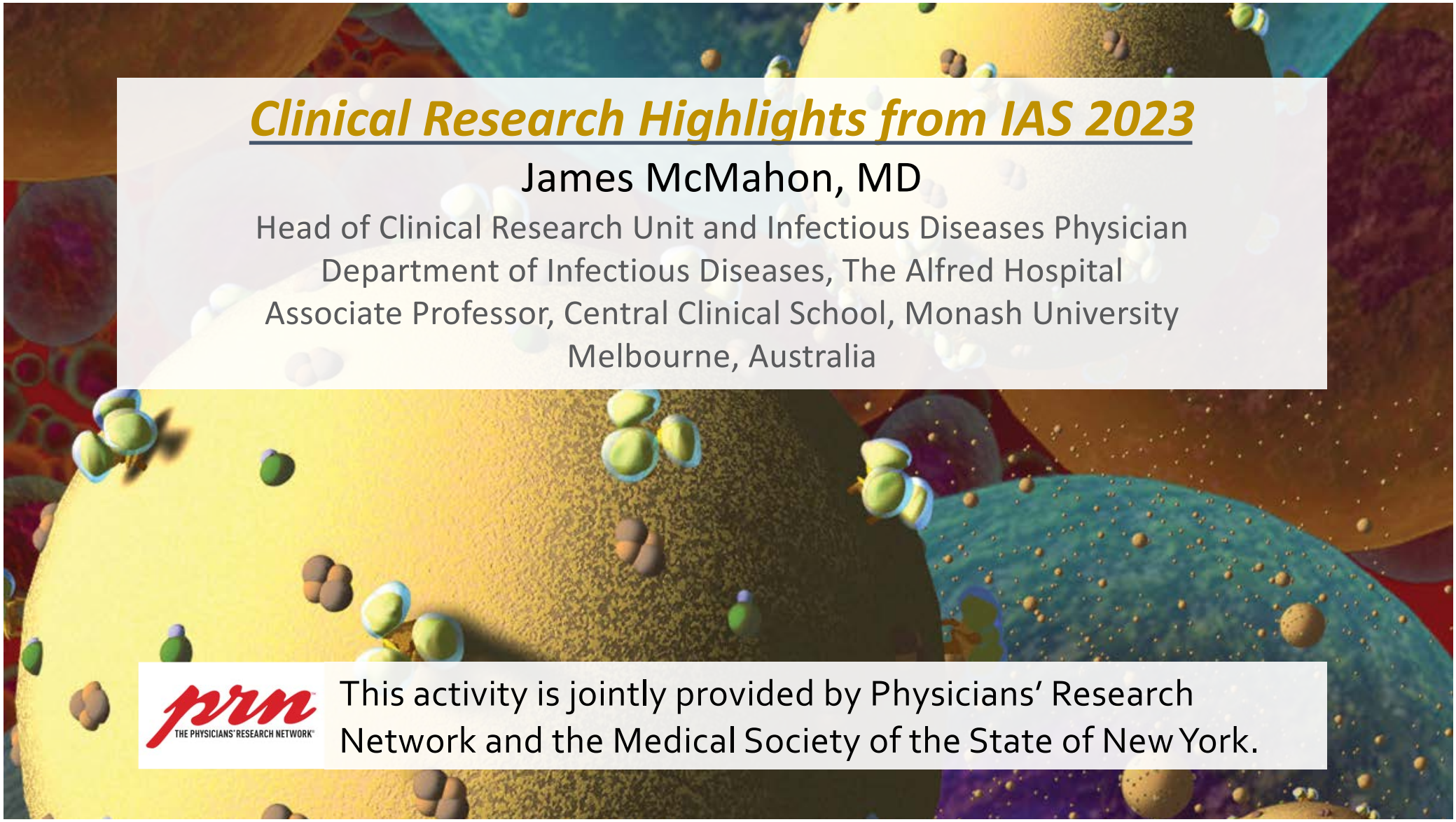


Clinical Research Highlights from IAS 2023

James McMahon, MD

Head of Clinical Research Unit and Infectious Diseases Physician
Department of Infectious Diseases, The Alfred Hospital
Associate Professor, Central Clinical School, Monash University
Melbourne, Australia

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

Overview

- REPRIEVE
- DEFINE
- Doravirine / Islatravir in treatment Naïve 48 Weeks
- ADVANCE / NAMSAL

- Plenary Highlights
  - Katherine Bar (UPenn) – bNAbs
  - Andrew Grulich (Kirby) – HIV prevention
  - Claudia Cortes (Chile) – Long acting ART

Slide acknowledgments – Stephen Grinspoon, William Short, Jurgen Rockstroh, Francois Venter

• Steven Grinspoon, MD Massachusetts General Hospital and Harvard Medical School

Key REPRIEVE Results and the Utility of Statins Among PWH: What Have We Learned?

The REPRIEVE trial: Developing a cardiovascular disease prevention strategy for people living with HIV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

BACKGROUND

The risk of cardiovascular disease is increased among persons with human immunodeficiency virus (HIV) infection, so data regarding primary prevention strategies in this population are needed.

METHODS

In this phase 3 trial, we randomly assigned 7769 participants with HIV infection with a low-to-moderate risk of cardiovascular disease who were receiving antiretroviral therapy to receive daily pitavastatin calcium (at a dose of 4 mg) or placebo. The primary outcome was the occurrence of a major adverse cardiovascular event, which was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause.

RESULTS

The median age of the participants was 50 years (interquartile range, 45 to 55); the median CD4 count was 621 cells per cubic millimeter (interquartile range, 448 to 827), and the HIV RNA value was below quantification in 5250 of 5997 participants (87.5%) with available data. The trial was stopped early for efficacy after a median follow-up of 5.1 years (interquartile range, 4.3 to 5.9). The incidence of a major adverse cardiovascular event was 4.81 per 1000 person-years in the pitavastatin group and 7.32 per 1000 person-years in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.90; P=0.002). Muscle-related symptoms occurred in 91 participants (2.3%) in the pitavastatin group and in 53 (1.4%) in the placebo group; diabetes mellitus occurred in 206 participants (5.3%) and in 155 (4.0%), respectively.

CONCLUSIONS

Participants with HIV infection who received pitavastatin had a lower risk of a major adverse cardiovascular event than those who received placebo over a median follow-up of 5.1 years. (Funded by the National Institutes of Health and others; REPRIEVE ClinicalTrials.gov number, NCT02344290.)

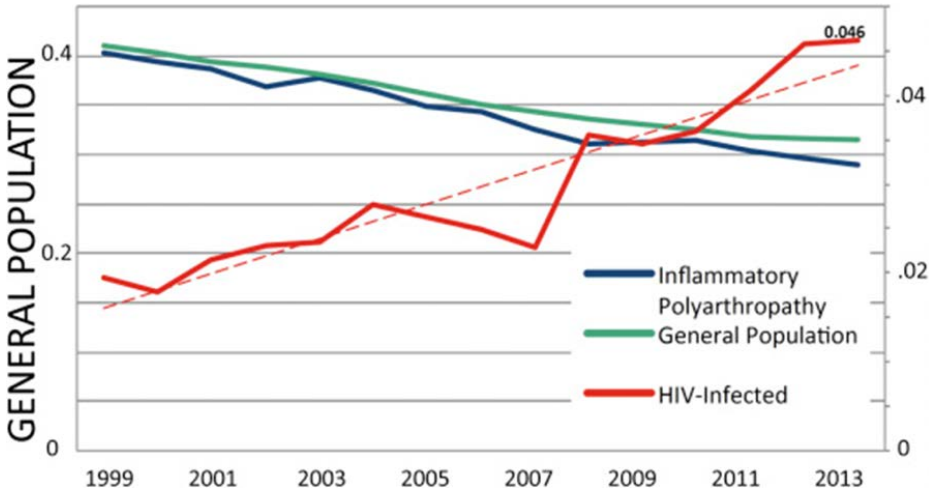
The authors' affiliations are listed in the Appendix. Dr. Grinspoon can be contacted at sgrinspoon@mgh.harvard.edu or at the Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St., 5 Longfellow Pl., Suite 207, Boston, MA 02114.

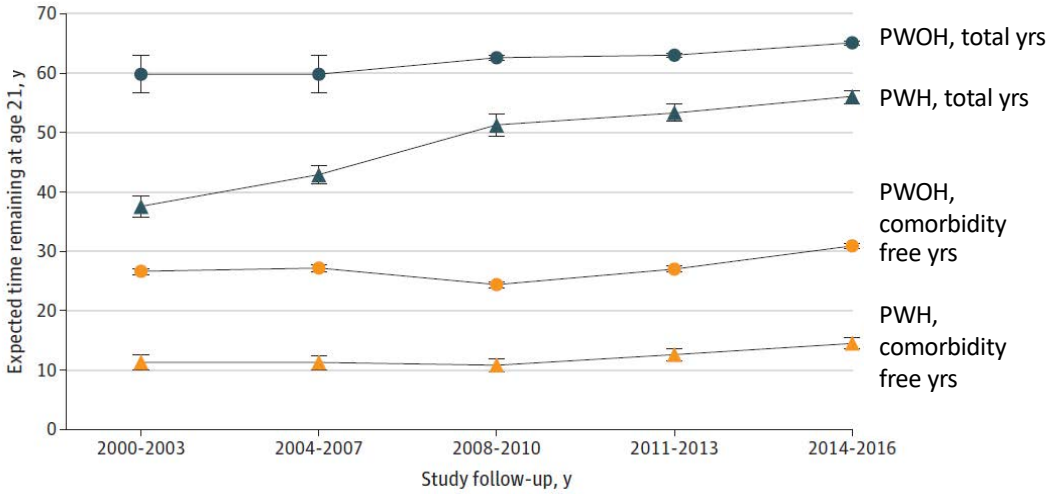
*A list of the REPRIEVE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 23, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2304146

Cardiovascular Disease is Increasing in PWH, Contributing to a Persistent Comorbidity Gap





Marcus et al., JAMA Network Open 2020; Feinstein et al., Am J Card 2016

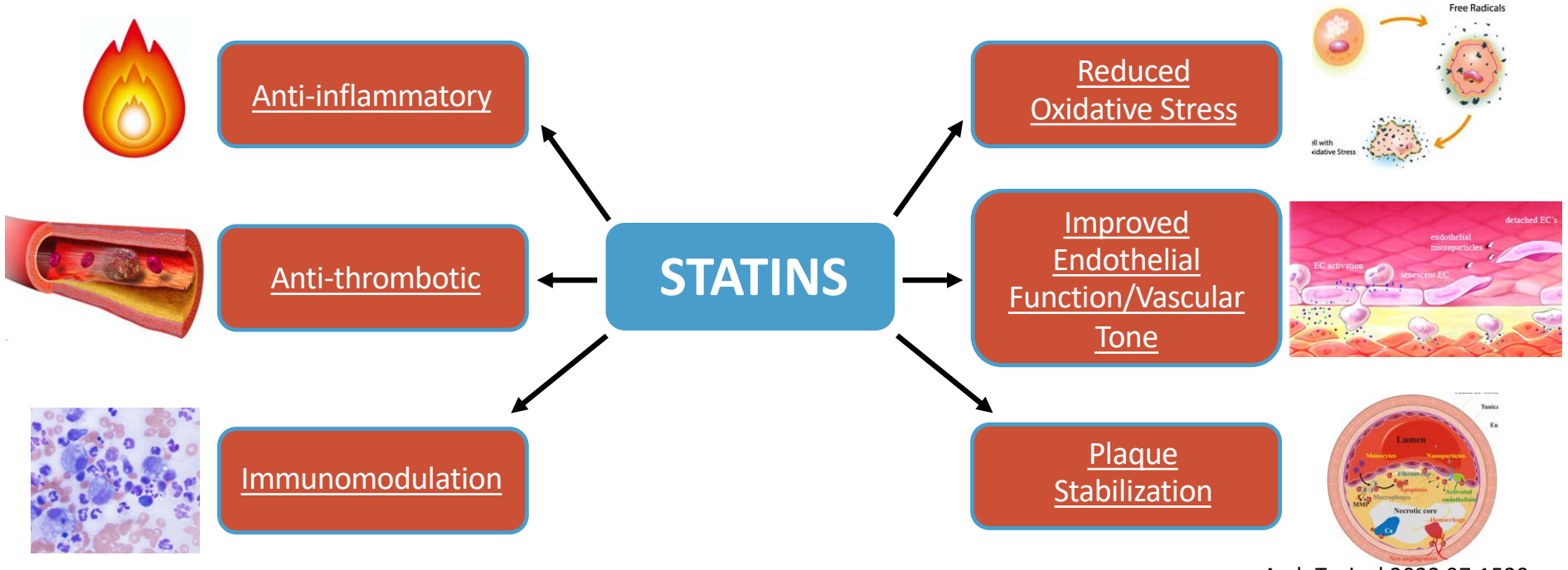
Study Rationale

- PWH demonstrate increased cardiovascular disease (CVD) (50-100%) and excess plaque controlling for traditional risk, even at a young age
- ART reduces comorbidities (SMART) but residual immune activation persists, even with good viral suppression - ART alone is not sufficient to prevent CVD
- Statins lower LDL cholesterol, a main driver of CVD in PWH, but also residual immune activation and inflammation, including among PWH
- Pitavastatin is a moderate intensity statin, unaffected by ART, with good LDL and anti-inflammatory properties
- We hypothesized pitavastatin would prevent MACE through these effects in PWH, at low to moderate risk, for whom statins not typically prescribed under current guidelines

MACE = major adverse cardiovascular events = REPRIEVE primary endpoint = composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined (i.e. unknown cause therefore could be cardiac) cause

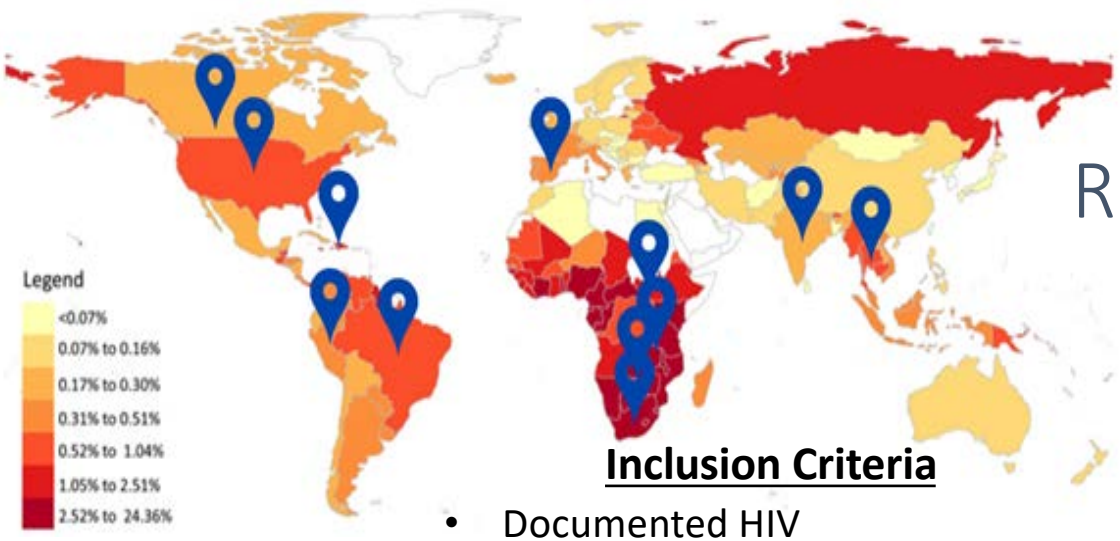
Beyond LDL: Pleiotropic Effects of Statins

- Statins primary effect is to inhibit HMG-CoA reductase to lower LDL cholesterol
- Statins have many other beneficial effects to reduce vascular disease



Arch Toxicol 2023 97:1529

REPRIEVE Study Population



Inclusion Criteria

- Documented HIV
- Receiving stable ART
- CD4+ > 100 cells/mm3
- Age ≥ 40 years, ≤ 75 years
- No known atherosclerotic cardiovascular disease (ASCVD)
- 10-yr ASCVD risk score
  - <7.5% LDL < 190 mg/dL
  - ≥7.5% and ≤ 10% LDL, < 160 mg/dL (4.1 mmol/L)
  - >10% and ≤15%, LDL < 130 mg/dL (3.4 mmol/L)
- Certain laboratory parameters

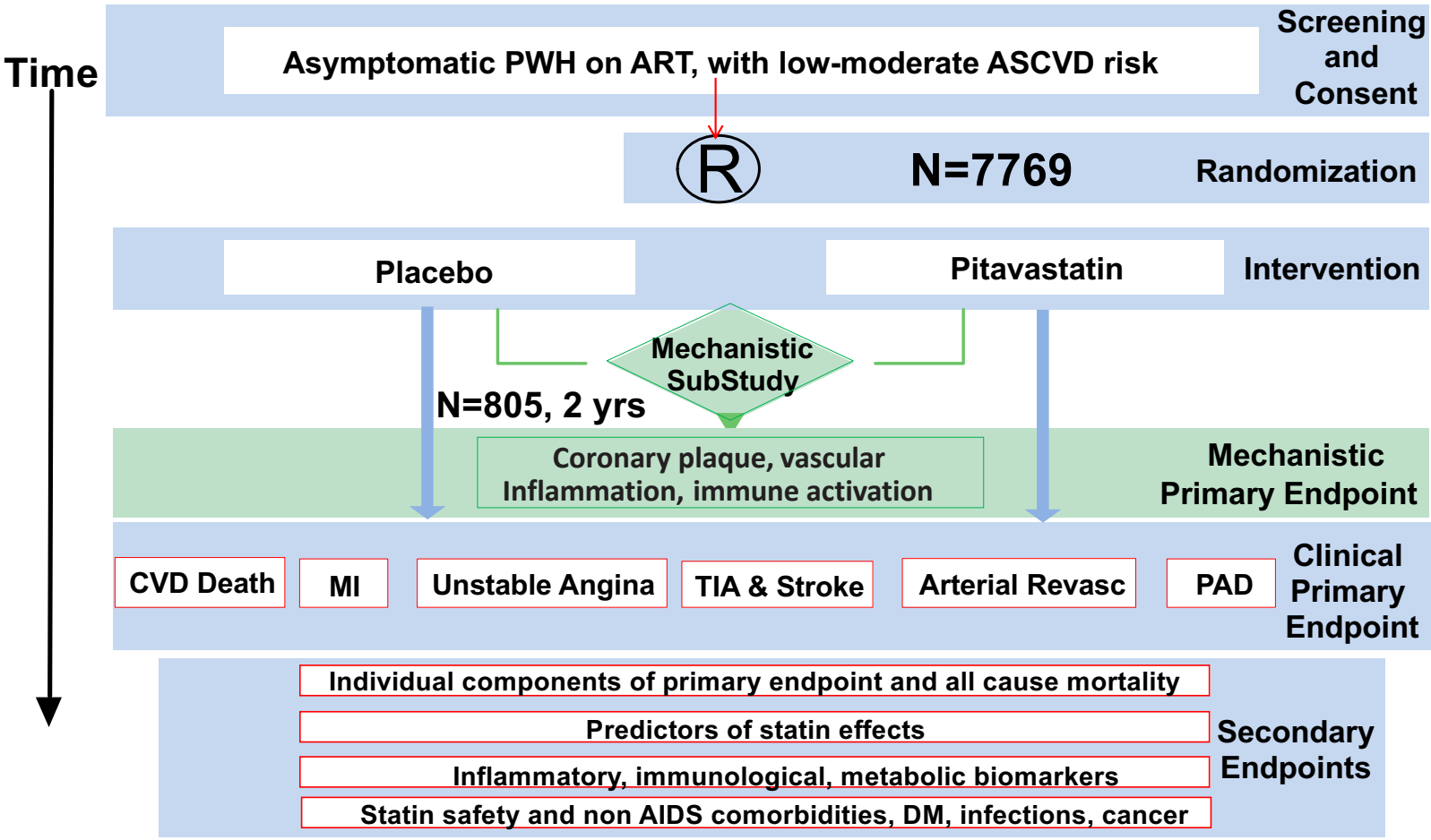
Exclusion Criteria

- Current use of statins, gemfibrozil, or PCSK9 inhibitors
- Known decompensated cirrhosis

NB:
< 5% low risk
5-7.5% borderline risk
7.5-20% intermediate risk
> 20% high risk

Note: For LDL, to convert from mg/dL to SI (in mmol/L) multiply by 0.02586

REPRIEVE Trial Schema



Global Enrollment

	High Income (N=118)	Latin America and Caribbean (N=15)	S. East/East Asia (N=2)	South Asia (N=2)	Sub-Saharan Africa (N=8)	Total (N=145)
Overall Statistics						
Total number screened	5,539	1,953	824	634	1,915	10,865
Total number enrolled	4,095	1,423	590	504	1,157	7,769
Percent of total enrollment	53%	18%	7.6%	6.5%	15%	100%

Baseline Characteristics		Total (N=7769)	Pitavastatin (N=3888)	Placebo (N=3881)
Age (years)	Median (Q1 – Q3)	50 (45-55)	50 (45-55)	50 (45-55)
Natal sex	Male	5350 (69%)	2677 (69%)	2673 (69%)
	Female	2419 (31%)	1211 (31%)	1208 (31%)
Gender identity	Cisgender	7367 (95%)	3687 (95%)	3680 (95%)
	Transgender spectrum	127 (2%)	63 (2%)	64 (2%)
	Not reported	275 (4%)	138 (4%)	137 (4%)
Race	White	2704 (35%)	1634 (35%)	1340 (35%)
	Black/African American	3208 (41%)	1569 (40%)	1639 (42%)
	Asian	1138 (15%)	571 (15%)	567 (15%)
CD4 count (cells/mm3)	Median (Q1 – Q3)	621 (448-827)	620 (449-832)	622 (445-824)
Nadir CD4 count (cells/mm3)	< 50 50-199 ≥ 200	1409 (18%) 2392 (31%) 3706 (48%)	688 (18%) 1202 (31%) 1859 (49%)	721 (19%) 1190 (31%) 1847 (47%)
HIV RNA (Copies/mL)	< LLQ LLQ - < 400 400+ Missing	5250 (88%) 617 (10%) 130 (2%) 1772	2641 (88%) 305 (10%) 63 (2%) 879	2609 (87%) 312 (10%) 67 (2%) 893
ASCVD risk score, (%)	Median (Q1 – Q3)	4.5 (2.1-7.0)	4.5 (2.1-7.0)	4.5 (2.2-7.0)
LDL-C (mg/dL)	Median (Q1 – Q3)	108 (87-128)	109 (87-128)	108 (87-127)

Baseline ART Regimen and Duration

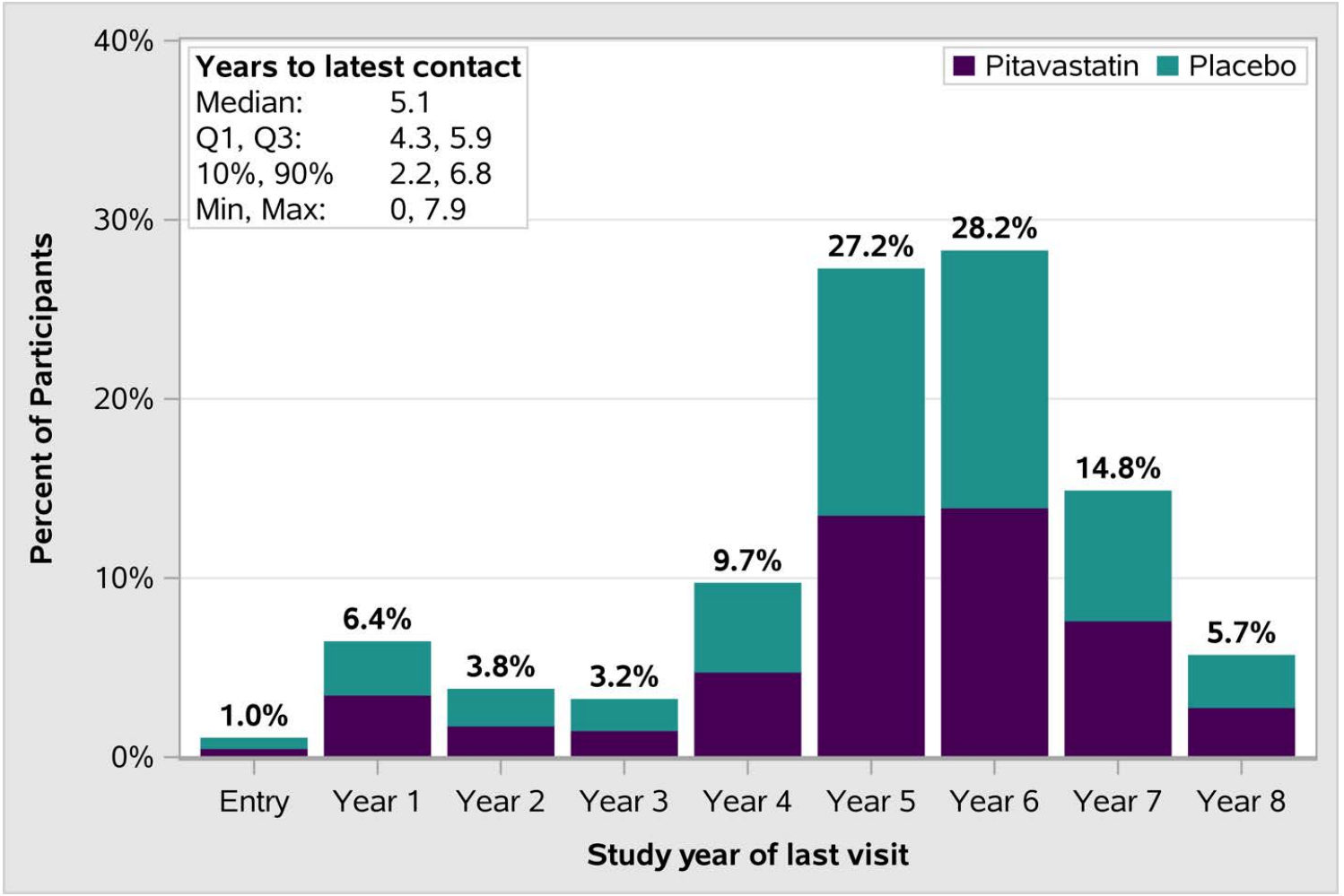
		Pitavastatin (N=3888)	Placebo (N=3881)	Total (N=7769)	High Income (N=4095)	Latin America and Caribbean (N=1423)	S. East/East Asia (N=590)	South Asia (N=504)	Sub-Saharan Africa (N=1157)
Total ART use (years)	<5	847 (22%)	857 (22%)	1704 (22%)	675 (16%)	490 (34%)	55 (9%)	143 (28%)	341 (29%)
	5-10	1190 (31%)	1118 (29%)	2308 (30%)	1115 (27%)	462 (32%)	123 (21%)	205 (41%)	403 (35%)
	10+	1851 (48%)	1904 (49%)	3755 (48%)	2303 (56%)	471 (33%)	412 (70%)	156 (31%)	413 (36%)
Entry ART regimen class	NRTI + NNRTI	1843 (47%)	1826 (47%)	3669 (47%)	996 (24%)	815 (57%)	466 (79%)	410 (81%)	982 (85%)
	NRTI + INSTI	998 (26%)	993 (26%)	1991 (26%)	1875 (46%)	85 (6%)	3 (1%)	3 (1%)	25 (2%)
	NRTI + PI	728 (19%)	708 (18%)	1436 (18%)	674 (16%)	442 (31%)	105 (18%)	82 (16%)	133 (11%)
	NRTI-sparing	95 (2%)	108 (3%)	203 (3%)	164 (4%)	18 (1%)	9 (2%)	9 (2%)	3 (0%)
	Other NRTI-containing	224 (6%)	246 (6%)	470 (6%)	386 (9%)	63 (4%)	7 (1%)	0 (0%)	14 (1%)
Entry ART regimen duration (years)	<1	1128 (29%)	1133 (29%)	2261 (29%)	1441 (35%)	414 (29%)	251 (43%)	64 (13%)	91 (8%)
	1-3	1134 (29%)	1150 (30%)	2284 (29%)	1277 (31%)	415 (29%)	165 (28%)	128 (25%)	299 (26%)
	3-5	611 (16%)	628 (16%)	1239 (16%)	472 (12%)	231 (16%)	61 (10%)	103 (20%)	372 (32%)
	5+	1015 (26%)	970 (25%)	1985 (26%)	905 (22%)	363 (26%)	113 (19%)	209 (41%)	395 (34%)

Recent Events and Trial Closure

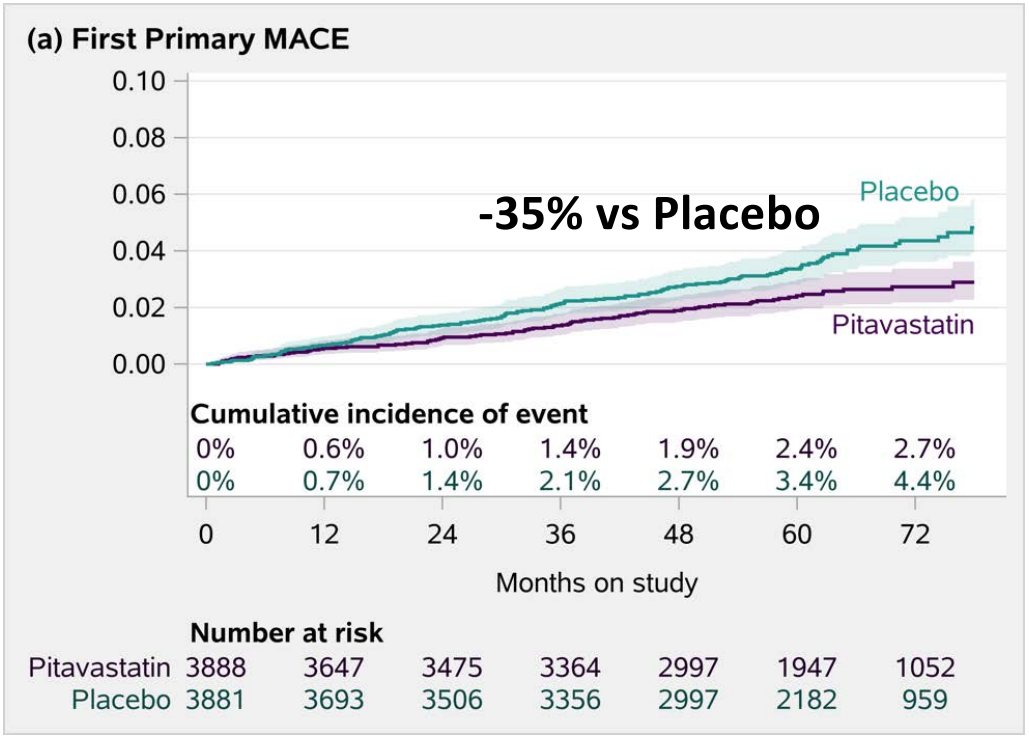
- REPRIEVE is an events driven trial with 85% power to detect a HR of 0.70 with 288 planned events
- ***The DSMB convened at 75% of information and closed the trial for efficacy***, concluding there were no unanticipated safety concerns and that the benefits outweighed the risk of statin therapy in this group

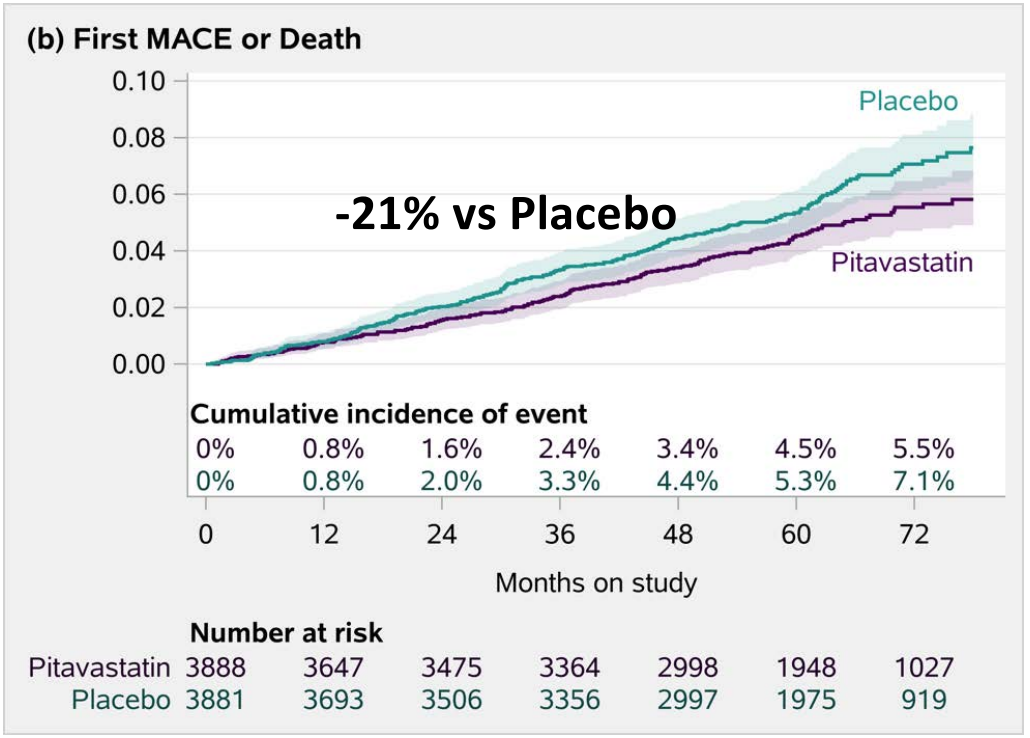
DSMB = data and safety monitoring board

Duration of Follow-Up at Time of DSMB



Primary and Key Secondary Endpoints

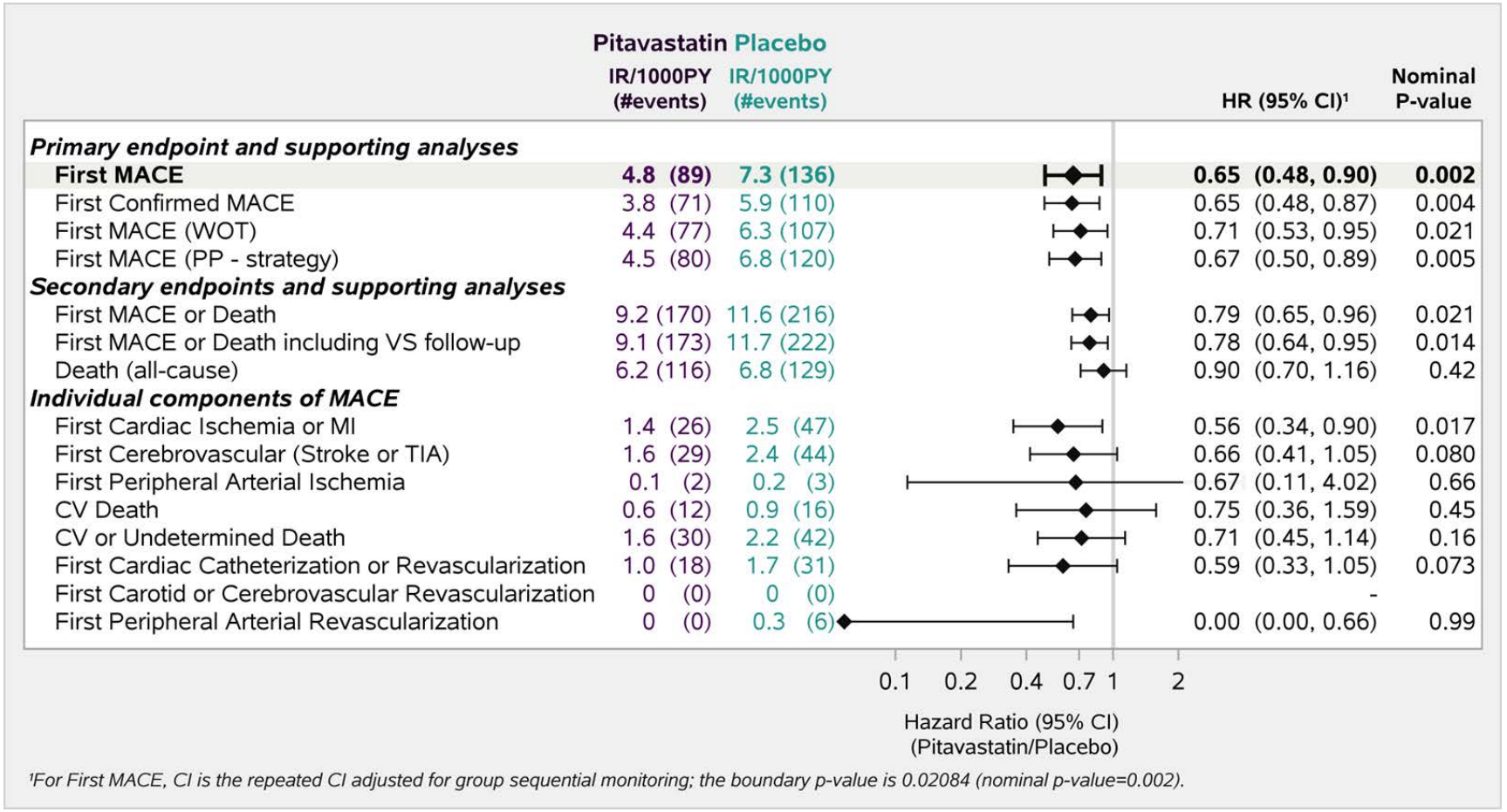




Additional Findings

- Greater than 80% in both groups remained in follow up
- Adherence was *very good to excellent* in the great majority of participants
- Adverse event-related discontinuation was low in each group (2% vs 1% pitavastatin vs placebo)
- Clinical initiation of a non-study statin occurred in 5.7% pitavastatin and 9.6% of placebo-treated participants, below threshold of concern
- All events adjudicated vis a vis relationship to COVID; only one MACE event definitely related

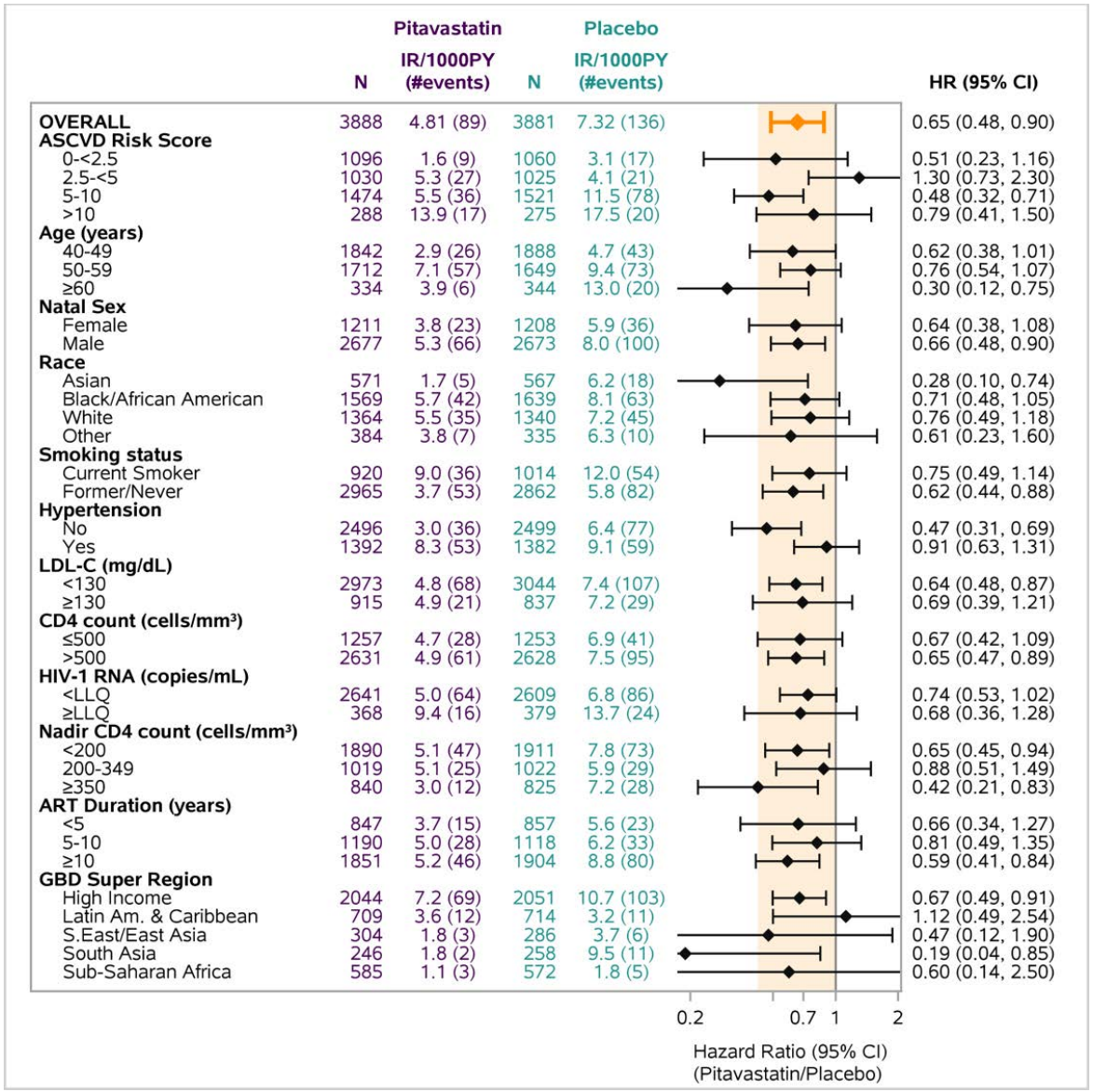
Primary Endpoints and MACE Components



	Pitavastatin IR/1000PY (#events)	Placebo IR/1000PY (#events)	HR (95% CI)[1]	Nominal P-value
Primary endpoint and supporting analyses				
First MACE	**4.8 (89)**	**7.3 (136)**	**0.65 (0.48, 0.90)**	**0.002**
First Confirmed MACE	3.8 (71)	5.9 (110)	0.65 (0.48, 0.87)	0.004
First MACE (WOT)	4.4 (77)	6.3 (107)	0.71 (0.53, 0.95)	0.021
First MACE (PP - strategy)	4.5 (80)	6.8 (120)	0.67 (0.50, 0.89)	0.005
Secondary endpoints and supporting analyses				
First MACE or Death	9.2 (170)	11.6 (216)	0.79 (0.65, 0.96)	0.021
First MACE or Death including VS follow-up	9.1 (173)	11.7 (222)	0.78 (0.64, 0.95)	0.014
Death (all-cause)	6.2 (116)	6.8 (129)	0.90 (0.70, 1.16)	0.42
Individual components of MACE				
First Cardiac Ischemia or MI	1.4 (26)	2.5 (47)	0.56 (0.34, 0.90)	0.017
First Cerebrovascular (Stroke or TIA)	1.6 (29)	2.4 (44)	0.66 (0.41, 1.05)	0.080
First Peripheral Arterial Ischemia	0.1 (2)	0.2 (3)	0.67 (0.11, 4.02)	0.66
CV Death	0.6 (12)	0.9 (16)	0.75 (0.36, 1.59)	0.45
CV or Undetermined Death	1.6 (30)	2.2 (42)	0.71 (0.45, 1.14)	0.16
First Cardiac Catheterization or Revascularization	1.0 (18)	1.7 (31)	0.59 (0.33, 1.05)	0.073
First Carotid or Cerebrovascular Revascularization	0 (0)	0 (0)	-	
First Peripheral Arterial Revascularization	0 (0)	0.3 (6)	0.00 (0.00, 0.66)	0.99

[1]*For First MACE, CI is the repeated CI adjusted for group sequential monitoring; the boundary p-value is 0.02084 (nominal p-value=0.002).*

WOT – as-treated analysis

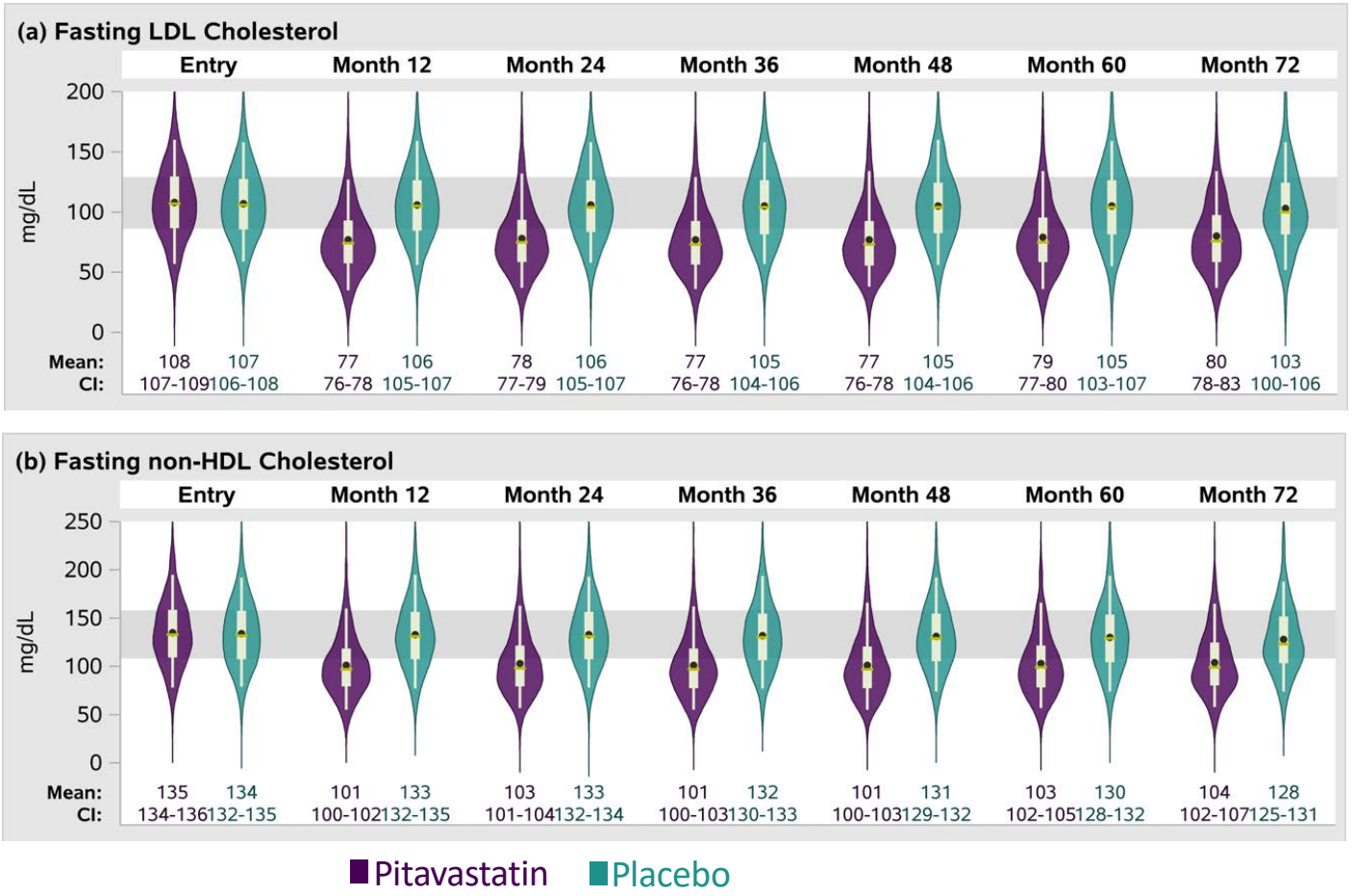


Effects on Key Subgroups

- Very consistent affect across major subgroups
- No treatment modification based on LDL, age, sex
- Generally consistent effects across race and GBD regions
- No treatment modification based on CD4, nadir CD4, HIV RNA, ART Duration

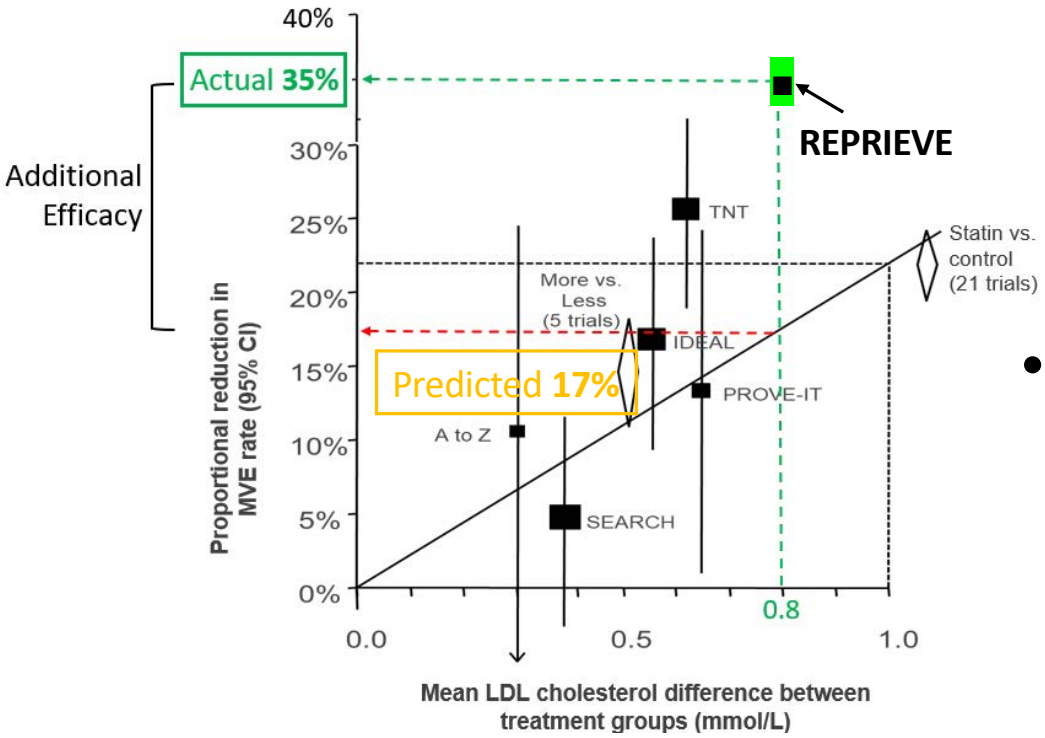
GBD = global burden of disease

Effects on LDL and NON-HDL Cholesterol



- 30% reduction in LDL in pitavastatin group, no change in placebo
- Durable effect over time

Effect Larger than Anticipated Based on Lowering of LDL



Note: 35% is point estimate, CI % is 17 – 52%

- **LDL lowering matters but statin effect is beyond what is expected for LDL lowering alone**

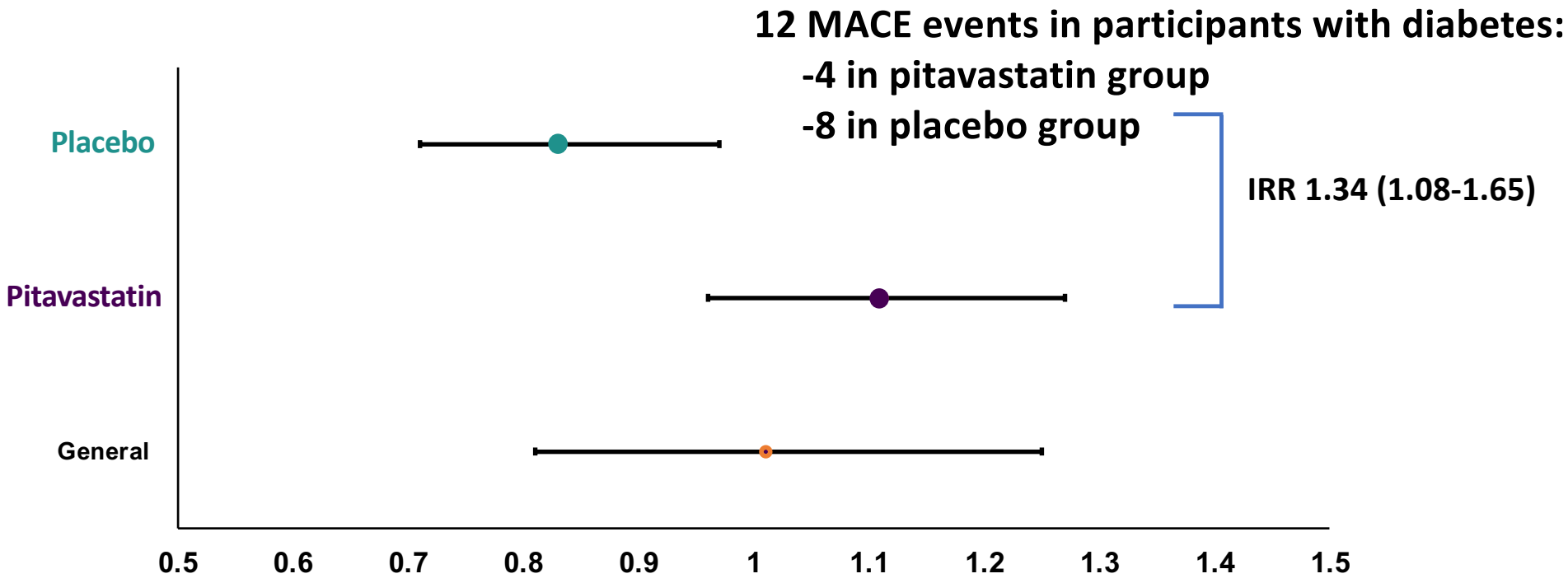
Lancet 2010; 376: 1670-81

Safety

- DSMB concluded no unanticipated safety concerns
- Serious adverse events similar in each group: IRR 1.02 (0.92-1.14)
- Muscle-related symptoms were higher in the pitavastatin group but were mostly mild and only 1% withdrew for muscle-related symptomatology
- Diabetes rates increased in the pitavastatin group, but this increase was consistent with that seen in prior statin studies, was not significantly above rates demonstrated for the general population, and very few withdrew due to diabetes
- No effect on Grade 3 ALT or rhabdomyolysis was seen

IRR: incidence rate ratio

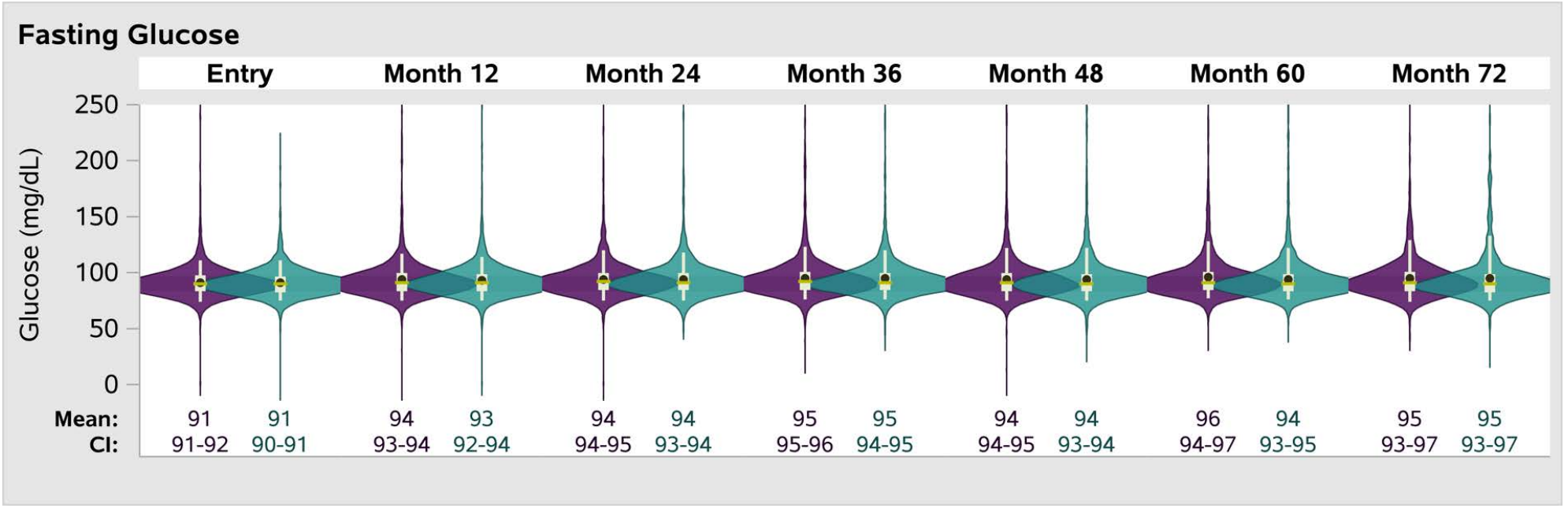
Diabetes Rates in REPRIEVE vs. General Population Aged 45-64 per US Centers for Disease Control



IRR: incidence rate ratio

Centers for Disease Control and Prevention. Incidence of Newly Diagnosed Diabetes. https://www.cdc.gov/diabetes/data/statistics-report/newly-diagnosed-diabetes.html#print

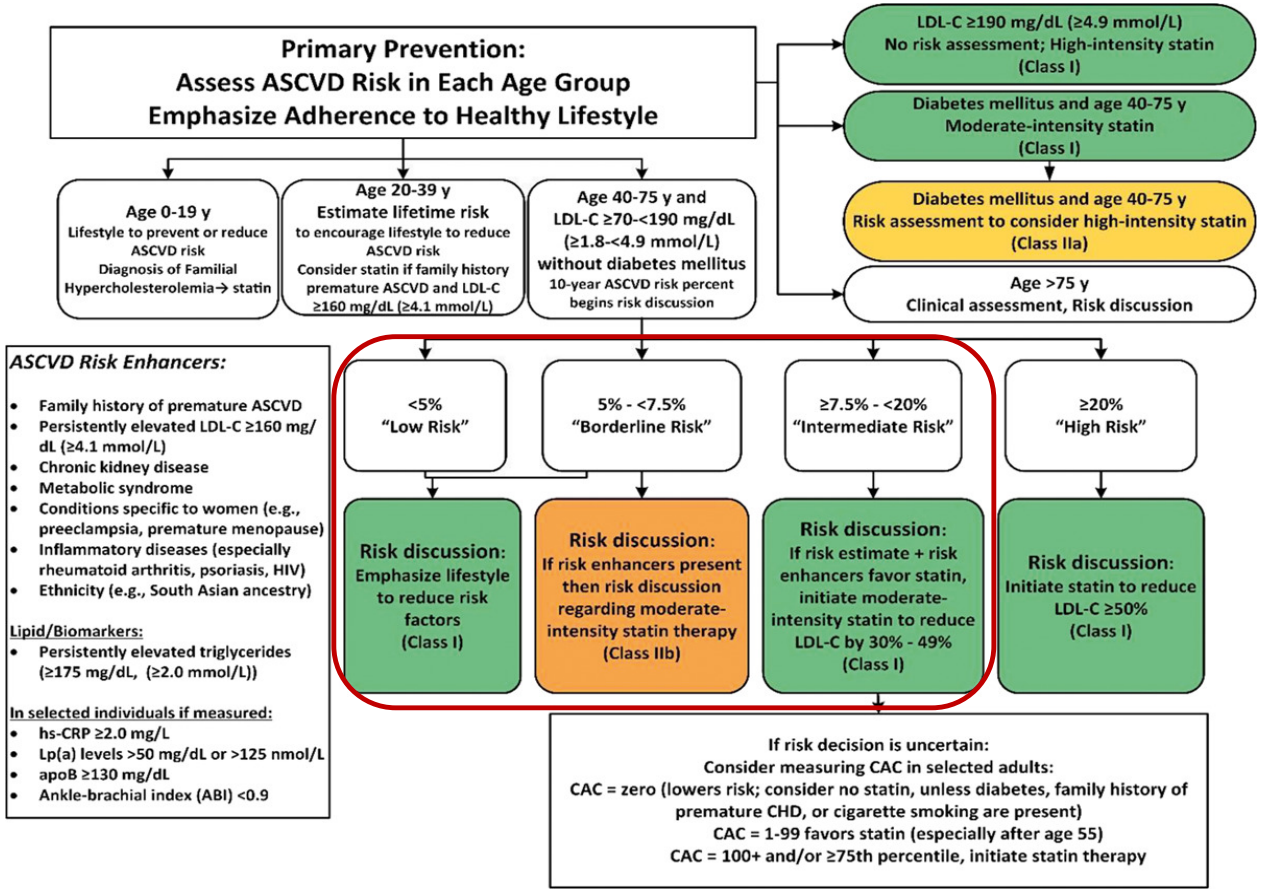
Effects on Glucose



Violin plots presenting Kernel estimate of probability density function, and mean (circle), median (yellow dash), Q1-Q3 (box) and P5-P95 (whiskers). Union of within treatment group IQRs at baseline is shown in gray shading for reference. 95% confidence intervals for means are shown in the axis table.

How Might the Findings of REPRIEVE Impact the Recommendations for Statin Therapy (2019 ACC/AHA Guidelines)?

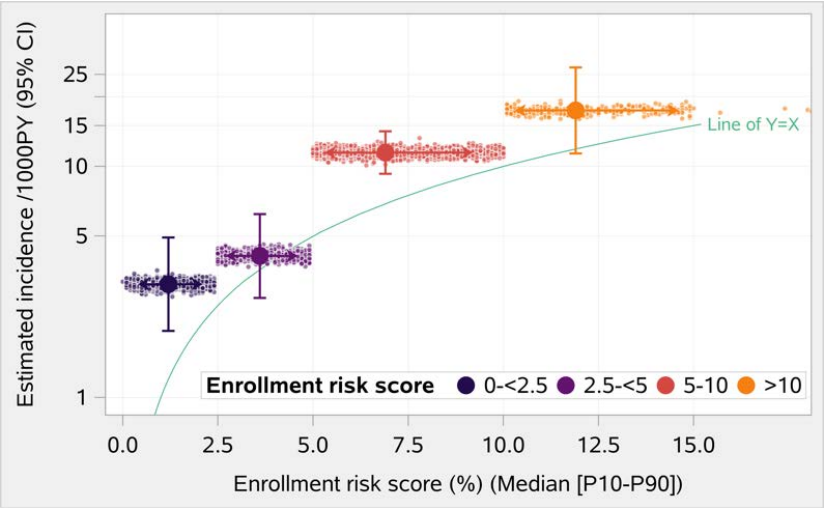
- HIV was recently considered a risk enhancer, but its use in primary prevention had not been studied
- Previously unknown if PWH with low to moderate risk should be put on a statin and whether statin therapy would be successful in this context?
- √ REPRIEVE has taught us that yes this is the case, statin therapy will prevent MACE in low to moderate risk PWH

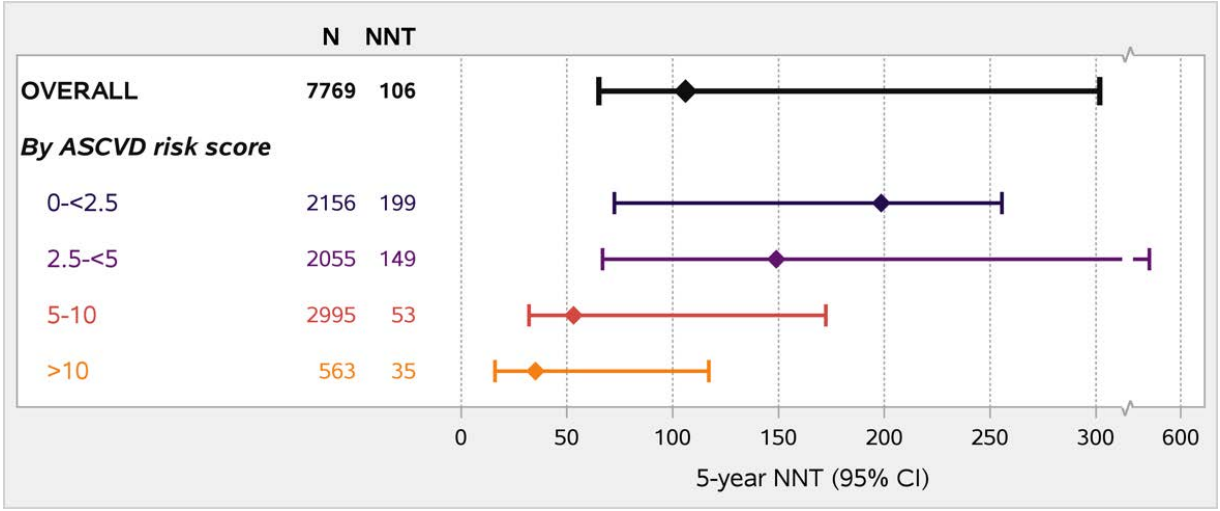


Spectrum of Statin Intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

5-Yr Number Needed To Treat (NNT) to Prevent One MACE Event





Increasing CVD with increasing ASCVD risk score

Decreasing NNT with increasing ASCVD risk score

NNT = number needed to treat

JUPITER (Rosuvastatin 20mg vs placebo as primary prevention for > men 50 and women > 60 with hs CRP > 2 and low LDL (i.e. low-mod risk. N=17k). 2-, 3-, 4-, and 5-year NNT values are 95, 49, 31, and 25, respectively for the primary endpoint (all vascular events), and 98, 59, 39, and 32, respectively for AMI, stroke, or death. Ridker, N Engl J Med. 2008; *359*: 2195–2207

JUPITER Controversy - A Critical Reappraisal. Arch Intern Med 2010 Jun 28;170(12):1032-6. No difference in death from CVD, stopped early (median follow up 1.9 years) mortality curves converging, first author patent on hsCRP, 7 pharma authors

Implications for Care of PWH

- Statin therapy, with lifestyle counselling, should be considered for PWH, even those with low to moderate predicted traditional risk, to reduce major cardiovascular events and death
- For PWH, the decision to take a statin should be individualized
  - Shared decision making between individual and clinician
  - All relevant factors including statin risks and benefits should be considered, including but not limited to the results of REPRIEVE. This may include drug interactions, metabolic factors, and patient preferences
  - All conversations about risk should emphasize a heart healthy lifestyle, ideal diet, counselling on smoking, blood pressure, dyslipidemia, other CVD risks

Will Pitavastatin be Available After REPRIEVE?

- The data from REPRIEVE are specific to pitavastatin, chosen because:
  - ✓little interaction with ART
  - ✓potent lipid lowering and anti-inflammatory effects
- Pitavastatin is available in many countries, but if it is not available, other statins that do not interact with ART may be effective
- Generic pitavastatin calcium will be more broadly available after Nov. 2023 when patent expires

Next Steps for Main Study

- Assess CVD mechanisms across global burden of disease regions, and effects in key groups by race, sex, and region, and by underlying CVD rates
- Assess mechanism of MACE reduction, LDL lowering vs effects on inflammation
- Identify statin effects on non-CVD events including COVID, HIV-related, cancer
- Assess accuracy of pooled cohort equation

Conclusions

Despite HIV being considered a risk equivalent, no prior trial has assessed a primary prevention strategy for this group, who would not typically be recommended for statin therapy

Among PWH 40-75, on ART, with low to moderate risk and normal range LDL, treatment with pitavastatin is effective and prevents MACE

Considerations should be given to expanding treatment guidelines in this regard

Implications

- Further analyses awaited
  - Effect on inflammation

- Interpretation by guideline groups: cardiology, HIV
    - Consideration of these findings for whole studied population or subgroups with higher CVD risk and lower number needed to treat?

William R. Short,[1] Moti Ramgopal,[2] Debbie P. Hagins,[3] Johnnie Lee,[4] Richard Bruce Simonson,[4] Tien-Huei Hsu,[4] Ping Xu,[5] David Anderson[4]

A Prospective, Randomized Trial to Assess a Protease Inhibitor–based Regimen Switch Strategy to Manage Integrase Inhibitor–related Weight Gain

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Midway Immunology and Research Center, Fort Pierce, FL, USA; [3]Chatham CARE Center, Savannah, GA, USA; [4]Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [5]Janssen Research & Development, LLC, Titusville, NJ, USA.

DEFINE STUDY

Introduction

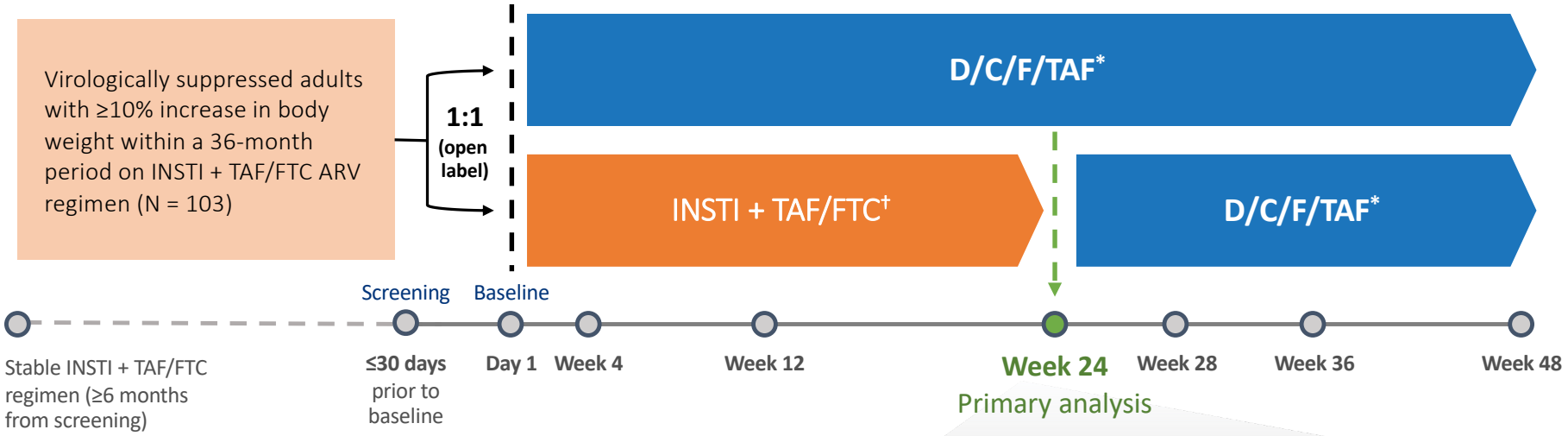
- INSTI-based ARV therapies are associated with greater weight gain than non-nucleoside reverse transcriptase inhibitor (NNRTI)– or boosted PI–based regimens, and these effects disproportionately impact Black and Hispanic individuals and women living with HIV-1[1-6]
- The mechanisms underlying INSTI-related weight gain are unknown, and whether this weight gain can be mitigated or reversed by switching ARV classes is unclear and under investigation
- DEFINE is the first prospective, randomized trial to explore the impact of switching from an INSTI- to a PI-based regimen to mitigate or reverse INSTI-related weight gain

Objective: To evaluate the percent change in body weight when switching to D/C/F/TAF compared to continuing INSTI + TAF/FTC in adults with HIV-1 who have experienced ≥10% body weight gain within the preceding 36 months

ARV, antiretroviral; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV-1, human immunodeficiency virus–1; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; TAF/FTC, tenofovir alafenamide/emtricitabine.

1. Bernardino JI, et al. *PLoS One*. 2019;14(1):e0209911. 2. Venter WDF, et al. *N Engl J Med*. 2019;381(9):803-815. 3. Bourgi K, et al. *Clin Infect Dis*. 2020;70(7):1267-1274.
4. Sax PE, et al. *Clin Infect Dis*. 2019;71(6):1379-1389. 5. Bedimo R, et al. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 4-7, 2019; Seattle, WA, USA.
6. Bourgi K, et al. *J Int AIDS Soc*. 2020;23(4):e25484.

DEFINE: A Phase 4, Randomized, Active-controlled, Open-label Multicenter Study



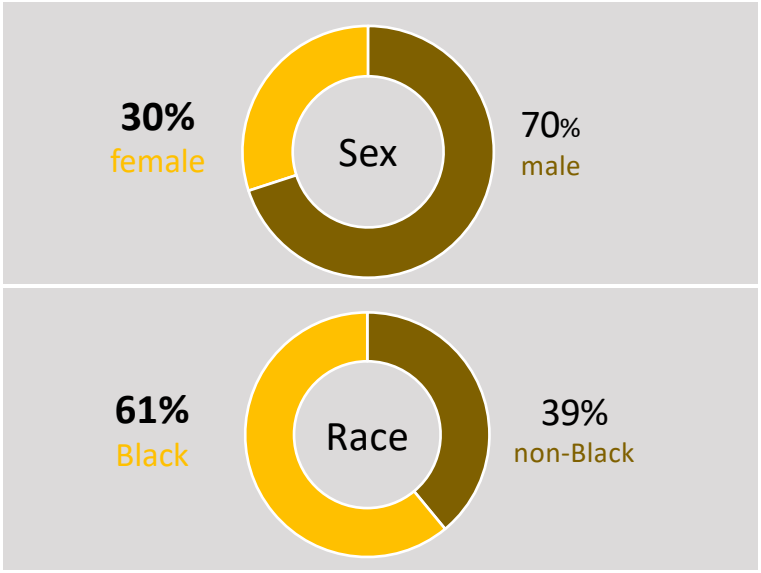
- Strategies were implemented to ensure a diverse study population representative of women and Black people living with HIV-1[1]
- Select exclusion criterion: Participants who initiated or discontinued concomitant medications associated with substantial weight change within 90 days of screening

Primary endpoint: Percent change in body weight from baseline at Week 24 (assessed using a mixed model for repeated measures based on the ITT set)

*D/C/F/TAF FDC (800/150/200/10 mg). †INSTI + TAF/FTC (per prescribing information).
ARV, antiretroviral; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC, fixed-dose combination; HIV-1, human immunodeficiency virus–1; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; MMRM, mixed model for repeated measures; TAF/FTC, tenofovir alafenamide/emtricitabine.

1. Dunn K, et al. An approach to improve diversity and inclusion in clinical trials: the DEFINE trial (D/C/F/TAF evaluated as a fixed-dose combination regimen in participants switching from an integrase inhibitor who have experienced rapid weight gain). Presented at: HIV DART; December 10, 2020; Virtual.

Participant Characteristics



Participant disposition

- At 24 weeks, >90% of participants were still in the study

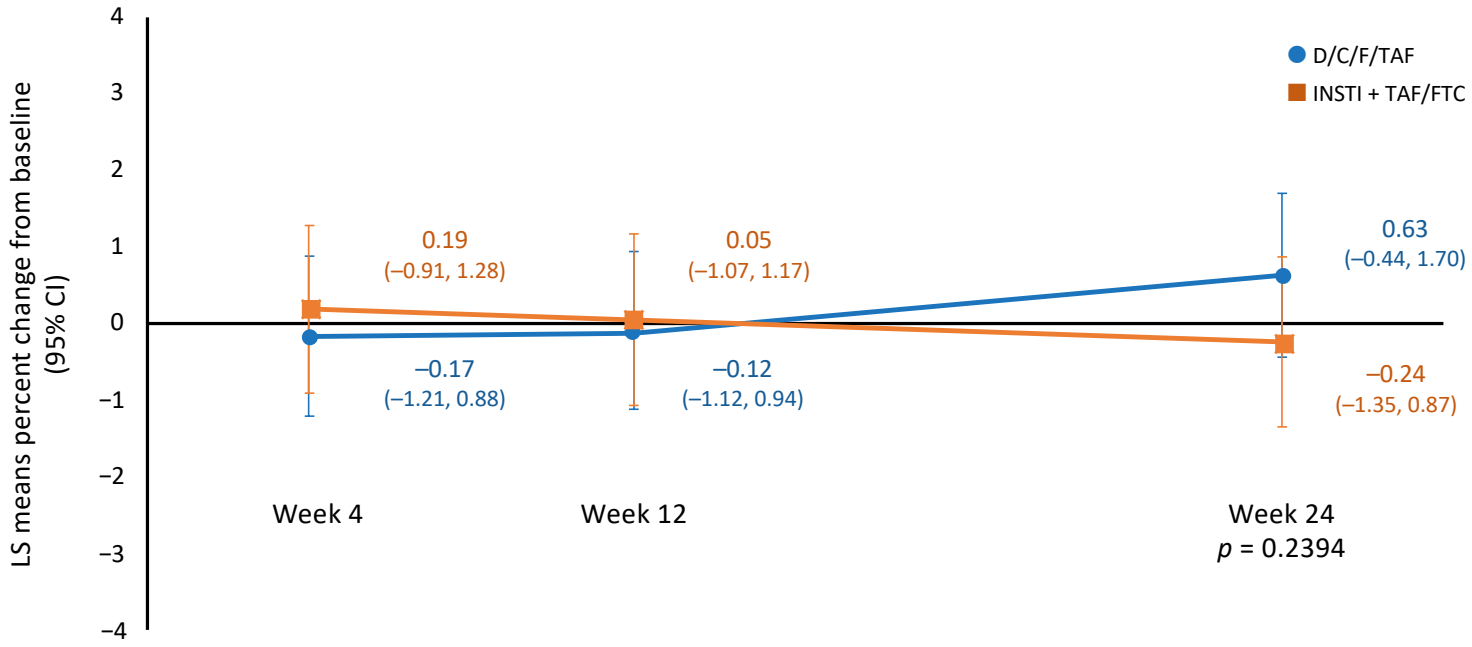
Baseline Demographics and Characteristics (ITT Set)

	Treatment arm		Total
	D/C/F/TAF	INSTI + TAF/FTC	
	n = 53	n = 50	N = 103
Age, years, median (range)	42.0 (22, 73)	49.0 (22, 69)	45.0 (22, 73)
BMI, kg/m², median (range)	31.4 (22, 61)	34.7 (22, 58)	32.7 (22, 61)
Body weight, kg, median (range)	94.5 (69, 188)	102.9 (70, 188)	100.2 (69, 188)
Hispanic or Latino ethnicity, n (%)	6 (11)	10 (20)	16 (16)
Percent weight gained on current regimen at baseline, median (range)*	12.8 (−4, 56)	15.7 (−15, 86)	14.2 (−15, 86)
Type of INSTI regimen at baseline, n (%)†			
EVG/c/TAF/FTC	5 (9)	7 (14)	12 (12)
DTG + TAF/FTC	4 (8)	4 (8)	8 (8)
BIC/TAF/FTC	44 (83)	39 (78)	83 (81)
Baseline CD4+, cells/mm³, median (range)	696.0 (205, 1543)	622.5 (153, 2059)	680.0 (153, 2059)

*One participant in the D/C/F/TAF arm did not have available data. †Percentages may not sum to 100% due to rounding.
BIC/TAF/FTC, bictegravir/tenofovir alafenamide/emtricitabine; BMI, body mass index; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; EVG/c/TAF/FTC, elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; INSTI, integrase strand transfer inhibitor; **ITT, intention-to-treat; TAF/**FTC, tenofovir alafenamide/emtricitabine.

No Significant Difference in Percent Change in Body Weight From Baseline to Week 24 Between Arms

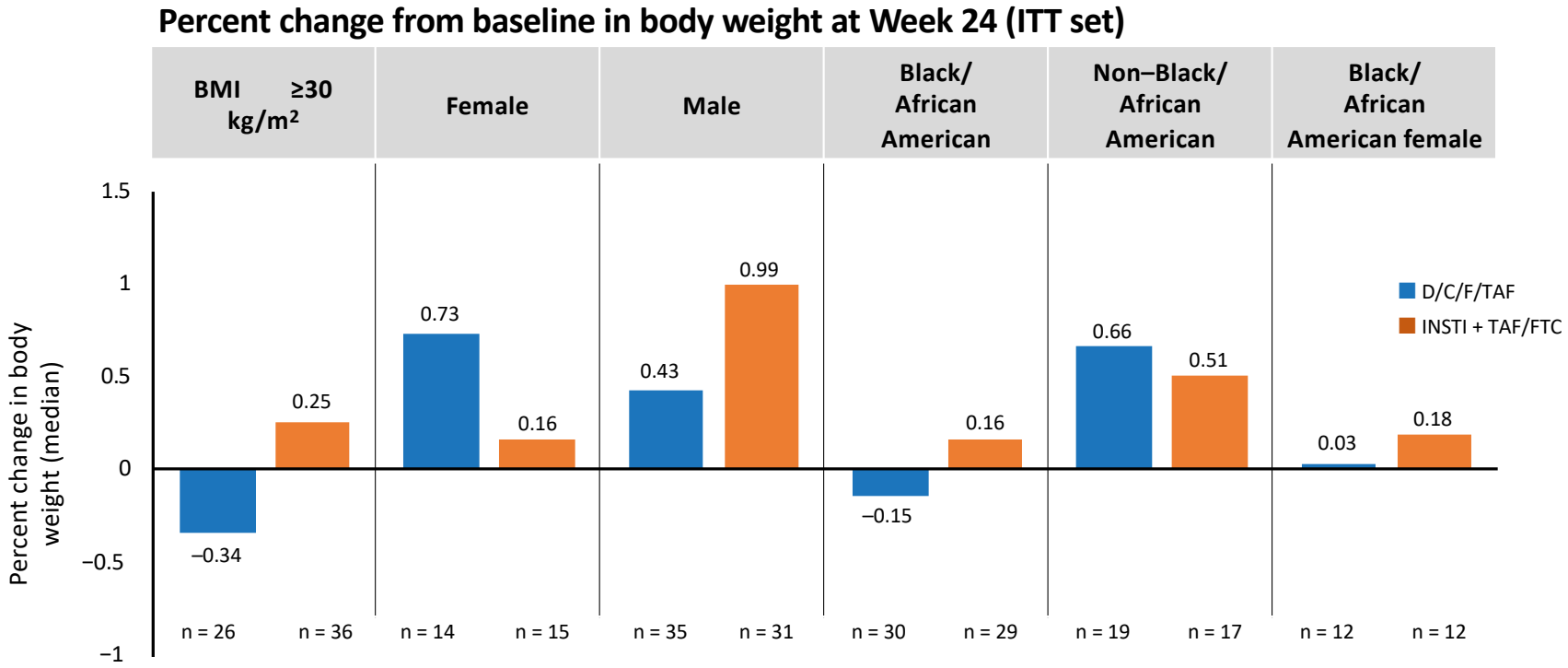
- **Percent change from baseline body weight over time (primary endpoint, ITT set)***



*LS means percent changes in body weight were calculated in the ITT set of randomized participants who had received ≥1 dose of the study drug using a MMRM, in which visits were repeated measures. Participants in the ITT set with baseline records and ≥1 postbaseline record were included.

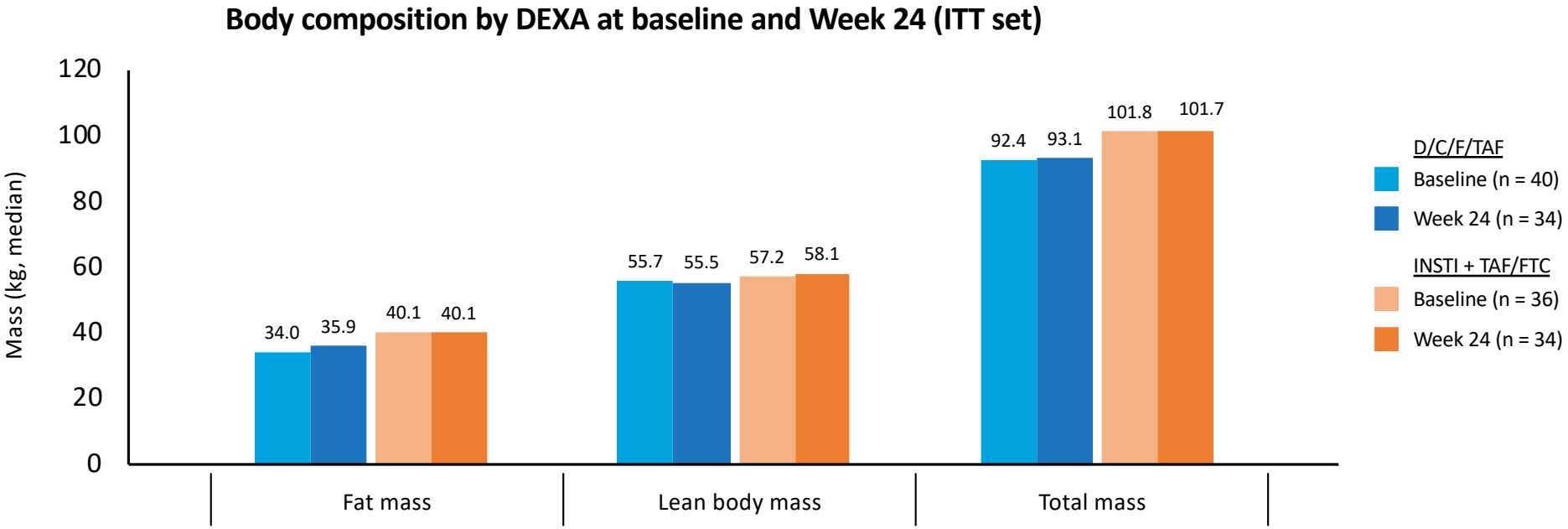
CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; LS, least squares; MMRM, mixed model for repeated measures; TAF/FTC, tenofovir alafenamide/emtricitabine.

Changes in Body Weight at Week 24 Were Consistent Among Key Subgroups



BMI, body mass index; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

Body Composition by DEXA Was Stable Over Time for Both Study Arms

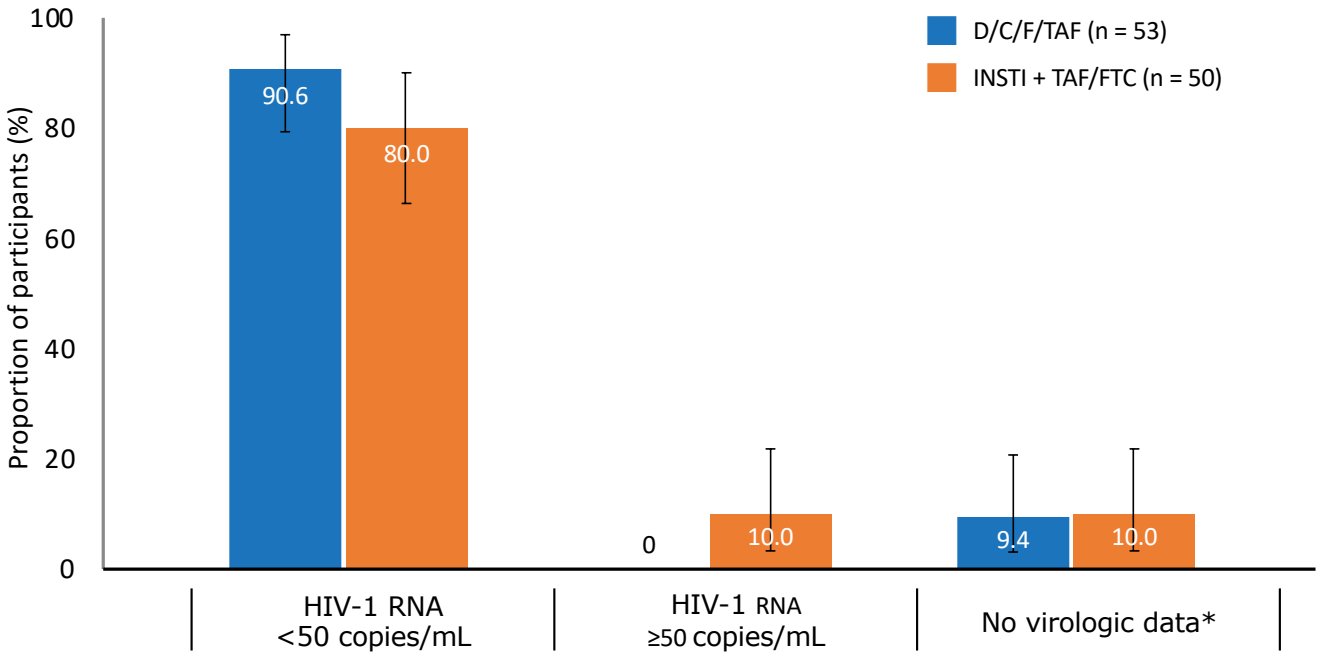


- DEXA measurements of appendicular and visceral fat also showed minimal changes between arms and from baseline

D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DEXA, dual x-ray absorptiometry; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

Efficacy at Week 24 Was Maintained Across Both Study Arms

Virologic response at Week 24 by FDA snapshot approach (ITT set)



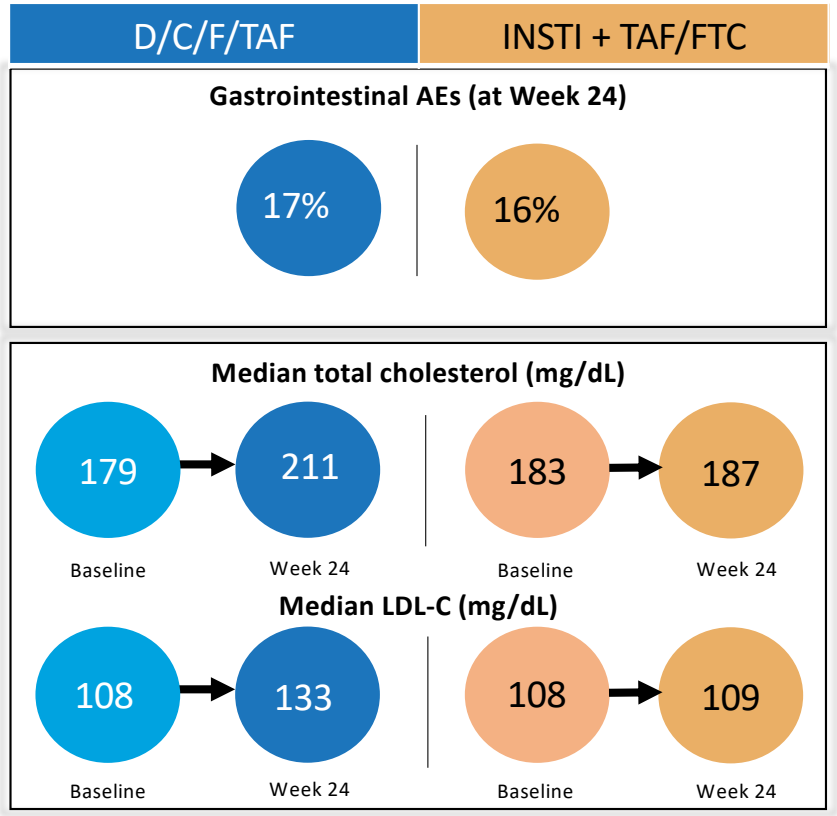
- At Week 24, virologic failure (HIV-1 RNA ≥50 copies/mL) was observed in 5 participants in the INSTI + TAF/FTC arm and none in the D/C/F/TAF arm
- CD4+ cell counts were relatively stable over time and similar between arms

Error bars show 95% CI.
*In the D/C/F/TAF arm, 2 (4%) participants discontinued due to AE/death, 2 (4%) participants discontinued due to other reasons with the last available HIV-1 RNA <50 copies/mL (or missing), and 1 (2%) participant had missing data during the window but was on-study; in the INSTI + TAF/FTC arm, 1 (2%), 2 (4%), and 2 (4%) participants were in these categories, respectively.
AE, adverse event; CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDA, US Food and Drug Administration; HIV-1, human immunodeficiency virus–1; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; TAF/FTC, tenofovir alafenamide/emtricitabine.

Switching to D/C/F/TAF Was Safe and Well Tolerated

Most Frequently Reported AEs and AEs of Interest by Preferred Term (Safety Analysis Set)

	Treatment arm			
	D/C/F/TAF n = 53		INSTI + TAF/FTC n = 50	
	Overall	Related	Overall	Related
Participants with ≥1 AE, n (%)	30 (57)	6 (11)	31 (62)	3 (6)
Most frequently reported AEs,* n (%)				
COVID-19	6 (11)	0	2 (4)	0
Diarrhea	3 (6)	3 (6)	4 (8)	3 (6)
Nausea	3 (6)	3 (6)	3 (6)	2 (4)
Hypertension	1 (2)	0	6 (12)	0
Proteinuria	0	0	3 (6)	0
AEs of interest, n (%)				
Lipid abnormalities	3 (6)	0	3 (6)	0
Bone	2 (4)	0	2 (4)	0
Hyperglycemia	1 (2)	0	3 (6)	0
Hepatotoxicity	1 (2)	1 (2)	2 (4)	0
Rash	1 (2)	1 (2)	1 (2)	0
Renal toxicity	0	0	3 (6)	0
Ocular (for posterior uveitis)	0	0	0	0



*Occurring in >5% of participants in either study arm, regardless of relatedness to the study drug.
AE, adverse event; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; LDL-C, low-density lipoprotein cholesterol; TAF/FTC, tenofovir alafenamide/emtricitabine.

Conclusions

DEFINE STUDY

- No significant change in body weight was observed 24 weeks after switching from an INSTI-based regimen to D/C/F/TAF among adults with HIV-1 infection who had experienced ≥10% INSTI-related weight gain
  - Findings were consistent across multiple endpoints, including BMI and waist circumference, and among key subgroups
  - Importantly, this study included a high representation of women and Black people living with HIV-1, and similar body weight changes were seen across treatment arms within these important subgroups at increased risk of weight gain
- In this prospective, randomized switch study comparing INSTI- and PI-based regimens, efficacy, safety, and tolerability were similar between treatment arms
  - These results are notable given the limited head-to-head comparison data available for boosted darunavir versus INSTIs
- Although the DEFINE study is ongoing, results at Week 24 suggest that INSTI-related weight gain may not be reversible through ARV switch and highlight the importance of including body weight and associated risk factors for metabolic health as pretreatment considerations

ARV, antiretroviral; BMI, body mass index; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV-1, human immunodeficiency virus–1; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor.

DOR/ISL (100/0.75 MG) QD COMPARED TO B/F/TAF AS INITIAL HIV-1 TREATMENT: 48 WEEK RESULTS FROM A DOUBLE-BLIND PHASE 3 TRIAL

Jurgen K Rockstroh et al.

Background

Islatravir (ISL, MK-8591) = nucleoside reverse transcriptase translocation inhibitor (NRTTI)

- Potent against NRTI resistant HIV-1 variants and a high barrier to the development of resistance
- Long half-life (~120 hours in adults)
- Potential for dosing once daily, once weekly, and less frequent administration

Doravirine (DOR) = non-nucleoside reverse transcriptase inhibitor (NNRTI)

- Active against wild-type HIV-1 and with some NNRTI mutations (RT: K103N, Y181C, G190A, K103N/Y181C, and E138K)
- Dosed once daily, without regard to food
- Low rates of CNS adverse events and favorable lipid profile compared with Efavirenz

In two phase 3 studies switching to DOR/ISL 100/0.75 mg non inferior to continuing prior ART through week 48 in maintaining VL suppression (Molina CROI 2023, Mills CROI 2023)

This is the study for initiating ART

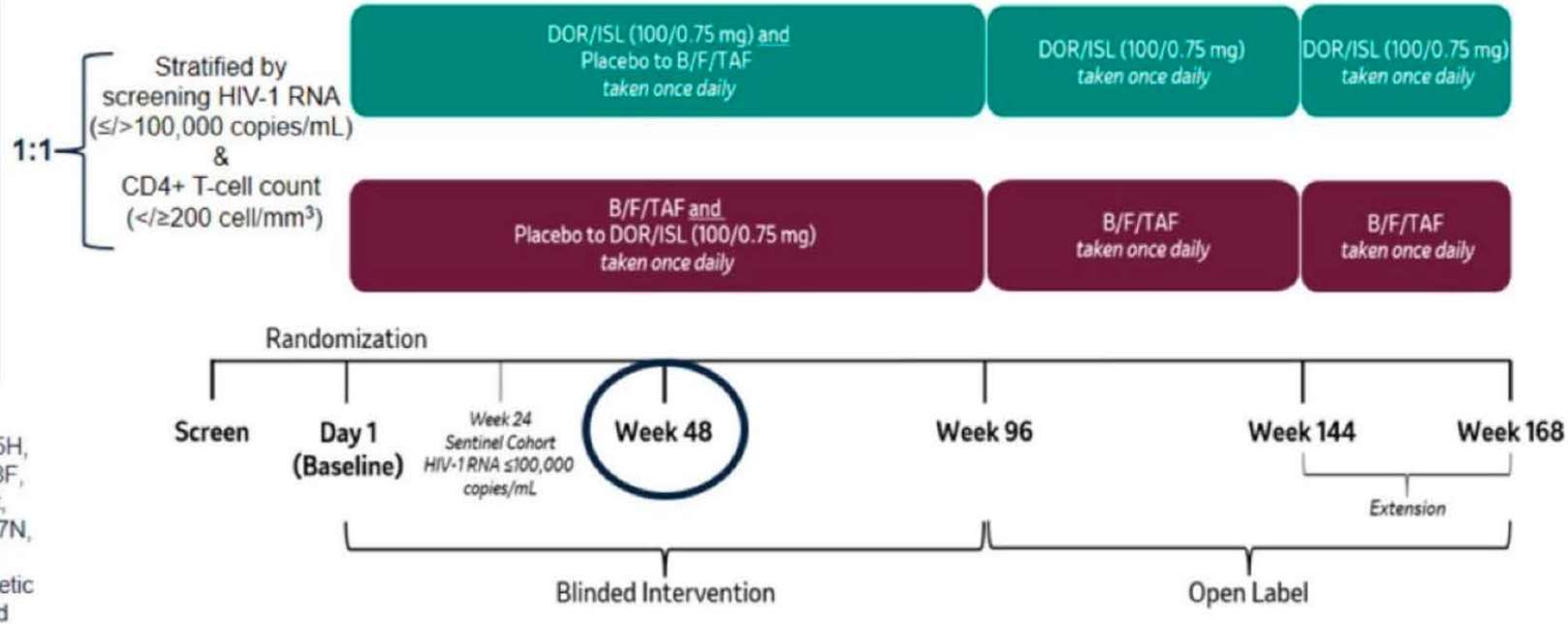
Design

Population

- PWH ≥18 years of age
- Plasma HIV-1 RNA ≥500 copies/mL at screening
- Treatment-naïve
- No virologic resistance*
- No diagnosis of active hepatitis, including HBV**

*V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L, Y318F, K65R/E/N, M184I/V, K70E, T69insert, Q151M,or ≥3 of the following M41L, D67N, K70R, L210W, T215F/Y, K219E/Q

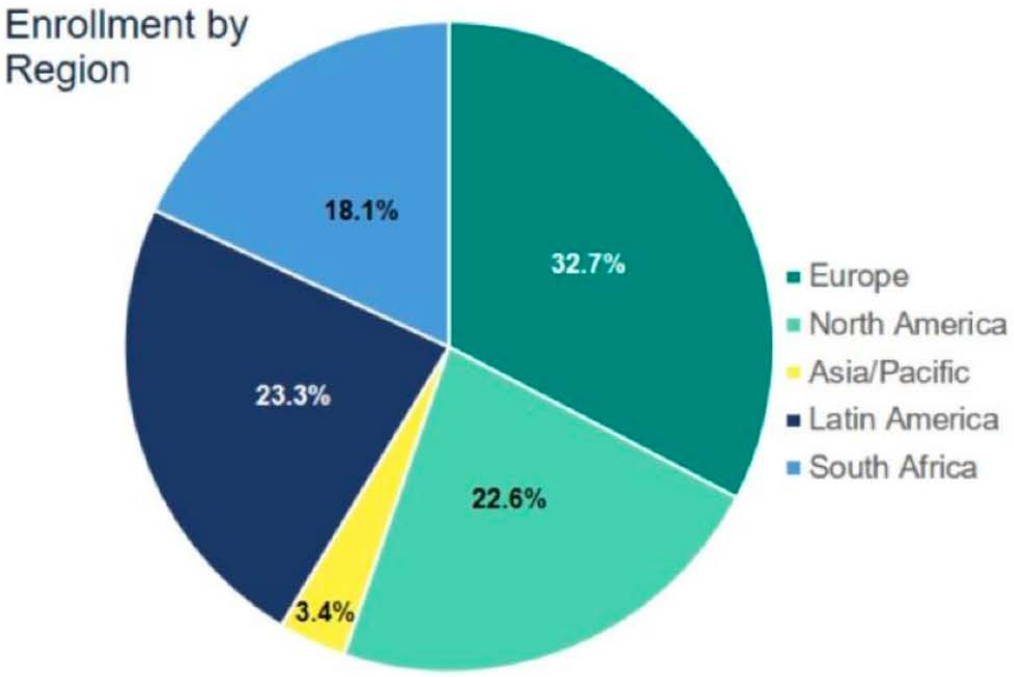
**Chronic HCV without significant synthetic hepatic dysfunction was not excluded

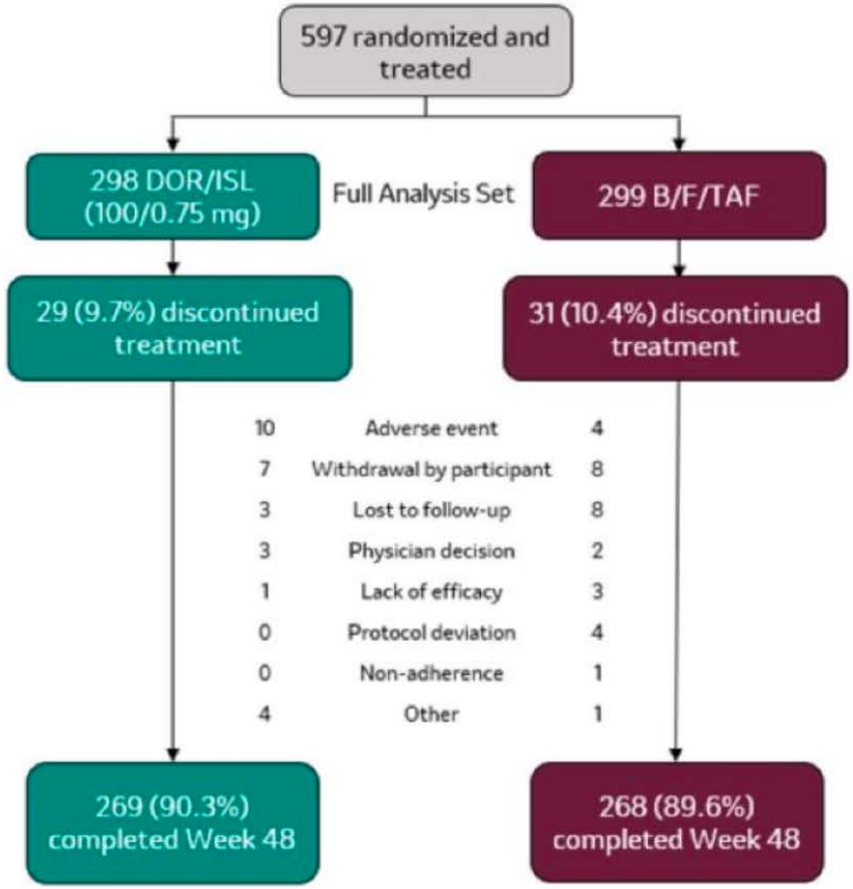


Primary Efficacy Endpoint: HIV-1 RNA <50 copies/mL at Week 48 (FDA snapshot approach), non-inferiority margin 10%

Population

- 90 study sites screened participants in 13 countries
- Recruitment Feb 28, 2020 – Dec 13, 2021
  - Planned population 680; enrollment stopped early due to decreases in lymphocytes in other studies evaluating ISL



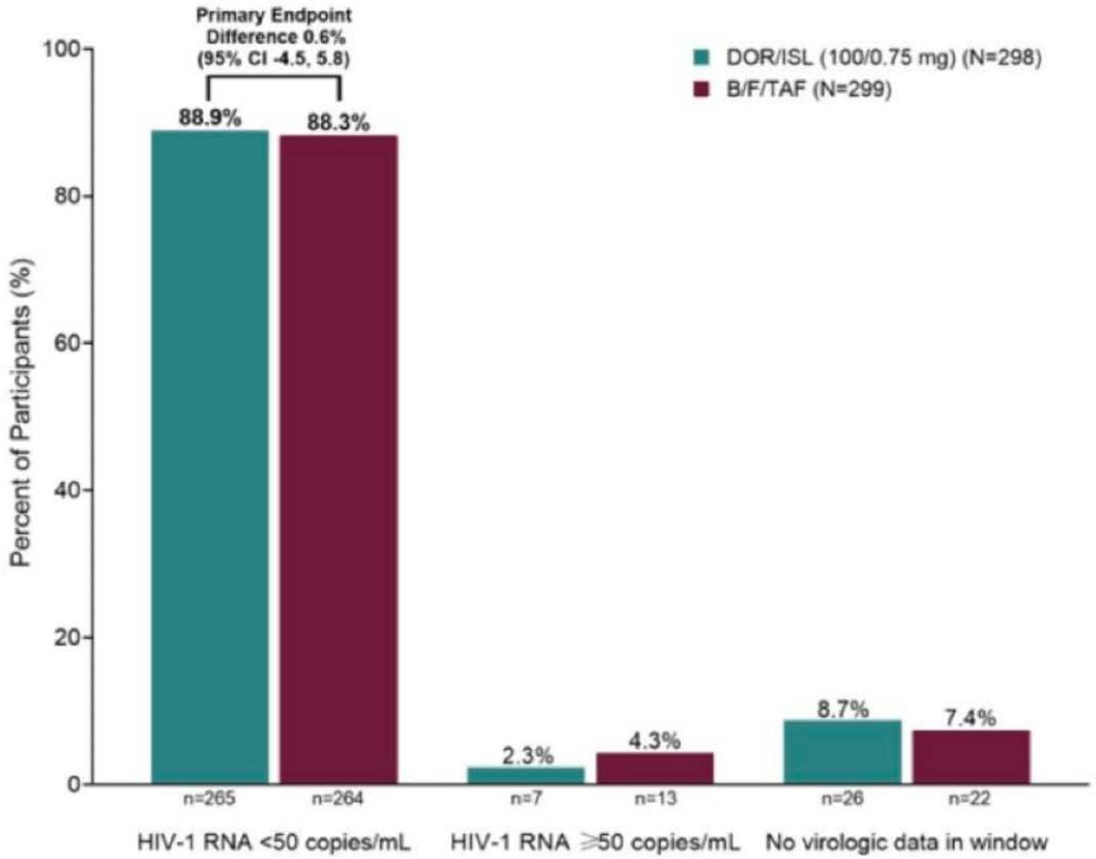


Baseline

Demographic/Characteristic	DOR/ISL (100/0.75 mg) (N=298)	B/F/TAF (N=299)
Female sex at birth, n (%)	77 (25.8)	70 (23.4)
Age (years), median (range)	32 (18-70)	34 (18-77)
18 to 49 , n (%)	261 (87.6)	260 (87.0)
Race, n (%)		
Asian	16 (5.4)	20 (6.7)
Black or African American	85 (28.5)	88 (29.4)
White	172 (57.7)	169 (56.5)
Hispanic or Latino Ethnicity, n (%)	123 (41.3)	112 (37.5)
Baseline plasma HIV-1 RNA (copies/mL)		
Median (range)	23,004 (39-3,893,336)	27,487 (39-3,409,353)
≤100,000, n (%)	244 (81.9)	239 (79.9)
>100,000, n (%)	54 (18.1)	60 (20.1)
Baseline CD4+ T-cell count (cells/mm^3)		
Median (range)	373 (19-1761)	356 (19-1504)
≥200, n (%)	237 (79.5)	239 (79.9)
<200, n (%)	61 (20.5)	60 (20.1)

Primary Outcome

DOR/ISL **non-inferior** to B/F/TAF for the primary endpoint of HIV-1 RNA <50 copies/mL at Week 48



Protocol Defined VF

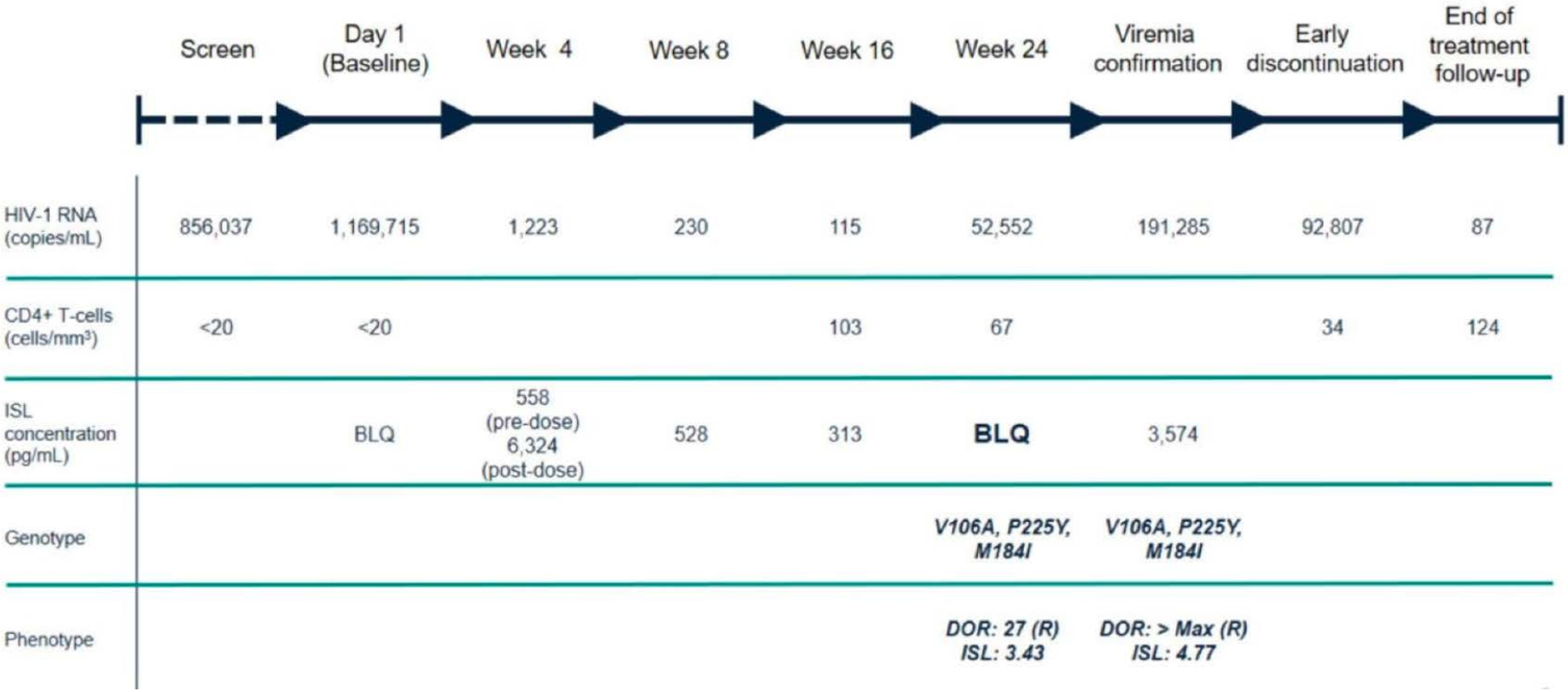
Low ISL levels when resistance emerged

Group	Week	Virologic Failure	Treatment-Emergent Resistance-Associated Substitutions	Phenotype
DOR/ISL	24	*Incomplete response*	NNRTI: V106A, P225H NRTI: M184I	R: DOR
B/F/TAF	8	*Rebound*	None	S: F, TAF
B/F/TAF	36	*Rebound*	No result provided	N/a
B/F/TAF	24	*Incomplete response*	None	S: B, F, TAF
B/F/TAF	36	*Incomplete response*	None	S: B, F, TAF

Incomplete Virologic Response: 2 consecutive (2-4 weeks apart) HIV-1 RNA ≥200 copies/mL at or after Week 24 in the absence of previous suppression of HIV-1 RNA to <50 copies/mL.
Virologic Rebound: 2 consecutive (2-4 weeks apart) HIV-1 RNA ≥200 copies/mL after achieving HIV-1 RNA <50 copies/mL at any time during the study.

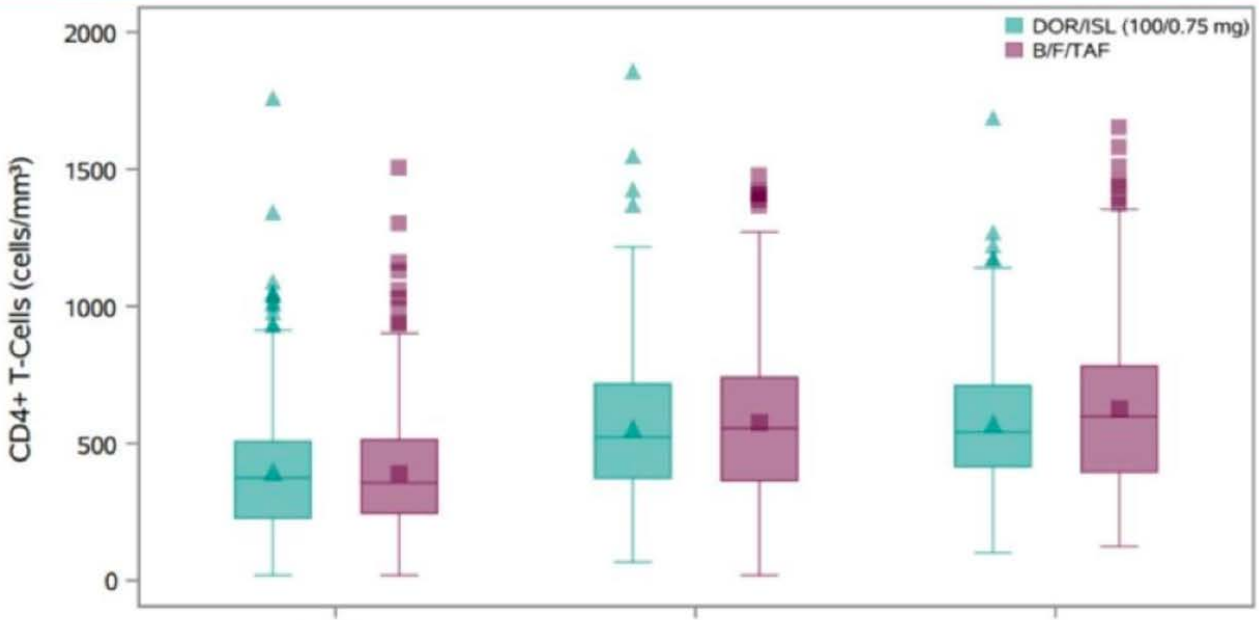
N/a, unable to report a result

DOR/ISL Participant with virologic failure and HIV drug resistance



	Screen	Day 1 (Baseline)	Week 4	Week 8	Week 16	Week 24	Viremia confirmation	Early discontinuation	End of treatment follow-up
HIV-1 RNA (copies/mL)	856,037	1,169,715	1,223	230	115	52,552	191,285	92,807	87
CD4+ T-cells (cells/mm^3)	<20	<20			103	67		34	124
ISL concentration (pg/mL)		BLQ	558 (pre-dose) 6,324 (post-dose)	528	313	**BLQ**	3,574		
Genotype						***V106A, P225Y, M184I***	***V106A, P225Y, M184I***		
Phenotype						***DOR: 27 (R) ISL: 3.43***	***DOR: > Max (R) ISL: 4.77***		

CD4 counts

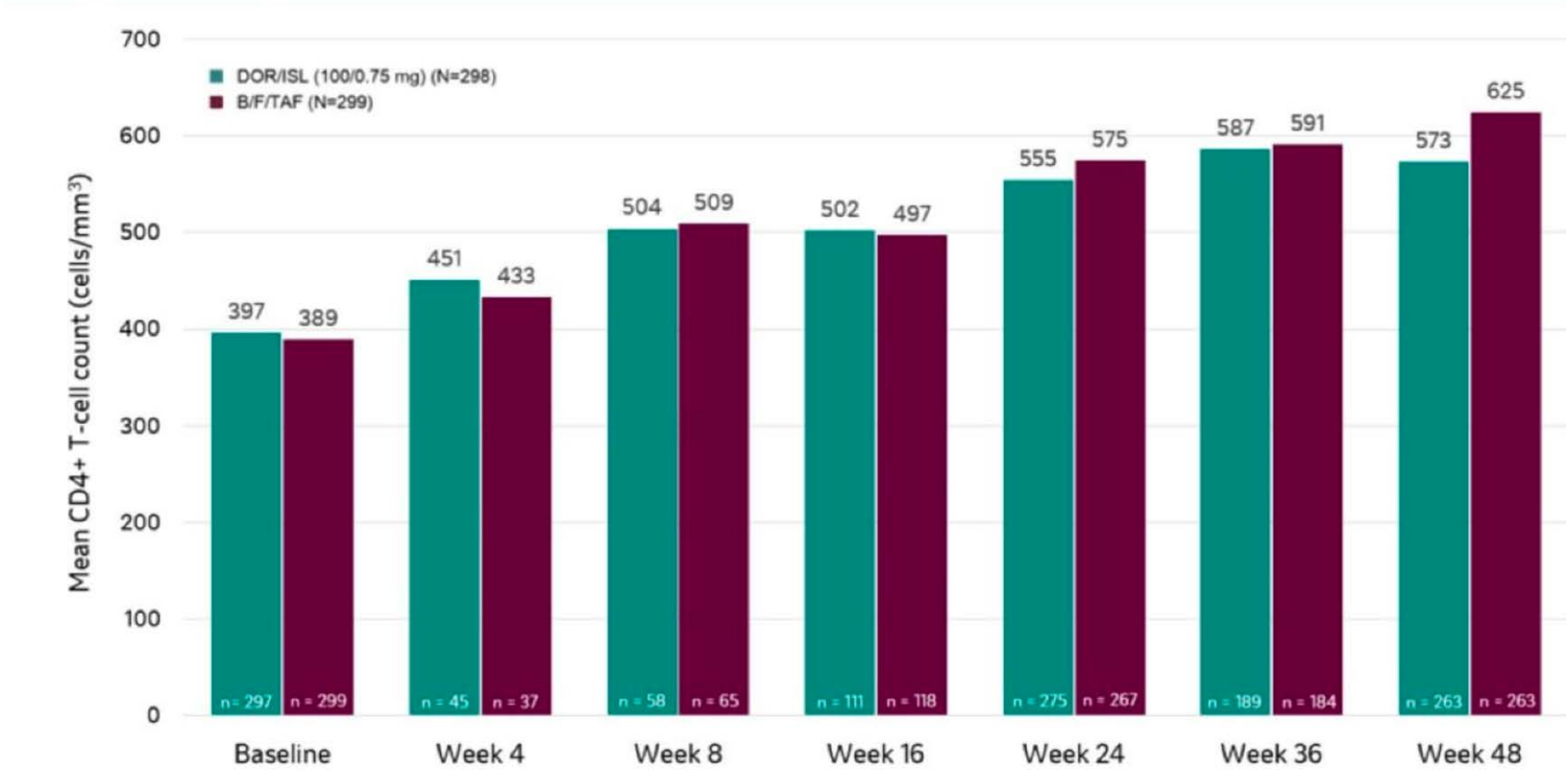


	Baseline		Week 24		Week 48	
n	297	299	275	267	263	263
Mean (cells/mm³)	397	389	555	575	573	625
Mean Change (cells/mm³)	-	-	154	190	182	234
Mean % Change	-	-	64%	79%	82%	103%

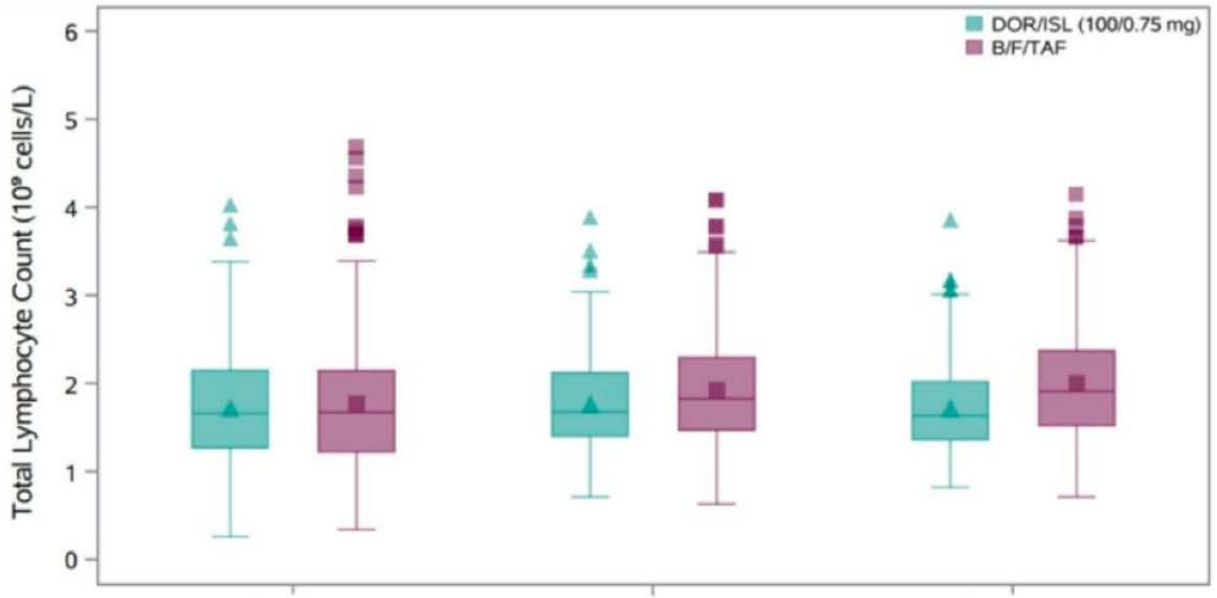
Difference -50, 95% CI -79, -21

Figure key: box represents the IQR (Q3-Q1), horizontal line represents the median, and symbol represents the mean.

CD4 counts


DOR/ISL (100/0.75 mg) (N=298)
B/F/TAF (N=299)
Mean CD4+ T-cell count (cells/mm³)
700
600
500
400
300
200
100
0
397
389
451
433
504
509
502
497
555
575
587
591
573
625
n = 297
n = 299
n = 45
n = 37
n = 58
n = 65
n = 111
n = 118
n = 275
n = 267
n = 189
n = 184
n = 263
n = 263
Baseline
Week 4
Week 8
Week 16
Week 24
Week 36
Week 48

Total lymphocyte counts



	Baseline		Week 24		Week 48	
n	291	296	270	266	253	254
Mean (10^9 cells/L)	1.72	1.77	1.77	1.92	1.72	2.00
Mean Change (10^9 cells/L)	-	-	0.02	0.16	0.01	0.21
Mean % Change	-	-	7.4%	18.8%	6.8%	24.1%

Difference -0.20, 95% CI -0.30, -0.10

Figure key: box represents the IQR (Q3-Q1), horizontal line represents the median, and symbol represents the mean.

Adverse Events Summary

n (%) of participants	DOR/ISL (100/0.75 mg) (N=298)	B/F/TAF (N=299)	Difference , % (95% CI)[a]
≥1 AE	270 (91)	258 (86)	4.3 (-0.8, 9.6)
Treatment-related[b] AE	78 (26)	75 (25)	1.1 (-5.9, 8.1)
Toxicity grade 3-4 AE	29 (10)	34 (11)	-1.6 (-6.7, 3.4)
Serious AE	18 (6)	16 (5)	0.7 (-3.2, 4.6)
Serious drug-related[b] AE	0 (0)	2 (0.7)	-0.7 (-2.4, 0.6)
Deaths	2 (0.7)[c]	0 (0.0)	0.7 (-0.6, 2.4)
AE resulting in discontinuation	22 (7.4)	10 (3.3)	4.0 (0.4, 7.9)
CD4+ T-cell or total lymphocyte count decrease requiring discontinuation[d]	16 (5.4)	6 (2.0)	nps
Treatment-related[b] AE resulting in discontinuation	15 (5.0)	8 (2.7)	2.4 (-0.8, 5.8)
Serious AE resulting in discontinuation	3 (1.0)	2 (0.7)	0.3 (-1.5, 2.3)
Serious treatment-related[b] AE resulting in discontinuation	0 (0.0)	2 (0.7)	-0.1 (-2.4, 0.6)

[a]Based on Miettinen & Nurminen method.
[b]Considered by the investigator to be related to the study drug.
[c]Neither death was considered drug-related (gunshot wound, *Pneumocystis jirovecii* pneumonia).
[d]Based on protocol specified criteria for decreases.

AE, adverse event; nps, not a prespecified endpoint.

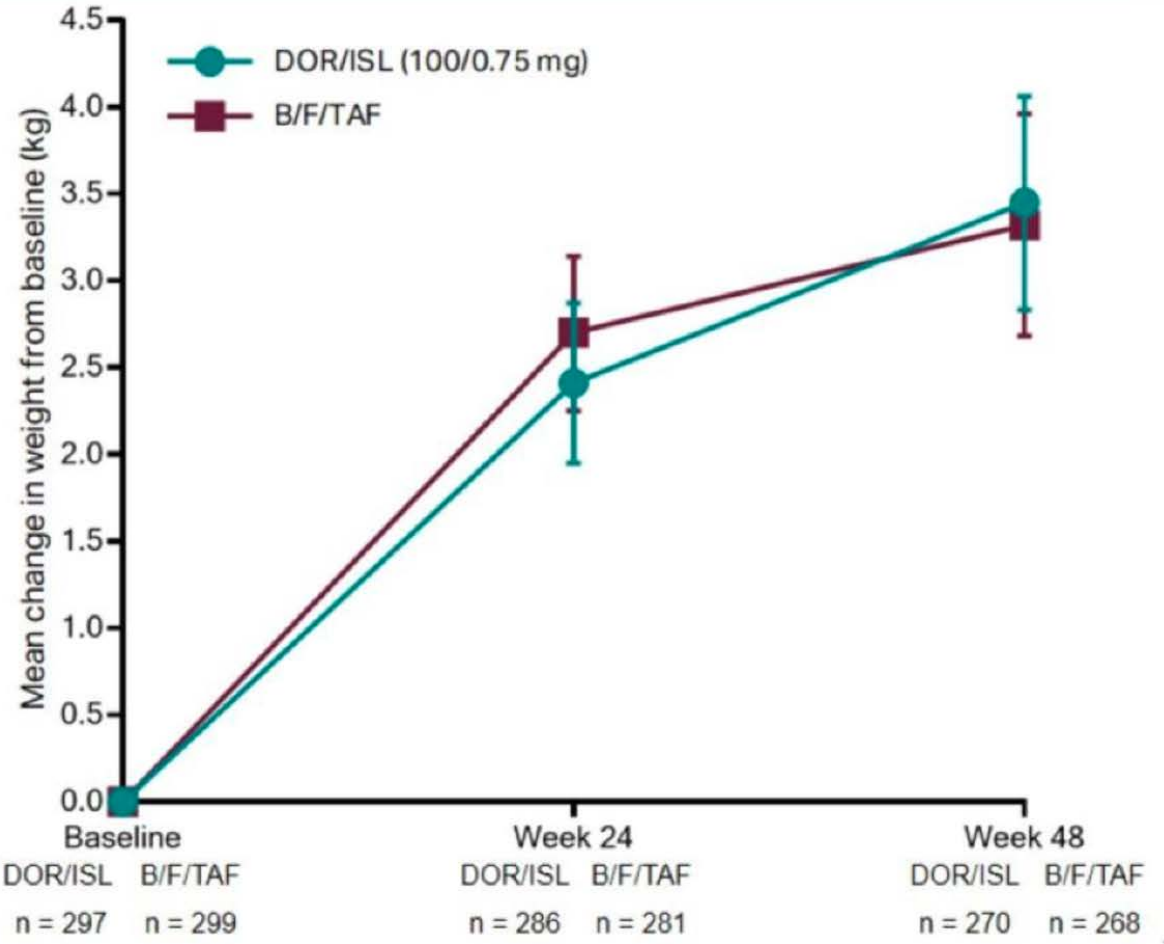
Frequent Adverse Events

n (%)	DOR/ISL (100/0.75 mg) (N=298)	B/F/TAF (N=299)
All causality events (≥5% in either group)		
COVID-19	41 (13.8)	49 (16.4)
Lymphocyte count decreased[a]	35 (11.7)	19 (6.4)
Headache[a]	32 (10.7)	32 (10.7)
Diarrhea[a]	26 (8.7)	19 (6.4)
Accidental overdose	17 (5.7)	16 (5.4)
Upper respiratory tract infection	15 (5.0)	15 (5.0)
Insomnia[a]	13 (4.4)	19 (6.4)
Weight increased[a]	10 (3.4)	15 (5.0)
Infection-related adverse events	162 (54.4)	153 (51.2)

[a]Also a treatment-related event that occurred in ≥5 participants in either group.

Mean change in weight (kg) at week 48

- DOR/ISL - 3.45 (95% CI 2.83, 4.06)
- B/F/TAF - 3.32 (95% CI 2.68, 3.96)
- ***Difference 0.15 (95% CI -0.71, 1.02)***



Conclusions

DOR/ISL (100/0.75 mg) was non-inferior to B/F/TAF for initial treatment of HIV-1 through 48 weeks

- One participant on DOR/ISL and 4 on B/F/TAF had virologic failure
- Participant taking DOR/ISL was non-adherent and had virologic failure at Week 24 with confirmed resistance to DOR

DOR/ISL (100/0.75 mg) was generally well-tolerated

Small differences in mean change for absolute CD4+ T-cells and total lymphocytes between treatment groups, with similar infection-related AEs

DOR/ISL 0.25mg program

Study Protocol	Phase	Population	Comparator	Design
051	3	Virologically suppressed	Baseline ART	Open-label; 2:1 randomization
052	3	Virologically suppressed	B/F/TAF	Blinded; 2:1 randomization
053	3	Initial treatment	B/F/TAF	Blinded; 1:1 randomization
054	3	Virologically suppressed or initial treatment, currently treated with DOR/ISL (100/0.75 mg)	Not applicable	Open-label, single arm, dose de-escalation

Hypertension and Weight Gain in ADVANCE and NAMSAL

W Francois Venter et al

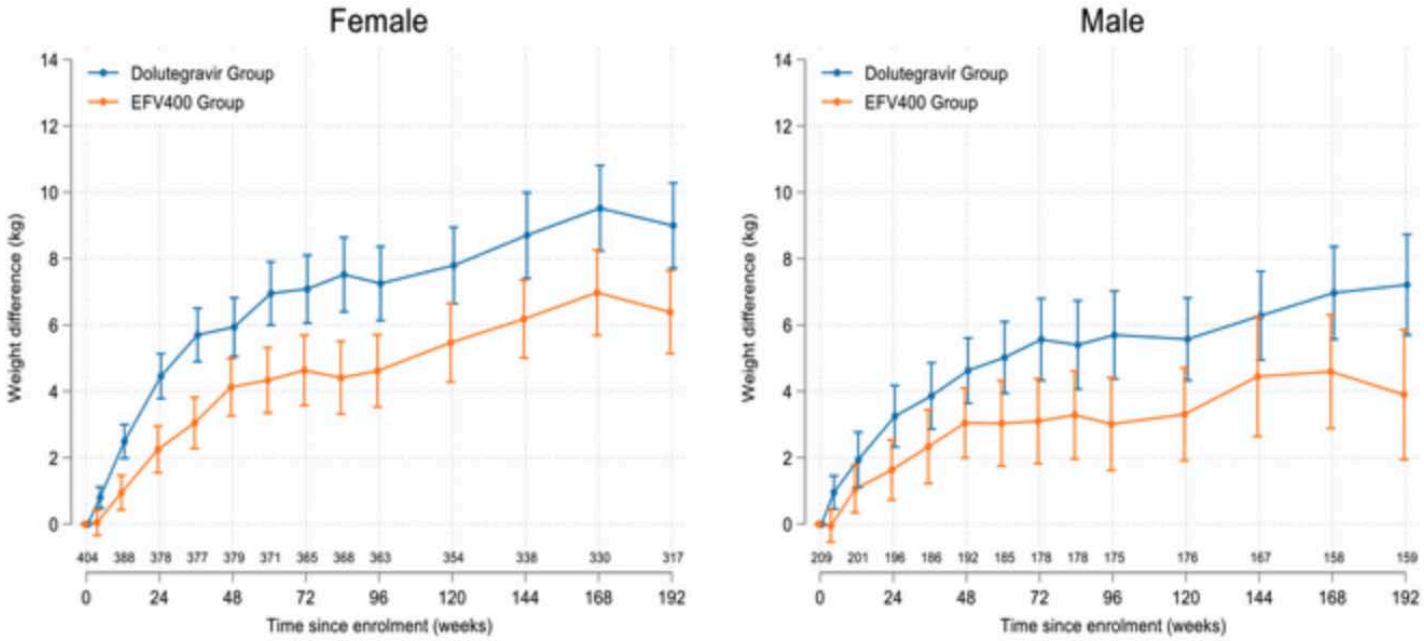
NAMSAL

Inclusion criteria: Treatment-naïve, HIV-1 RNA level > 500 copies/mL. Blood pressure measured at each visit. Hypertension not routinely treated.

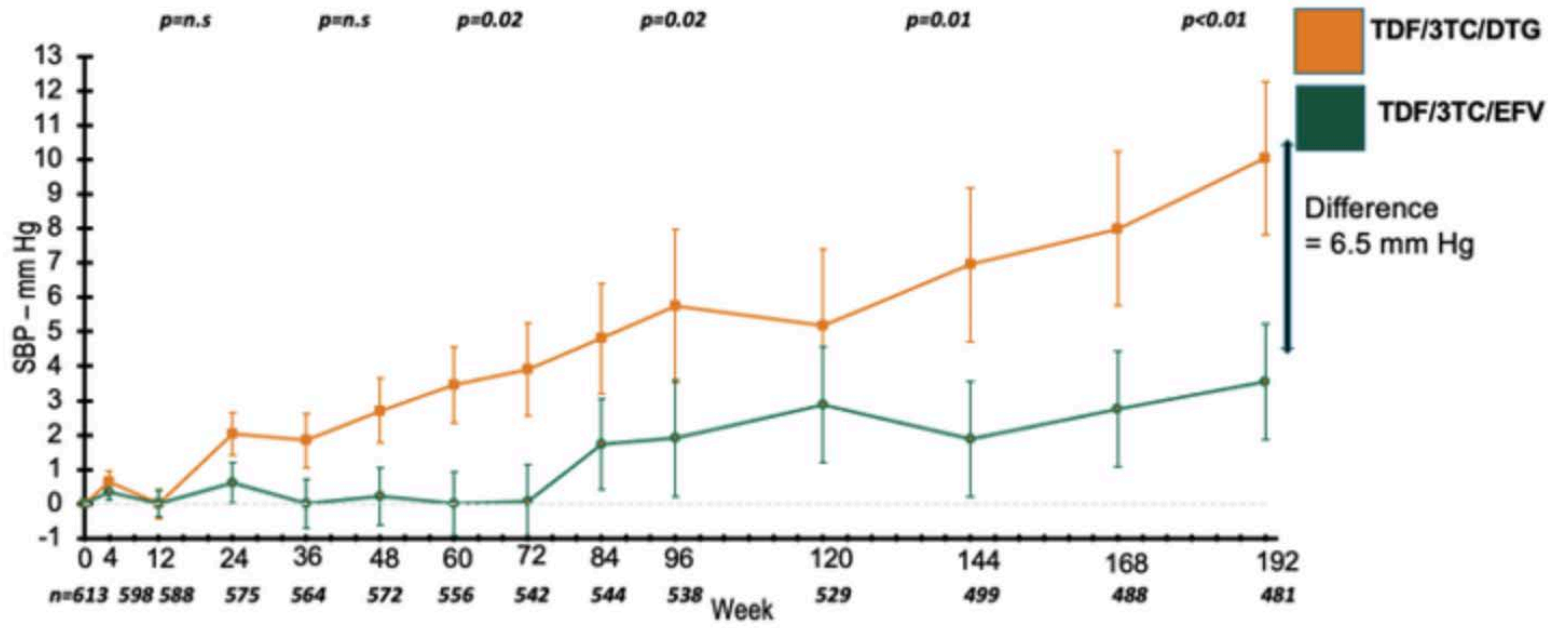
Study visits: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192

	TDF/FTC+DTG (n=310)	TDF/FTC/EFV (n=303)
Median age (years)	38	36
Female (%)	64%	68%
Black (%)	100%	100%
Weight (median, kg)	64	64
BMI (median, kg/m^2)	23	23
CD4+ cell count (mean, cells/uL)	289	271
Baseline HIV RNA (copies/mL)		
HIV RNA <100,000	103 (33%)	103 (34%)
HIV RNA 100-500,000	114 (37%)	105 (35%)
HIV RNA >500,000	93 (30%)	95 (31%)

NAMSAL - Weight Gain

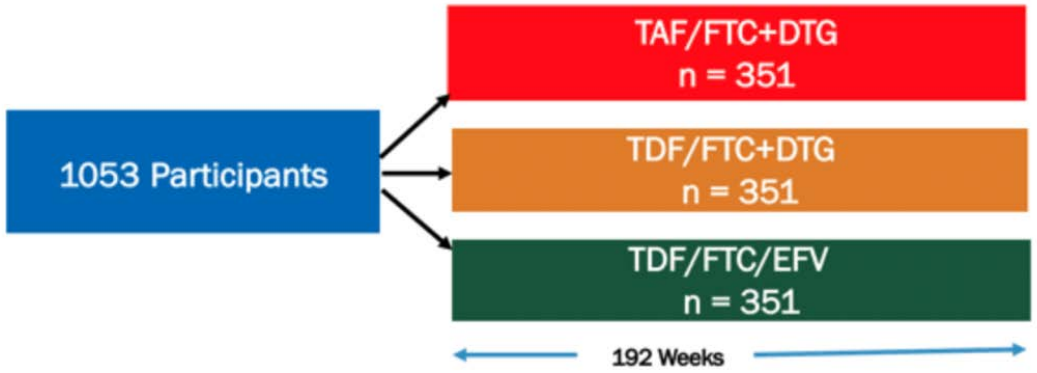


NAMSAL – Systolic Blood Pressure



ADVANCE

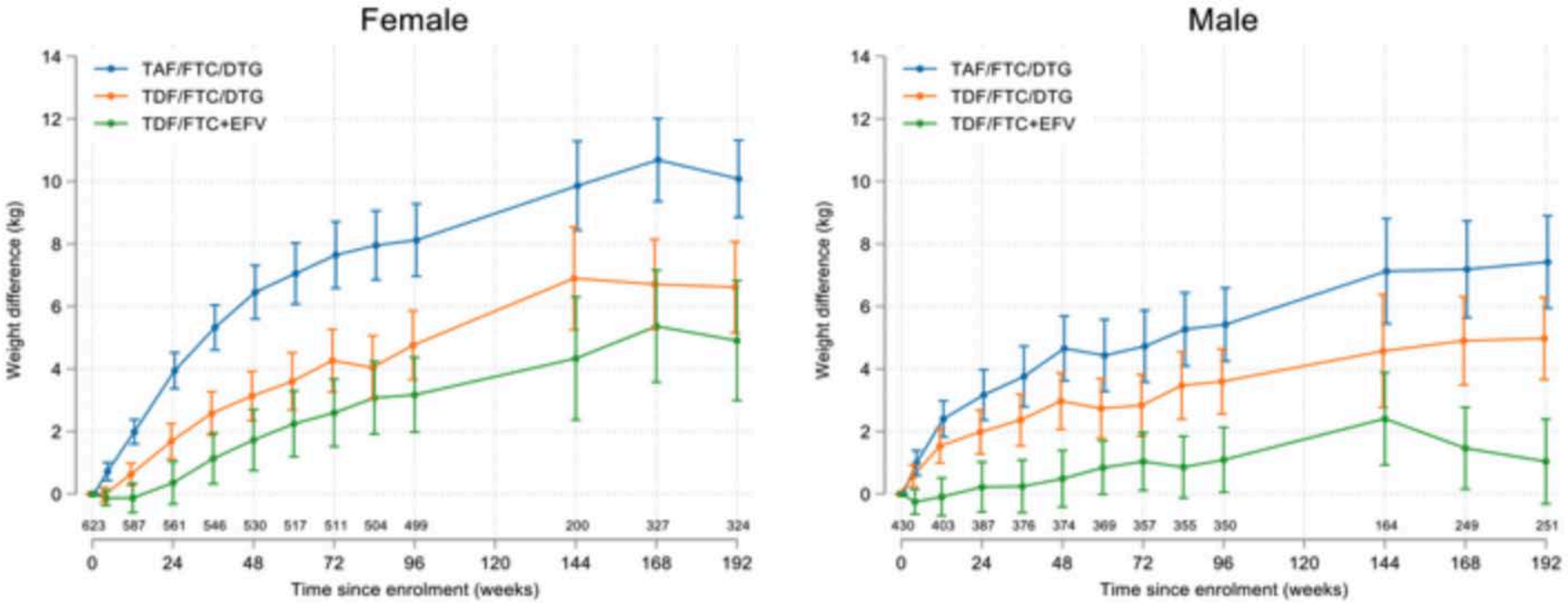
Inclusion criteria: Treatment-naïve, HIV-1 RNA level > 500 copies/mL.
Blood pressure measured at each visit
Treatment-emergent Grade 1 hypertension (SBP/DBP > 140/90) treated as part of routine clinical care



Study visits: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Median age (years)	32	32	32
Female (%)	61%	59%	57%
Black (%)	99%	100%	100%
Weight (median, kg)	66.1	66.4	66
BMI (median, kg/m^2)	24.1	24.1	24.1
CD4+ cell count (mean, cells/uL)	349	322	337
Baseline HIV RNA (copies/mL)			
HIV RNA <100,000	272 (77%)	279 (79%)	270 (77%)
HIV RNA 100-500,000	66 (19%)	62 (18%)	72 (21%)
HIV RNA >500,000	13 (4%)	10 (3%)	9 (3%)

ADVANCE – Weight Gain



ADVANCE – Hypertension

Treatment arm	TAF/FTC/DTG	TDF/FTC/DTG	TDF/FTC/EFV
HTN at baseline	36/351 (10%)	35/351 (10%)	41/351 (12%)
New hypertension	42/315 (13%)	33/316 (11%)	25/310 (8%)
New HTN Treated	42/42 (100%)	30/33 (91%)	22/25 (88%)

Treatment-emergent Grade 1 hypertension significantly higher for TAF/FTC/DTG versus TDF/FTC/EFV (p=0.038)

DTG and Hypertension – RCTs (Below), Observational Studies (Right)

Study	Hypertension outcomes
RESPOND	Higher risk of HTN for INSTI and TAF
Johannesburg 2023	Higher risk of HTN: DTG versus EFV
TSEPAMO	Higher risk of HTN: DTG versus EFV
REPRIEVE	Higher risk of HTN: DTG versus NNRTI
Zimbabwe	Higher risk of HTN: DTG versus EFV
US women	Higher risk of HTN: DTG versus PI
Pregnant women	Higher risk of HTN: DTG versus NNRTI

Trial (n)	Hypertension
1st line studies	
ADVANCE (192 wks)	Higher risk DTG vs EFV
NAMSAL (192 wks)	Higher risk DTG vs EFV
SPRING-1 (96 wks)	No difference DTG vs EFV
SINGLE (96 wks)	No difference DTG vs EFV
GEMINI	no results
FLAMINGO (96 wks)	Higher risk DTG vs DRV/r
ARIA	no results
SPRING 2 (96 wks)	DTG and RAL similar
INSPIRING	no results
ODYSSEY-A	no results
Gilead 1489/90	DTG and BIC similar

Trial	n	Hypertension
Switch / second-line studies		
SWORD		no results
STRIIVING		no results
TANGO		no results
SALSA		no results
2SD (48 weeks)		Higher risk DTG vs PI/r
VISEND (192 weeks)		Higher risk DTG vs PI/r
SAILING		no results
DAWNING		no results
NEAT 022 (48 weeks)		No difference DTG vs PI/r
D2EFT (48 weeks)		Higher risk DTG vs DRV/r
ODYSSEY-B		no results

Conclusions

In the NAMSAL and ADVANCE trials, first-line use of DTG was associated with significantly higher risks of treatment-emergent hypertension, especially when combined with TAF.

In NAMSAL, where hypertension was not consistently treated, risks of hypertension remained higher for TDF/3TC/DTG versus TDF/3TC/EFV through Week 192.

In ADVANCE, most cases of hypertension were successfully treated, and there was no significant difference between treatment arms by Week 192.


Thank You for Your Attendance!
Please visit us at:
www.prn.org