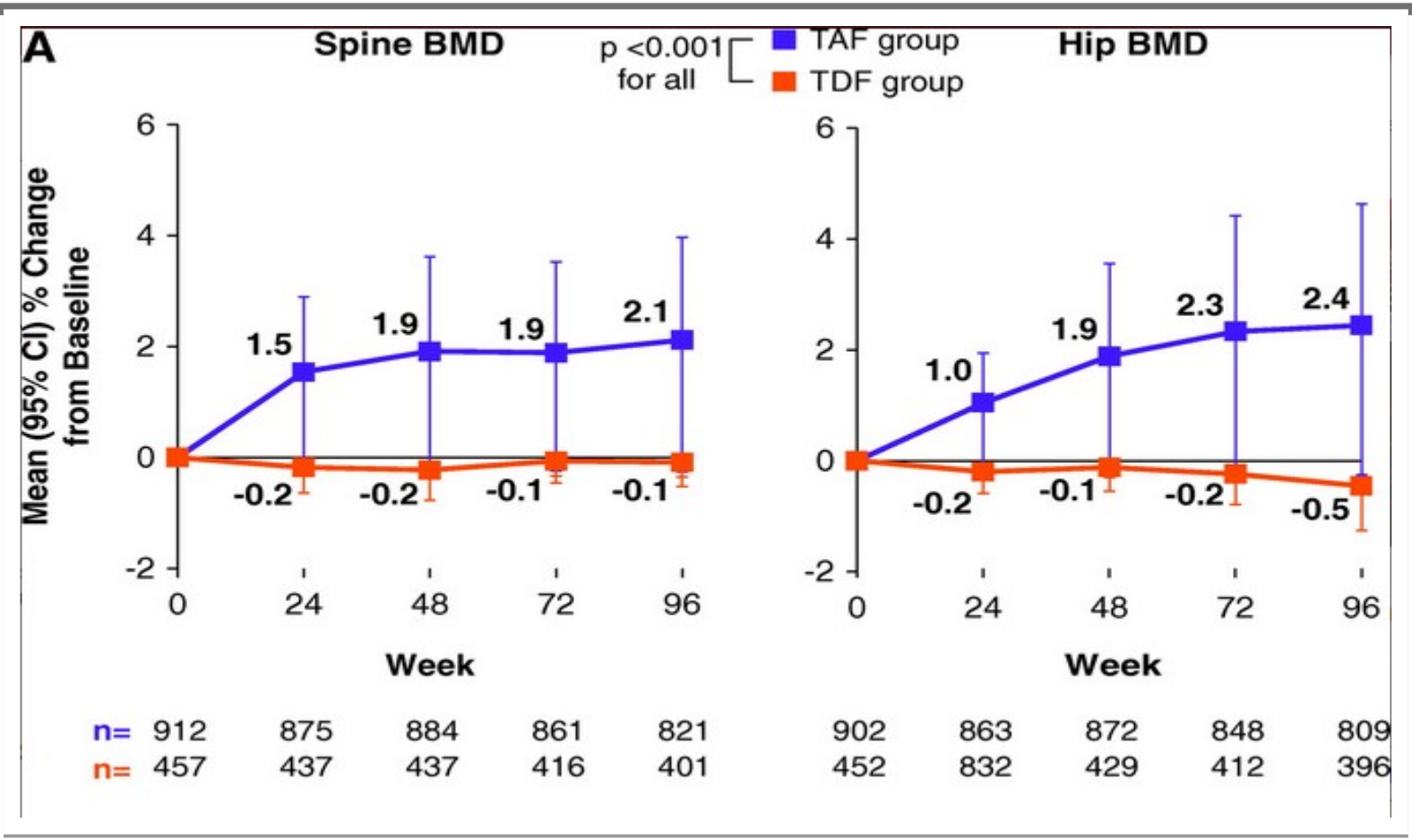



- Through Week 144, significantly greater losses in spine and hip BMD in TDF group
- No D/C due to bone AEs in TAF arm vs 6 in TDF arm

*p-value calculated using analysis of variance model including treatment as a fixed effect.

Arribas JR, J Acquir Immune Defic Syndr. 2017 Jun 1;75(2):211-218. doi: 10.1097/QAI.0000000000001350.

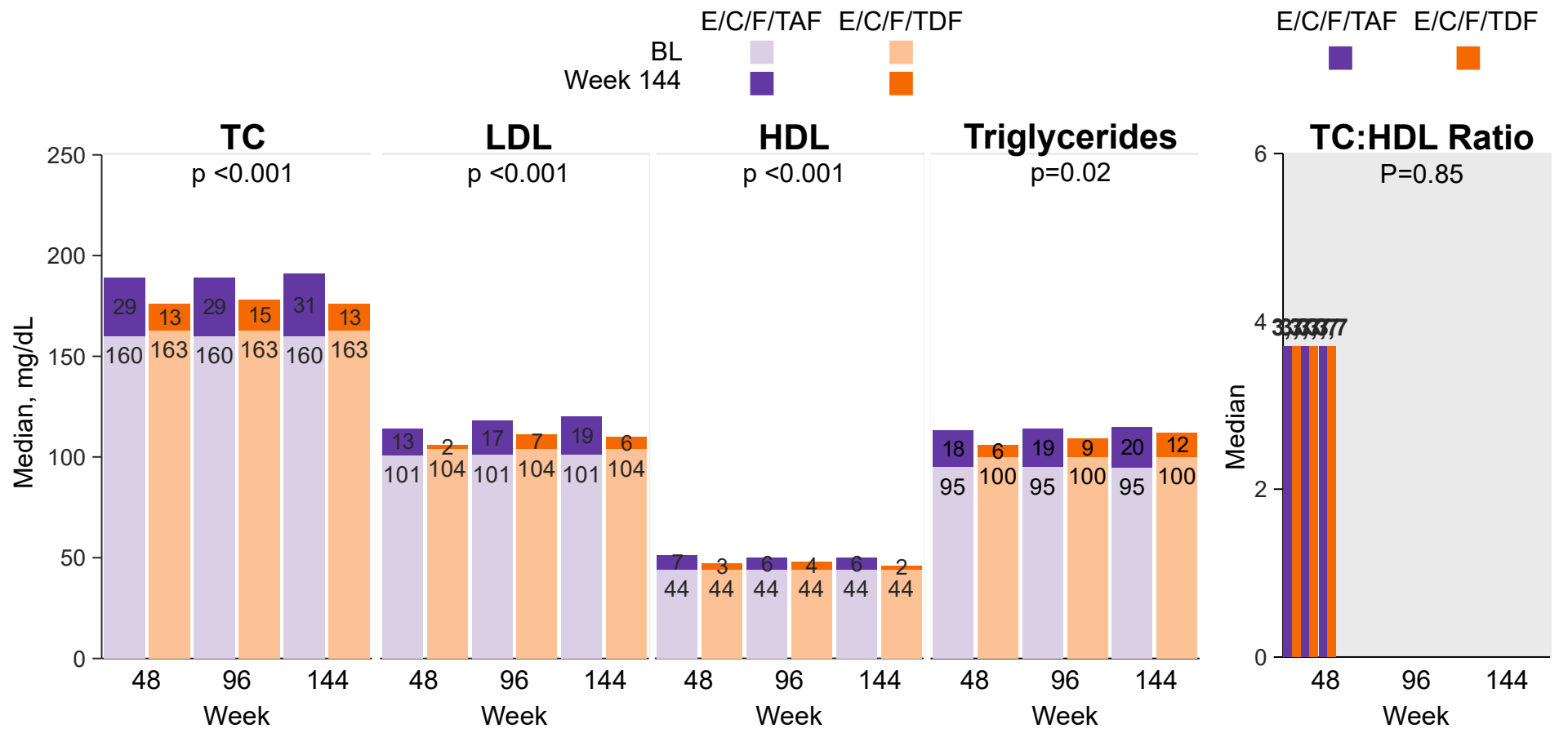
# Changes in Spine and Hip BMD through Week 96




**Switching to E/C/F/TAF from a regimen containing FTC/TDF + 3rd agent resulted in progressive increase in spine and hip BMD over 96 weeks**

DeJesus E, AIDS Res Hum Retroviruses. 2018 Apr;34(4):337-342. doi: 10.1089/AID.2017.0203. Epub 2018 Mar 20.

# Fasting Lipids through Week 144




- Participants on E/C/F/TAF had greater increases in TC, LDL, and HDL than those on E/C/F/TDF, with no difference in rate of initiation of lipid-modifying agents (E/C/F/TAF: 5.5% [n=48]; E/C/F/TDF: 5.8% [n=50])



Arribas JR, J Acquir Immune Defic Syndr. 2017 Jun 1;75(2):211-218. doi: 10.1097/QAI.0000000000001350.

# Editorial to 1717 study: ABC/3TC to FTC/TAF study

"TAF seems to be not only less toxic than TDF but also similar to ABC with regard to renal and bone safety…***The idea that NRTIs are inevitably toxic drugs is no longer true.*** Besides 3TC and FTC, TAF, and, possibly, ABC can be safely administered to most patients with HIV. ***The search for a less toxic pair of nucleosides could be reaching its end****."*

-Vivancos MJ, Moreno S. *Lancet HIV* 2018

# Advantages of TAF-Based Triple Therapy

- Years of experience in clinical trials and observational studies
- No proximal tubulopathy or bone toxicity in clinical trials, with improvement in renal and bone parameters after switch from TDF
- Less virologic failure and resistance with triple therapy vs. 2DC in observational cohort studies
- Activity against HBV in coinfected patients
- Some regimens appropriate for “rapid start” protocols

Arribas JR, *J Acquir Immune Defic Syndr*. 2017;75:211-218.

DeJesus E, *AIDS Res Hum Retroviruses,* 2018;34:337-342.

Teira R, et. al. EACS 2017. Milan, Italy. PE9/33