

# Antiretroviral therapy and its contribution to co-morbidities: Facts and Myths

Paddy Mallon

Professor of Microbial Diseases

Director, Centre for Experimental Pathogen Host Research  
(CEPHR)



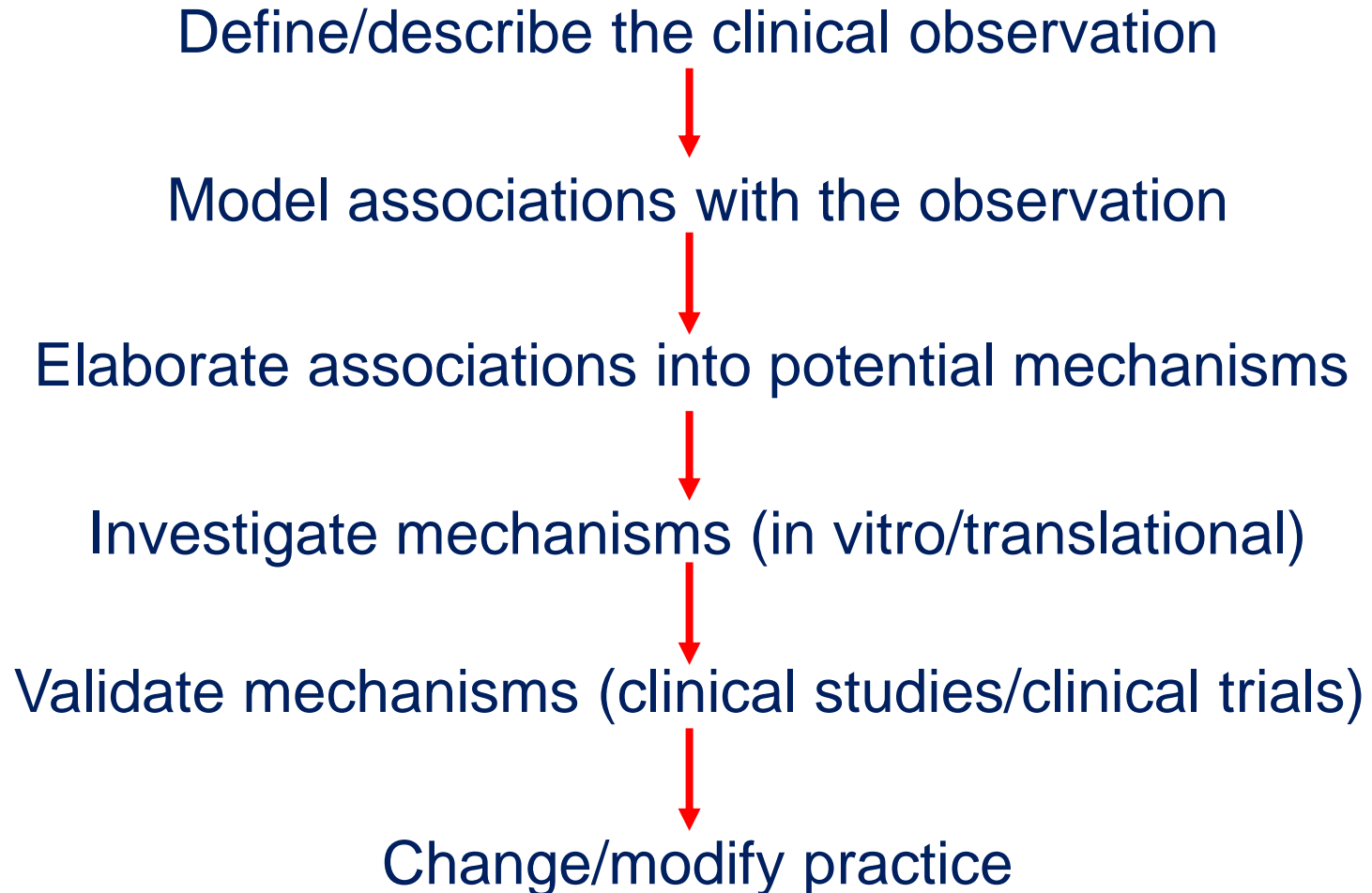
UCD School of  
Medicine

UCD School of Medicine  
[paddy.mallon@ucd.ie](mailto:paddy.mallon@ucd.ie)



# Dispelling myths – creating realities

## Pathway to research a clinical problem



# Co-morbidities– Myths vs Reality

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- Treatment with integrase strand transfer inhibitors leads to obesity
- Is loss of TDF-associated lipid lowering effect clinically relevant?
- Tenofovir disoproxil fumarate (TDF) causes *long-term* bone loss
- Abacavir contributes to increased risk of myocardial infarction

# Co-morbidities– Myths vs Reality

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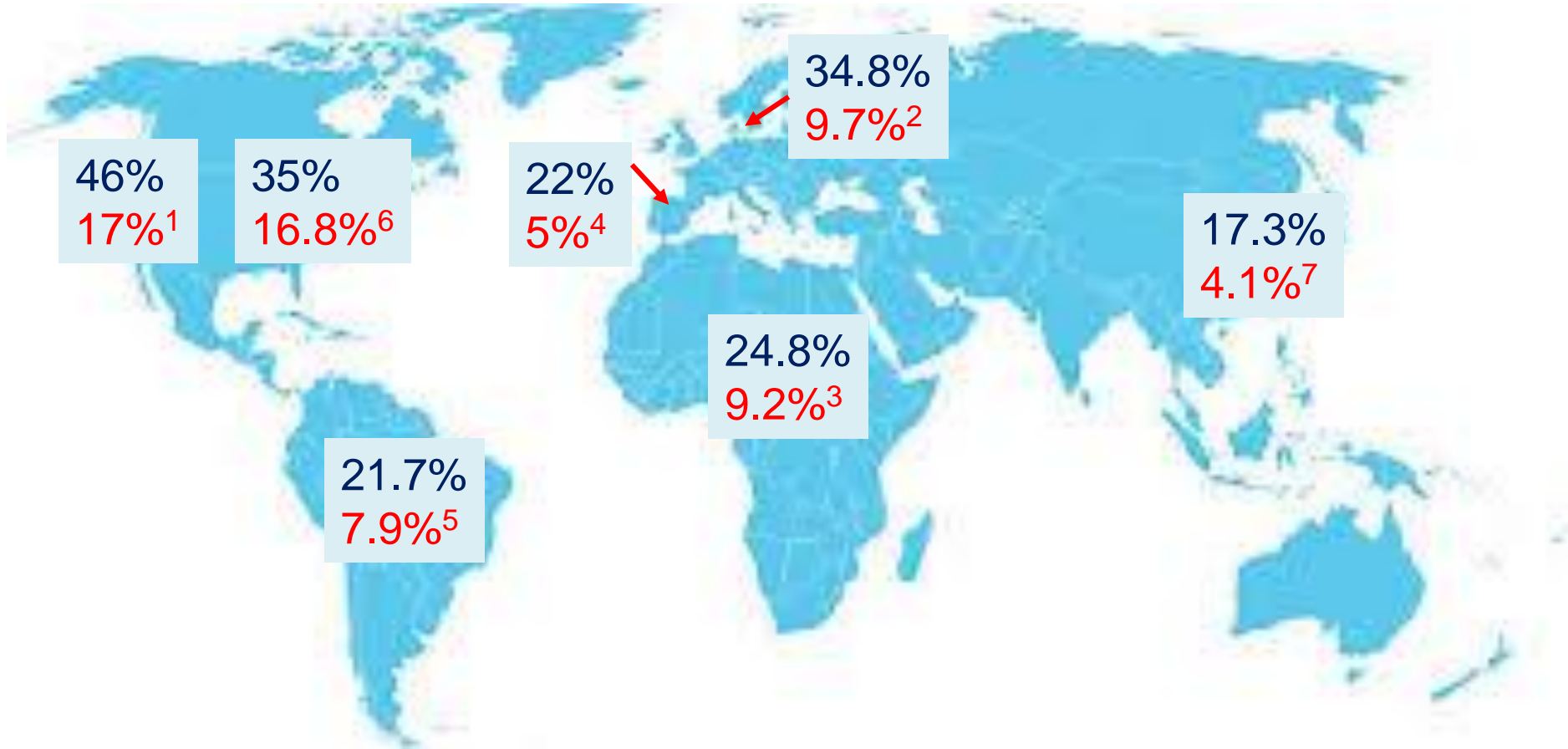
**Myth?**

**Reality?**

# HIV and Obesity

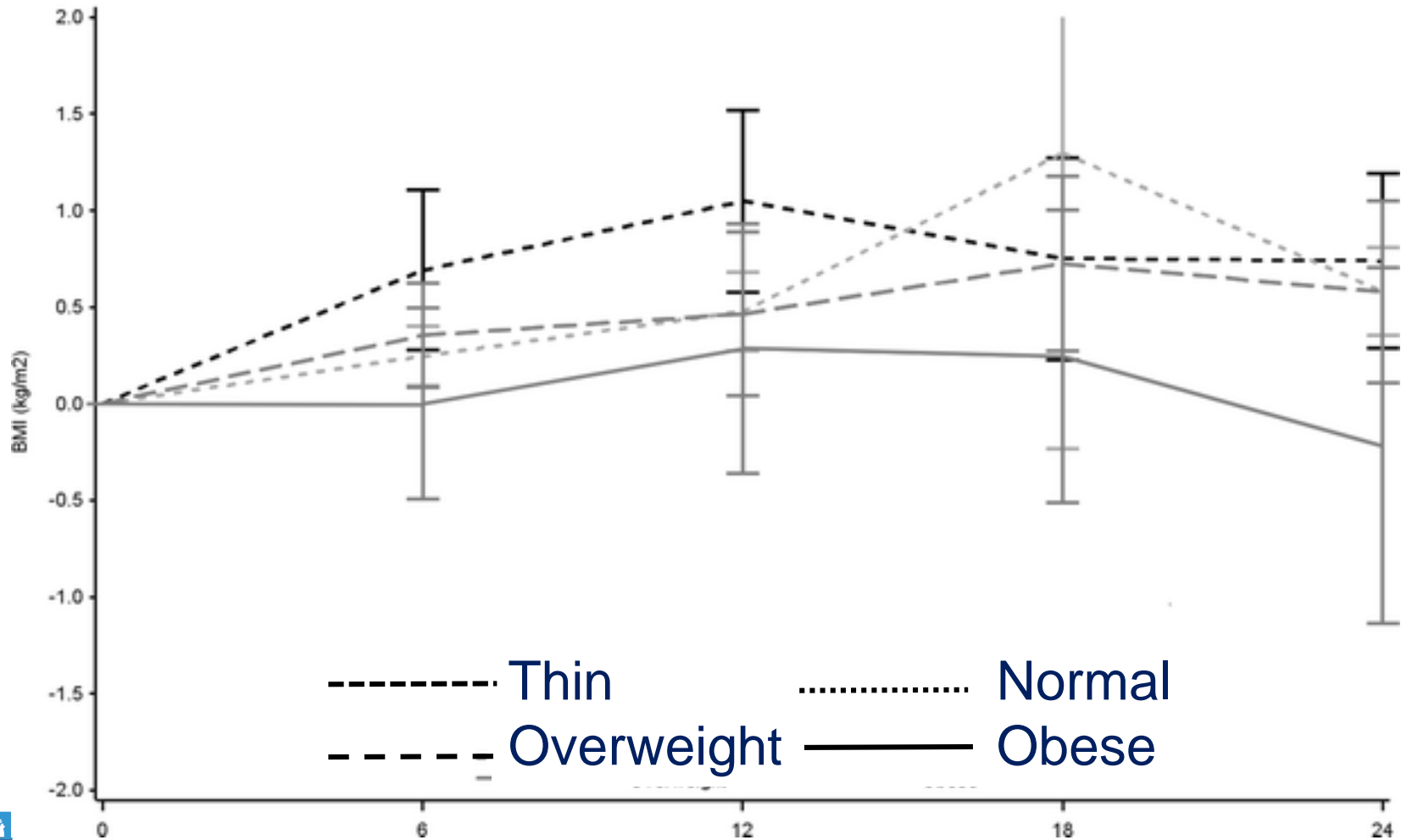
Overweight BMI >25 & <30 kg/m<sup>2</sup>

Obese BMI ≥30kg/m<sup>2</sup>



# Changes in BMI with ART initiation

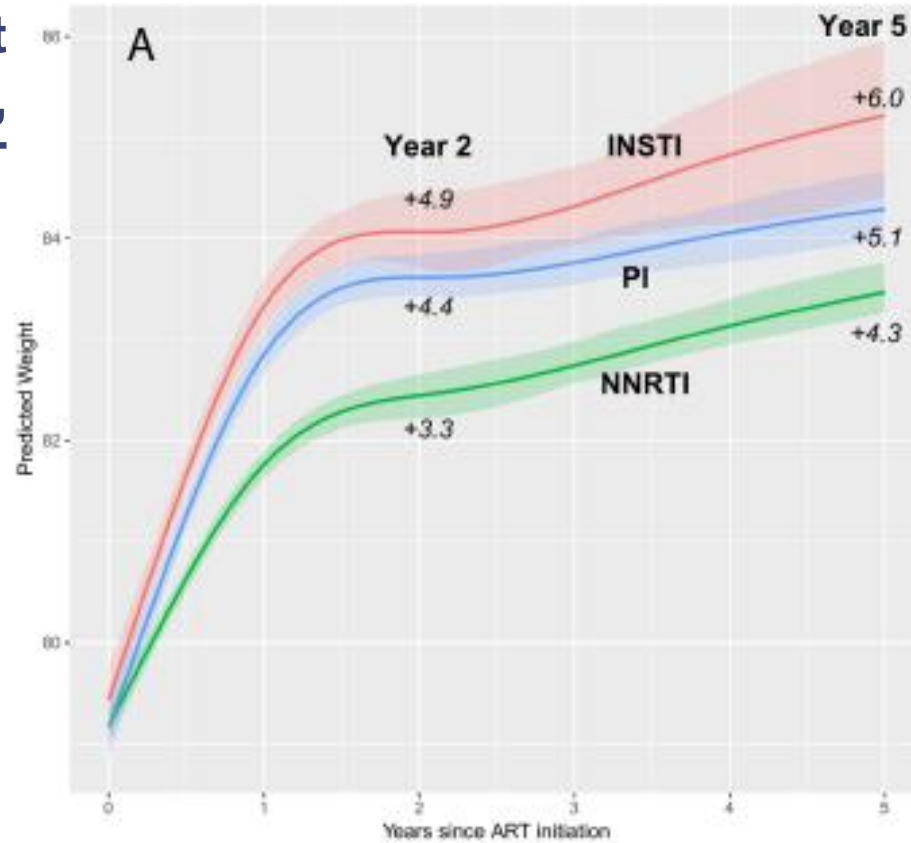
Côte d'Ivoire. N=755. Initiating ART (74% on EFV)



# Changes in weight with ART initiation

NA-ACCORD. N=24,001 initiating ART between 2007 and 2016  
Greater weight gain with initiation of INSTI

**Predicted weight changes over 5 Years, by class of ART**



Weight gain did not vary by gender or race (white / non-white)

# Changes in BMI with ART initiation

N= 1784 initiating ART in Brazil

Factors associated with incident obesity after ART initiation

Age at ART Initiation (per 10 year increase)

Sex: Female (ref male)

Sex: Transgender Women

Baseline Viral Load (copies/mL) Log<sub>10</sub>\*

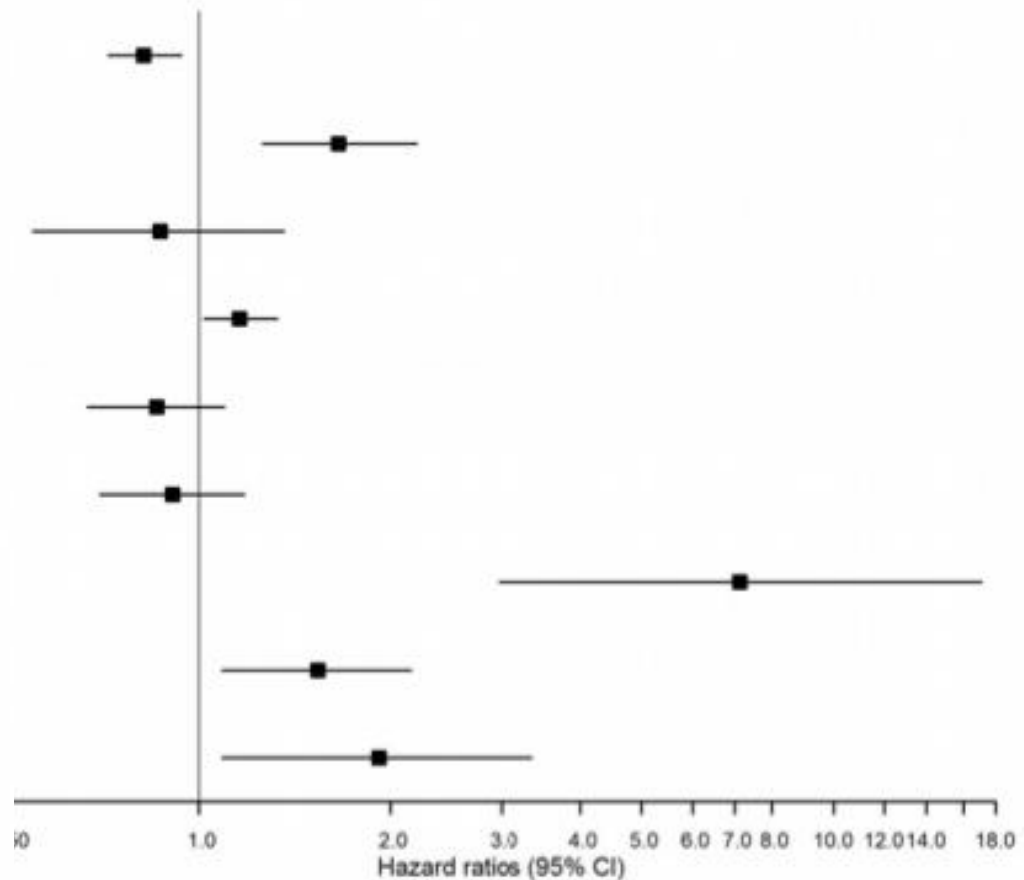
NRTI: AZT (ref TDF)

ART Core Drug: PI (ref NNRTI)

ART Core Drug: INSTI

Baseline Diagnosis of Hypertension

Baseline Diagnosis of Diabetes Mellitus





# Changes in BMI with ART initiation

N= 1,784 initiating ART in Brazil

Factors associated with incident obesity after ART initiation

Age at ART Initiation (per 10 year increase)

Sex: Female (ref male)

Sex: Transgender Women

Baseline Viral Load (copies/mL) Log<sub>10</sub>\*

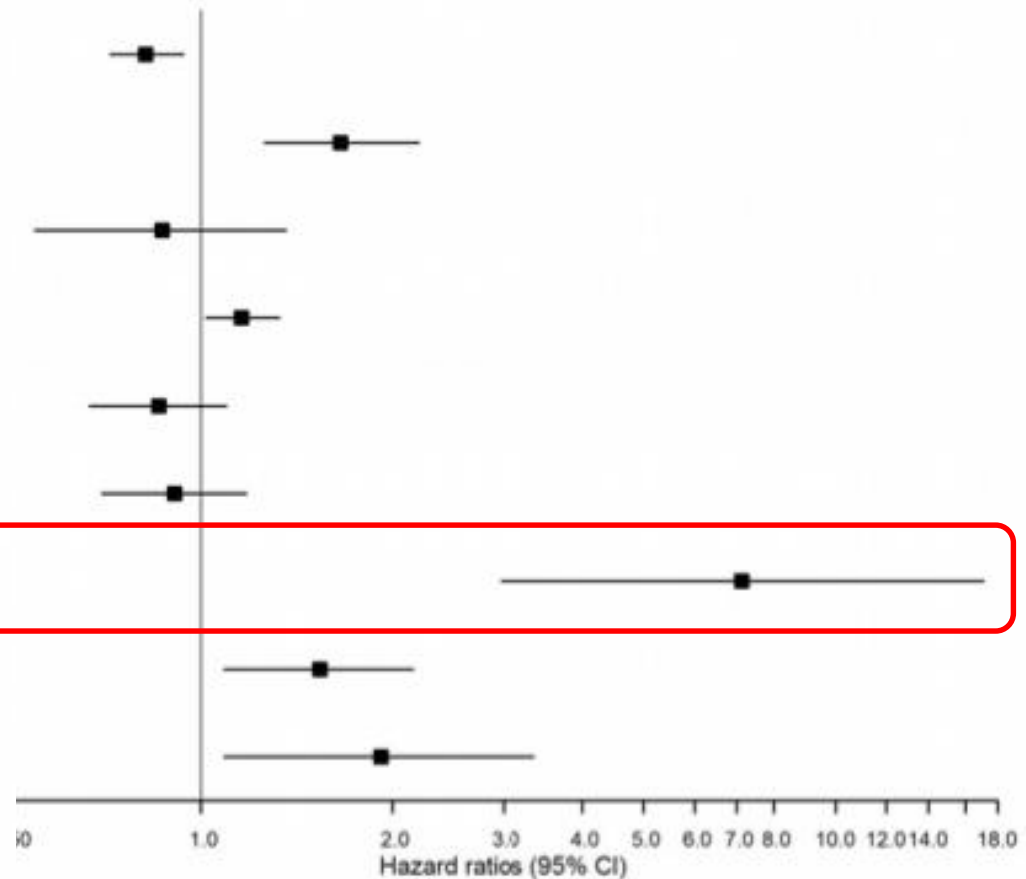
NRTI: AZT (ref TDF)

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ART Core Drug: INSTI

Baseline Diagnosis of Hypertension

Baseline Diagnosis of Diabetes Mellitus



# InSTI and weight gain - switch

ACTG A5001 and A5322. N=691.

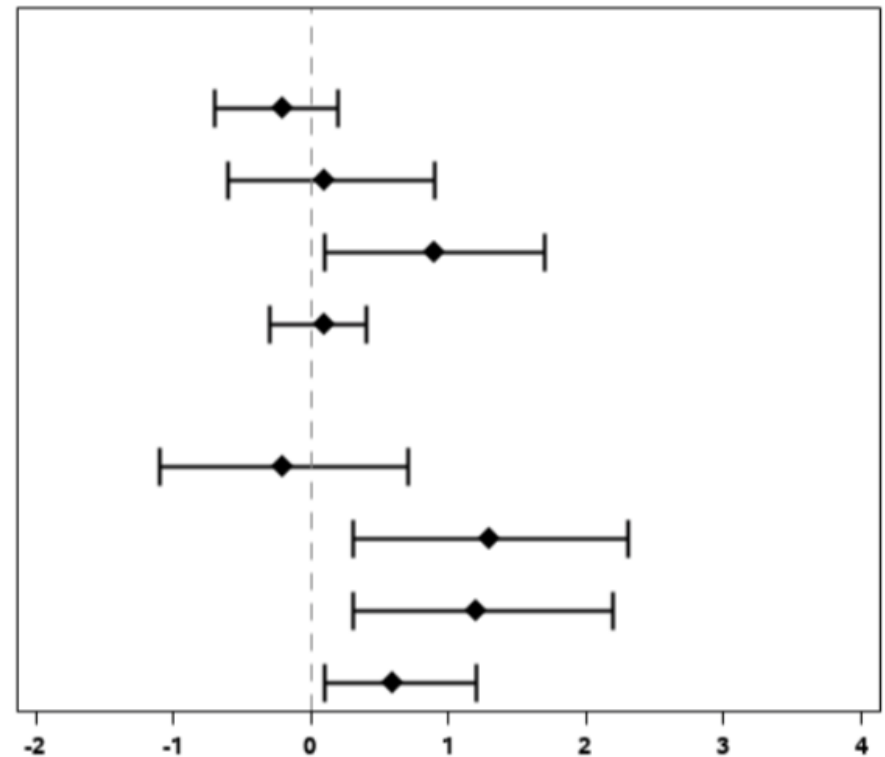
Virologically suppressed, switching to InSTI.

	Pre-post difference*
DTG (n=198)	1.0 (0.0009)
EVG (n=204)	0.5 (0.11)
RAL (n=289)	-0.2 (0.37)

\* Kg/yr

PI [ RAL  
EVG  
DOL  
InSTI

NNRTI [ RAL  
EVG  
DOL  
InSTI



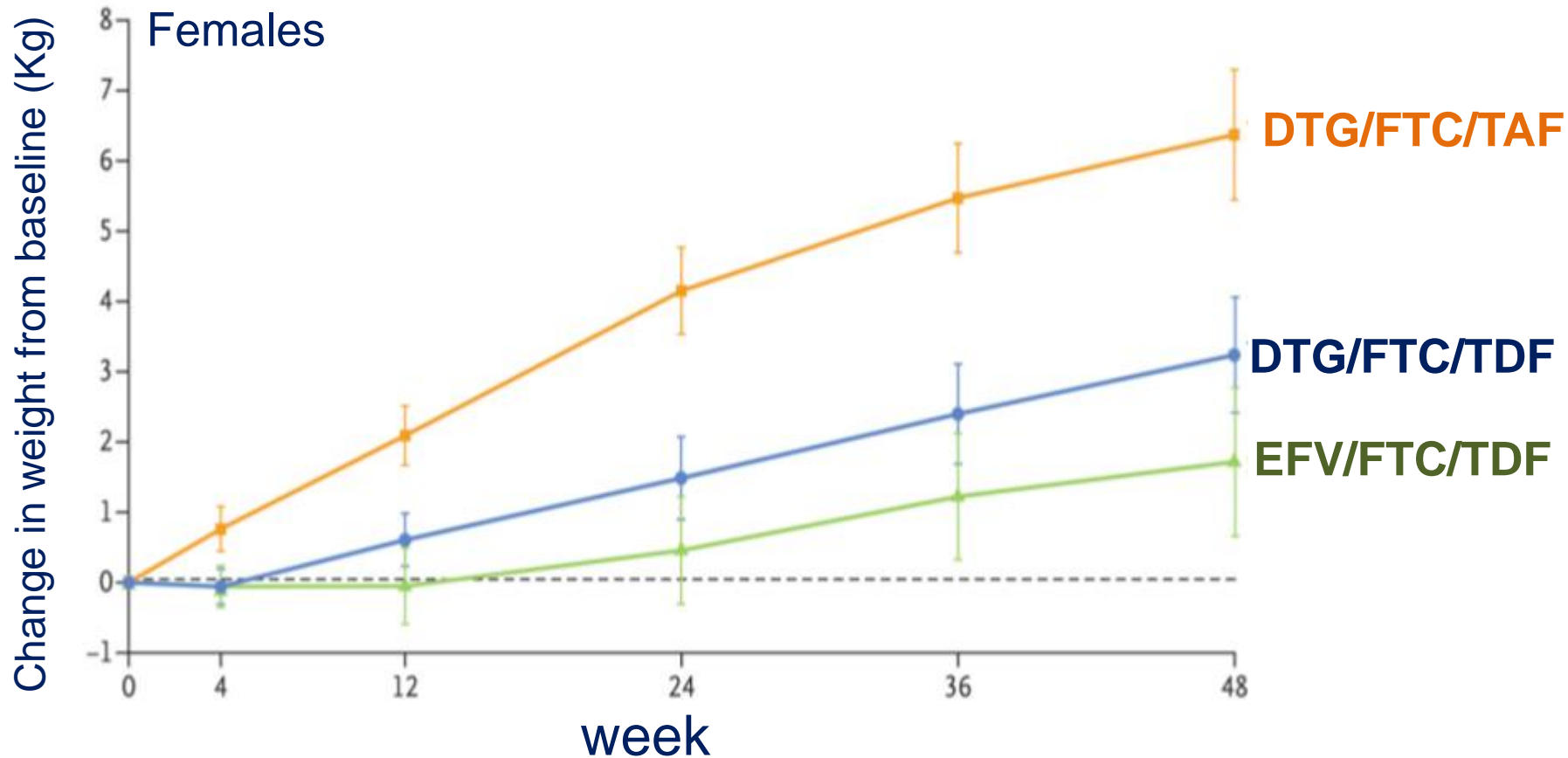
Is this removal of an adipose tissue toxicity or addition of a new toxicity or both?

# InSTI and weight gain - ADVANCE

Open label. RCT in South Africa<sup>1</sup>.

N= 1,053 ART naïve. 99% black, 59% female.

DTG/FTC/TDF vs DTG/FTC/TAF vs EFV/FTC/TDF

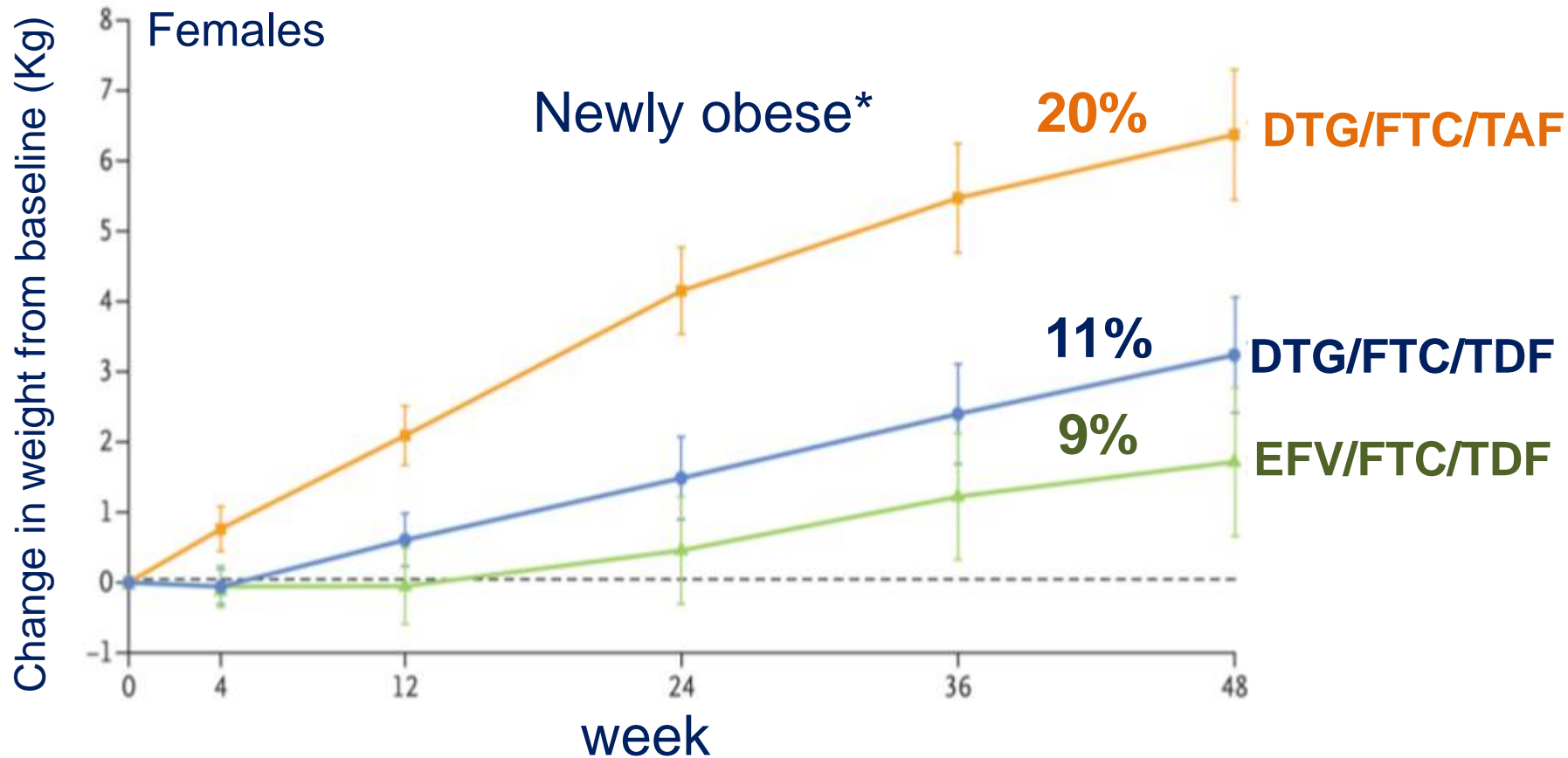


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8 Females

## NAMSAL Study

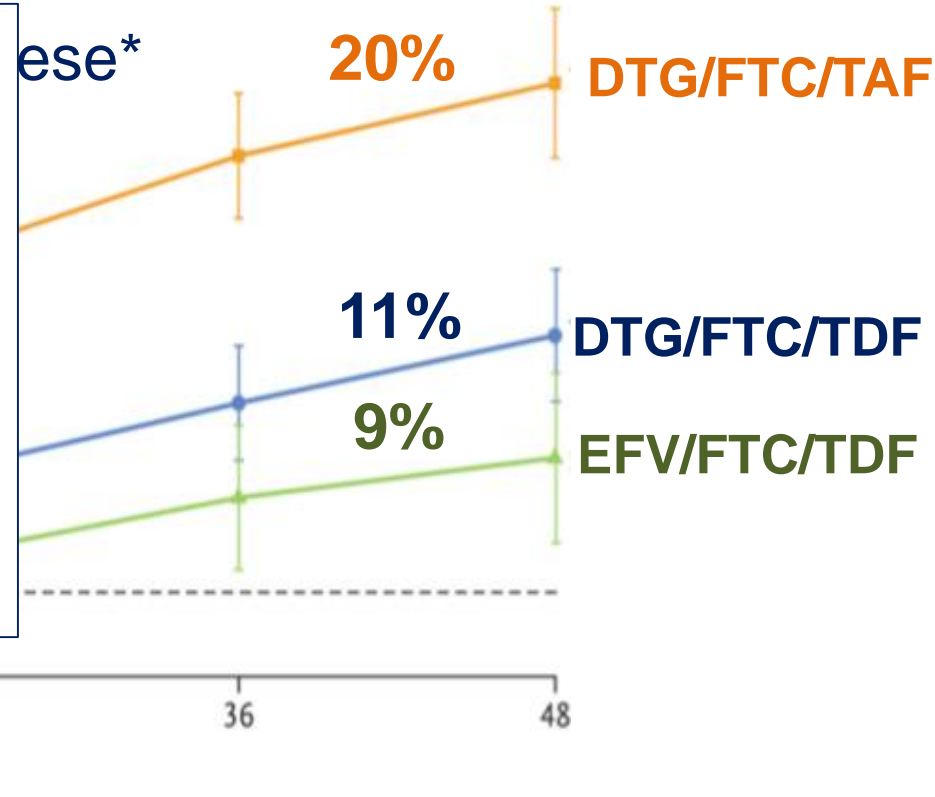
RCT. N=613.

Cameroon 65.9% female

**DTG/3TC/TDF 12.3%**

**EFV/3TC/TDF 5.4%**

**'few metabolic consequences'**



# Myths vs. realities – Obesity and InSTI



Define/describe the clinical observation



Model associations with the observation



Elaborate associations into potential mechanisms



Investigate mechanisms (in vitro/translational)



Validate mechanisms (clinical studies/clinical trials)



Change/modify practice

# Co-morbidities– Myths vs Reality

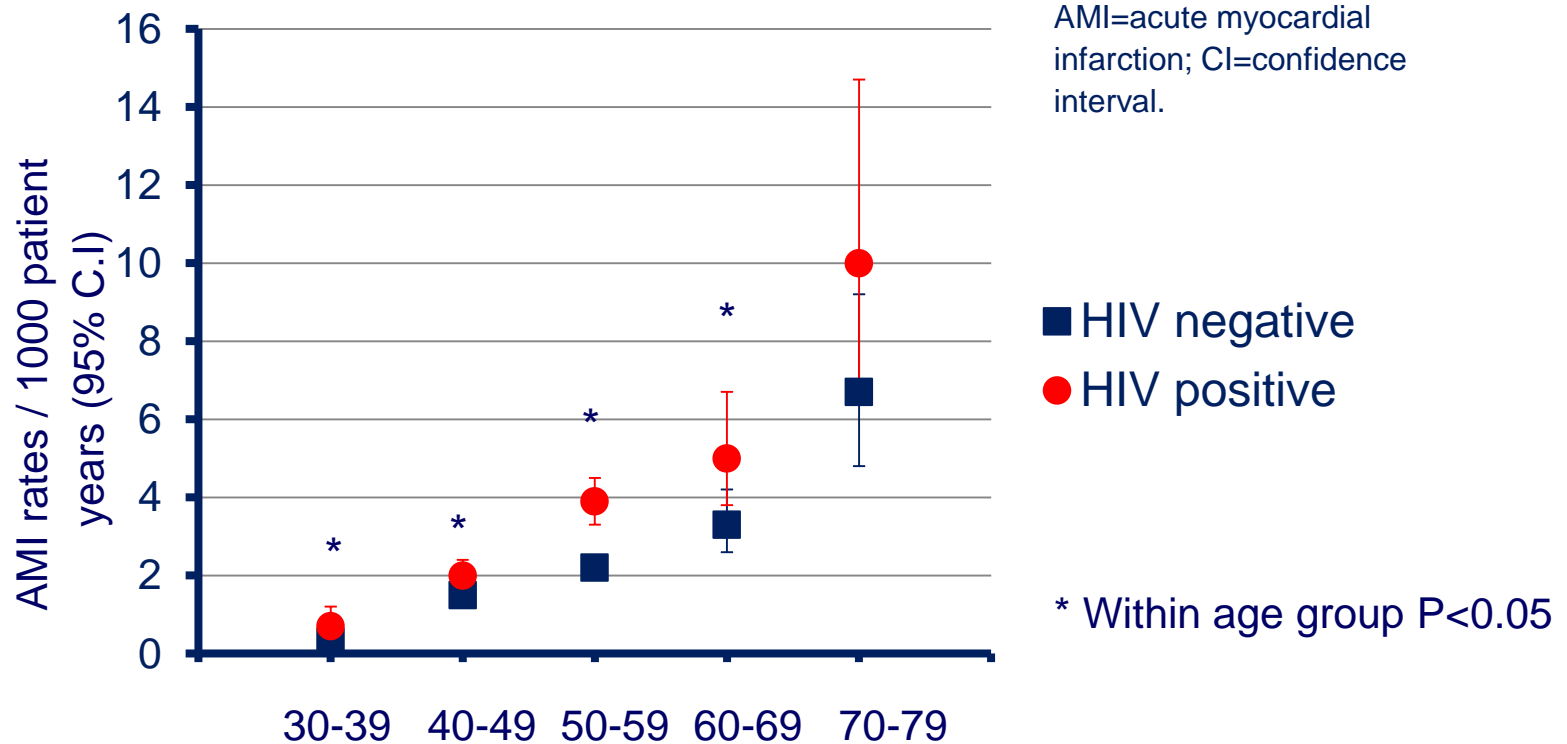
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**Myth?**

**Reality?**

# HIV and CVD – incidence of MI

AMI is more common in HIV-positive than HIV-negative populations<sup>1</sup>

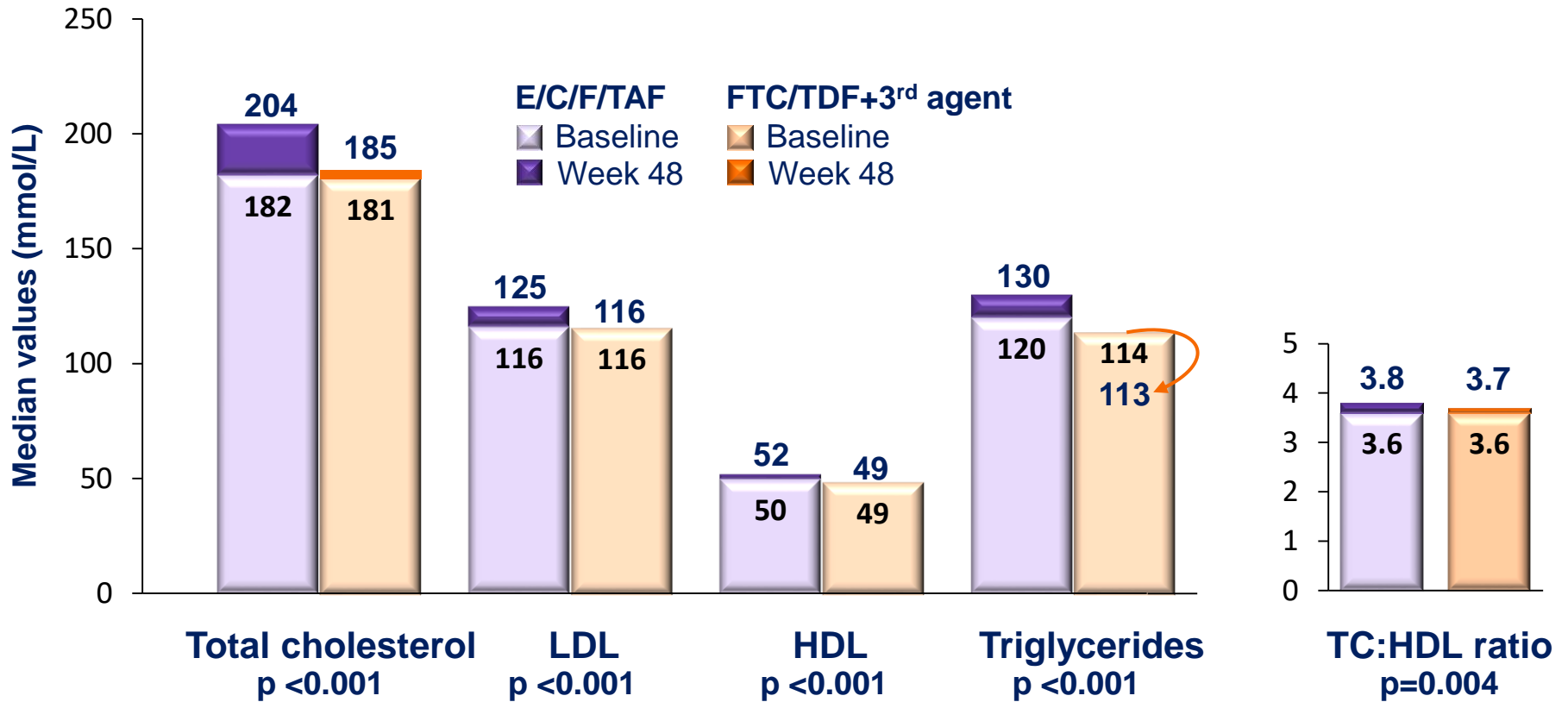


RR of MI with age not different between HIV and the general population risk estimates<sup>2</sup>



# Change in lipids with switch from TDF

Study 109: VIROLOGICALLY SUPPRESSED.  
 Switch from a TDF-containing ART to E/C/F/TAF  
 Changes in Fasting Lipids at Week 48



Patients initiating lipid-modifying medications:

E/C/F/TAF: 7.9%;

TDF-based regimen: 5.9%

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

A. Lacey<sup>1</sup>, W. Tinago<sup>1</sup>, N. Power<sup>2</sup>, E. Alvarez Barco<sup>1</sup>, A.J. Macken<sup>1</sup>, G. Sheehan<sup>2</sup>, J.S. Lambert<sup>2</sup>, A.G. Cotter<sup>1,2</sup>, P.W.G. Mallon<sup>1,2</sup>

<sup>1</sup>HIV Molecular Research Group, University College Dublin School of Medicine, Dublin, Ireland

<sup>2</sup>Mater Misericordiae University Hospital, Department of Infectious Diseases, Dublin, Ireland



UCD School of Medicine  
Scoil an Leighis UCD

Mater Misericordiae  
University Hospital

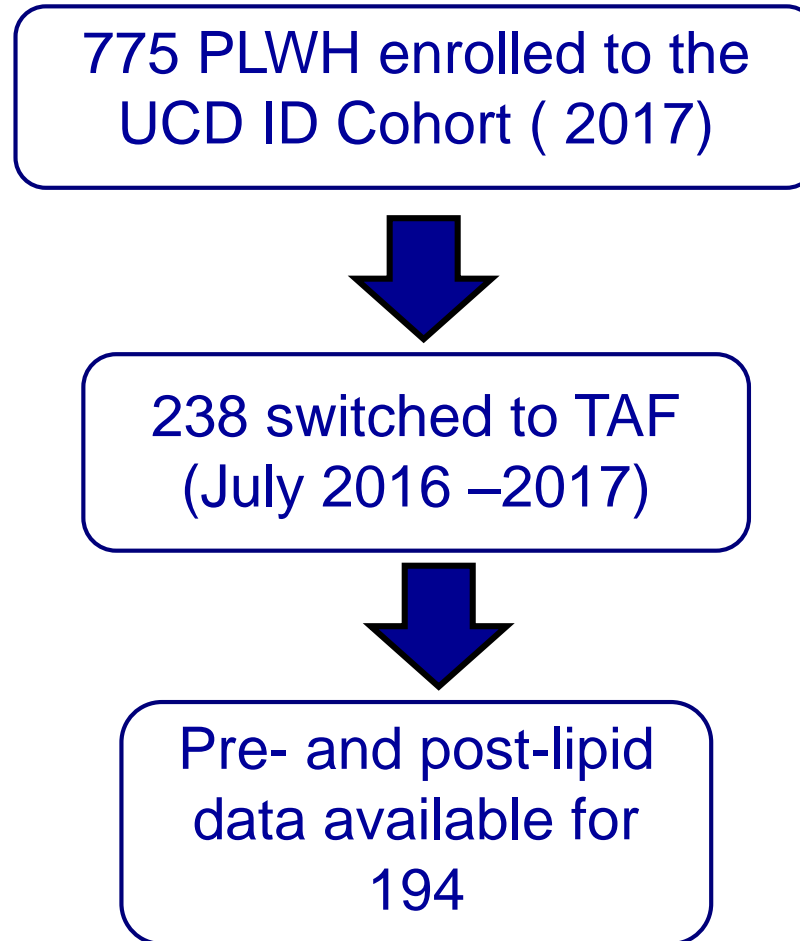


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16-18 MAY 2018

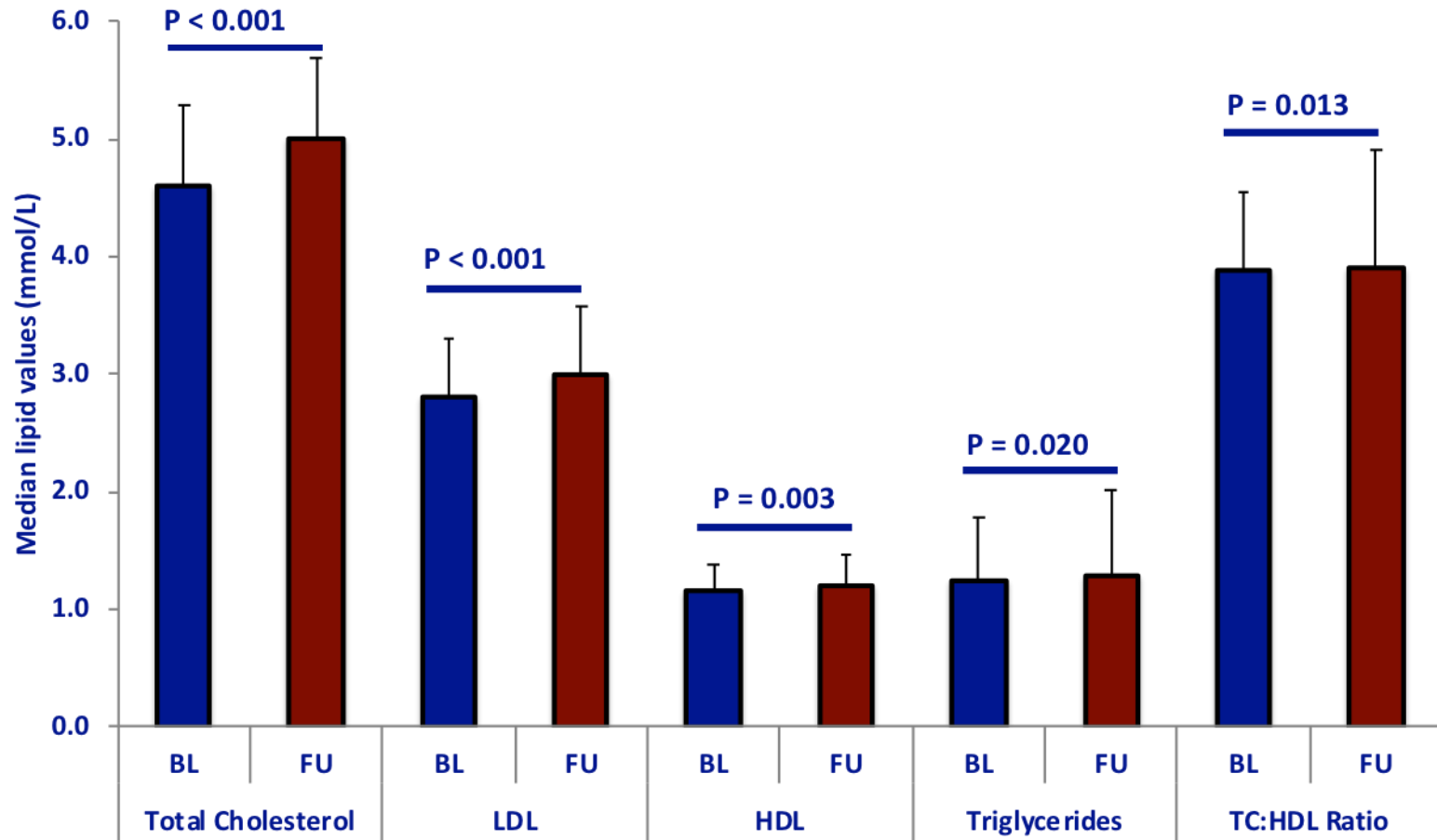


# Population breakdown

Followup lipids taken from first available lipid profile at least 7 days post switch (median 154 [112 – 217])



# Lipid Increases post switch (n=194)



P-values derived from Wilcoxon Signed-Rank test

# NCEP ATP III Lipid Guidelines

The National Cholesterol Education Programme released their Adult Treatment Panel III in 2016<sup>1</sup>

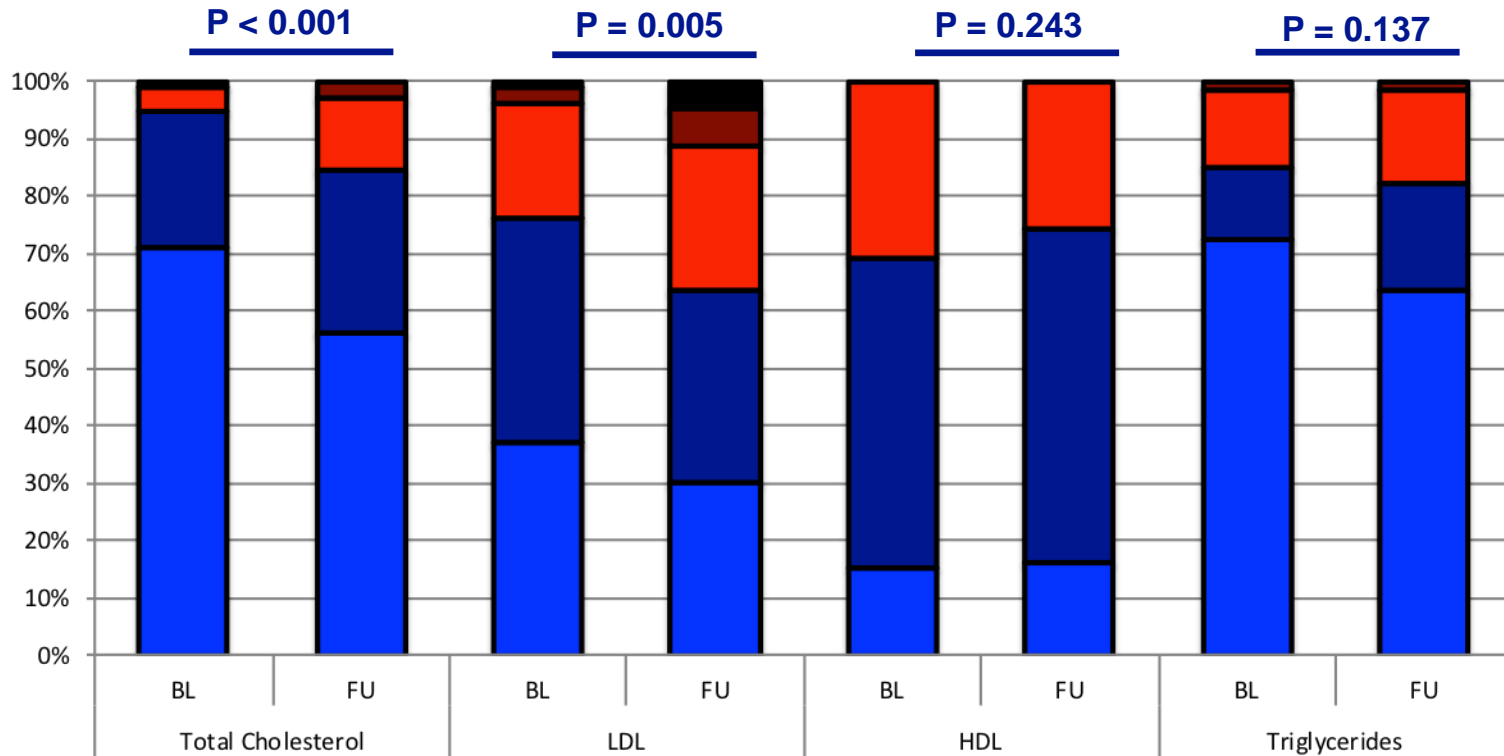
## Not Dyslipidaemia

## Dyslipidaemia

	Normal	Borderline Abnormal	Dyslipidaemia	Severe Dyslipidaemia	Very Severe Dyslipidaemia
Total Cholesterol (mmol/L)	<5.2	5.2 – 6.2	6.21 -7.2	>7.2	
LDL (mmol/L)	<2.5	2.5 – 3.3	3.31 – 4.1	4.11 – 4.9	>4.9
HDL (mmol/L)	>1.54	1.03 – 1.54	<1.03		
Triglycerides (mmol/L)	<1.7	1.7 – 2.25	2.26 – 5.64	>5.64	

1. Adult Treatment Guidelines III. National Institute of Health, National Cholesterol Education Programme. 2016

# Lipids stratified by NCEP ATPIII Guidelines



- Grade 5: Very Severe Dyslipidaemia; LDL > 4.9 mmol/l
- Grade 4: Severe Dyslipidaemia; TC > 7.2; LDL 4.11-4.9; TRG > 5.64 mmol/l
- Grade 3: Dyslipidaemia; TC 6.21-7.2; LDL 3.31-4.1; HDL < 1.03; TRG 2.26-5.64 mmol/l
- Grade 2: Borderline Abnormal; TC 5.2-6.2; LDL 2.5-3.3; HDL 1.03-1.54; TRG 1.7-2.25 mmol/l
- Grade 1: Normal, TC < 5.2; LDL < 2.5; HDL > 1.54; TRG < 1.7 mmol/l

P-Values derived from  
McNemar-Bowker test

Larger increases in those with higher baseline TC and LDL  
Lower increases in those on statins

# Lipid changes and TAF - OPERA database



OPERA database of electronic health records  
N=93,170 from 84 clinics across 18 US states

- Adults on TDF for >4 weeks
- Switch from TDF to TAF between Nov 2015 and March 2018
- 1 lipid panel  $\leq$ 6 months pre-switch from TDF
- $\geq$ 1 lipid panel after switch to TAF

N=2,769

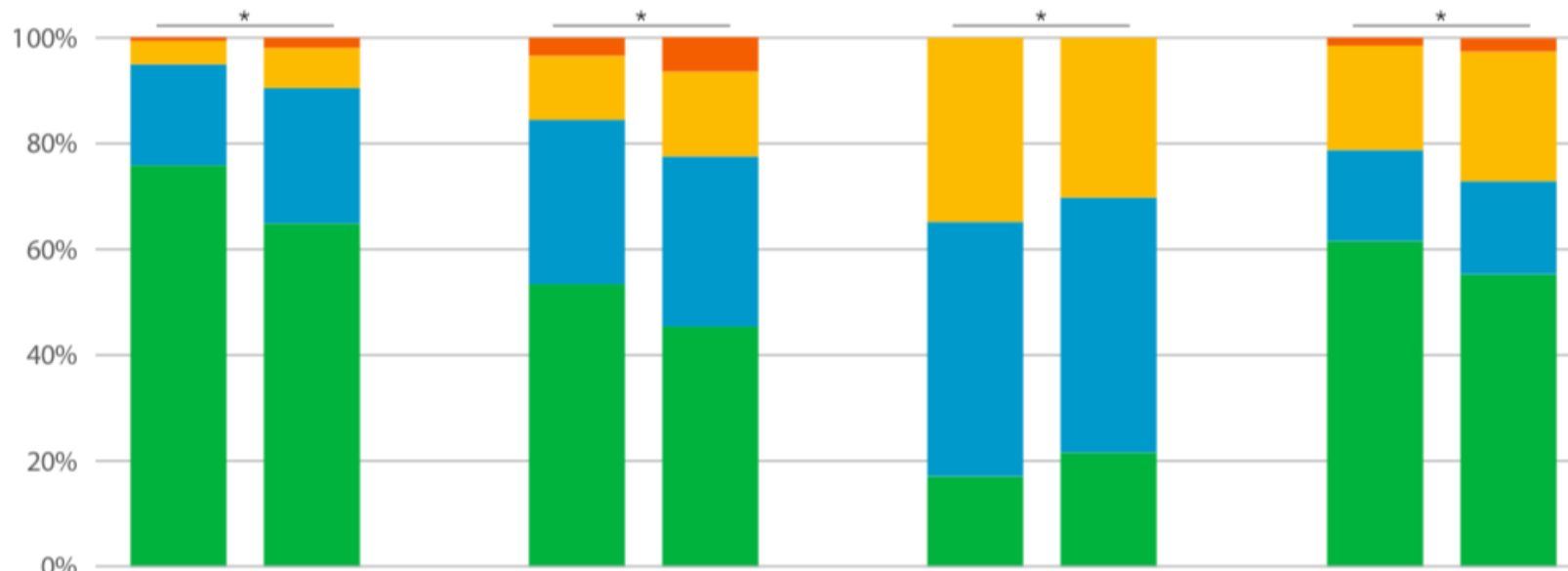
	At switch n (%)
Age $\geq$ 50 years	2769 (42.9)
Female	1010 (15.7)
African American	2126 (33.0)
Hispanic	1870 (29.0)
HIV RNA <200 copies/mL	5473 (84.8)

	Pre-switch n (%)	Post-switch n (%)
PI	1566 (24.3)	1228 (19.0)
NNRTI	2319 (35.9)	1546 (24.0)
INSTI	3007 (46.6)	4185 (64.9)
$\geq$ 1 anchor agent	527 (8.2)	563 (8.7)
Boosting agent	3292 (51.0)	3987 (61.8)
Statin	971 (15.1)	1696 (26.3)



# Lipid changes and TAF - OPERA database

Change in NCEP ATP-III Dyslipidaemia – whole cohort  
N=6,451



	TDF	TAF
<b>CHOL</b>		
Severe	0.7%	1.9%
Dyslipidemia	4.4%	7.6%
Borderline	19.1%	25.6%
Normal	75.9%	64.9%

	TDF	TAF
<b>LDL</b>		
Severe	3.4%	6.5%
Dyslipidemia	12.1%	16.0%
Borderline	31.1%	32.2%
Normal	53.4%	45.4%

	TDF	TAF
<b>HDL</b>		
Severe	NA	NA
Dyslipidemia	34.8%	30.2%
Borderline	48.1%	48.2%
Normal	17.1%	21.6%

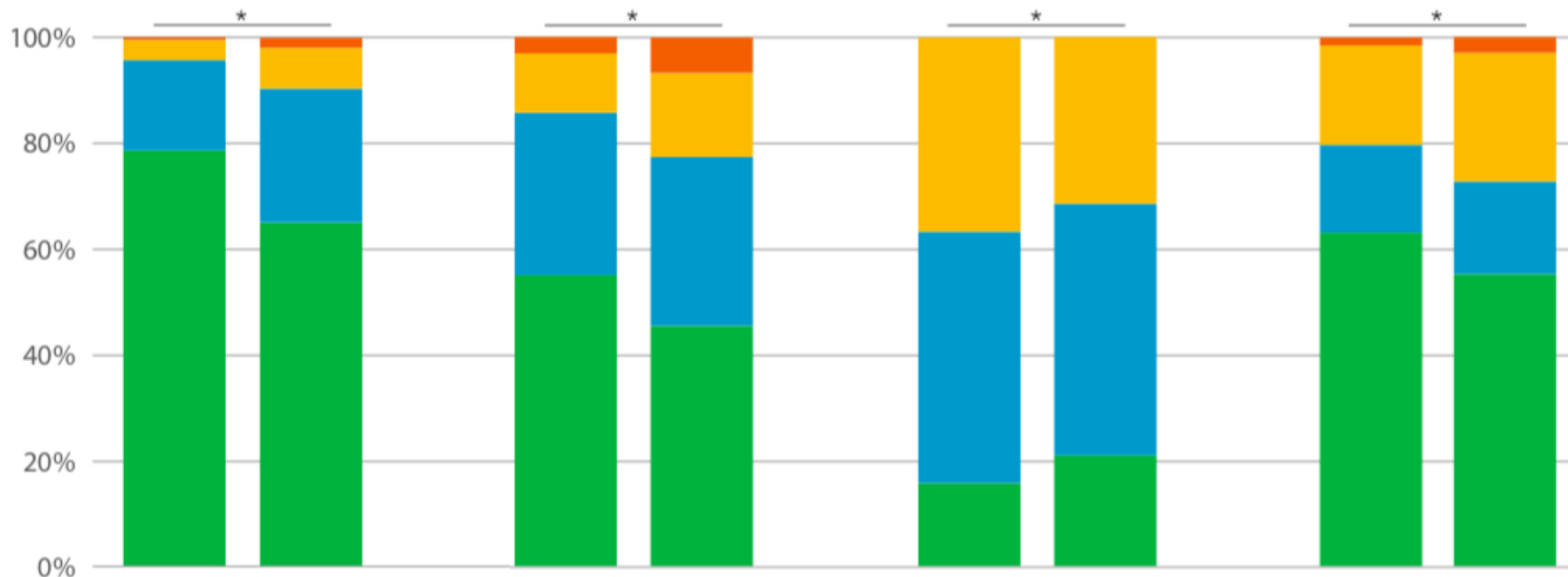
	TDF	TAF
<b>TG</b>		
Severe	1.5%	2.5%
Dyslipidemia	19.7%	24.5%
Borderline	17.2%	17.6%
Normal	61.6%	55.3%



# Lipid changes and TAF - OPERA database



Change in NCEP ATP-III Dyslipidaemia – only TDF-TAF switch  
N=4,328



	TDF	TAF
<b>CHOL</b>		
Severe	0.5%	1.9%
Dyslipidemia	3.8%	7.7%
Borderline	17.1%	25.3%
Normal	78.6%	65.0%

	TDF	TAF
<b>LDL</b>		
Severe	3.1%	6.7%
Dyslipidemia	11.2%	15.9%
Borderline	30.7%	31.9%
Normal	55.1%	45.5%

	TDF	TAF
<b>HDL</b>		
Severe	NA	NA
Dyslipidemia	36.7%	31.5%
Borderline	47.5%	47.6%
Normal	15.8%	21.0%

	TDF	TAF
<b>TG</b>		
Severe	1.5%	3.0%
Dyslipidemia	18.8%	24.3%
Borderline	16.6%	17.5%
Normal	63.1%	55.3%



# Myths vs. realities – Loss of TDF and lipids



Define/describe the clinical observation



Model associations with the observation



Elaborate associations into potential mechanisms



Investigate mechanisms (in vitro/translational)



Validate mechanisms (clinical studies/clinical trials)



Change/modify practice

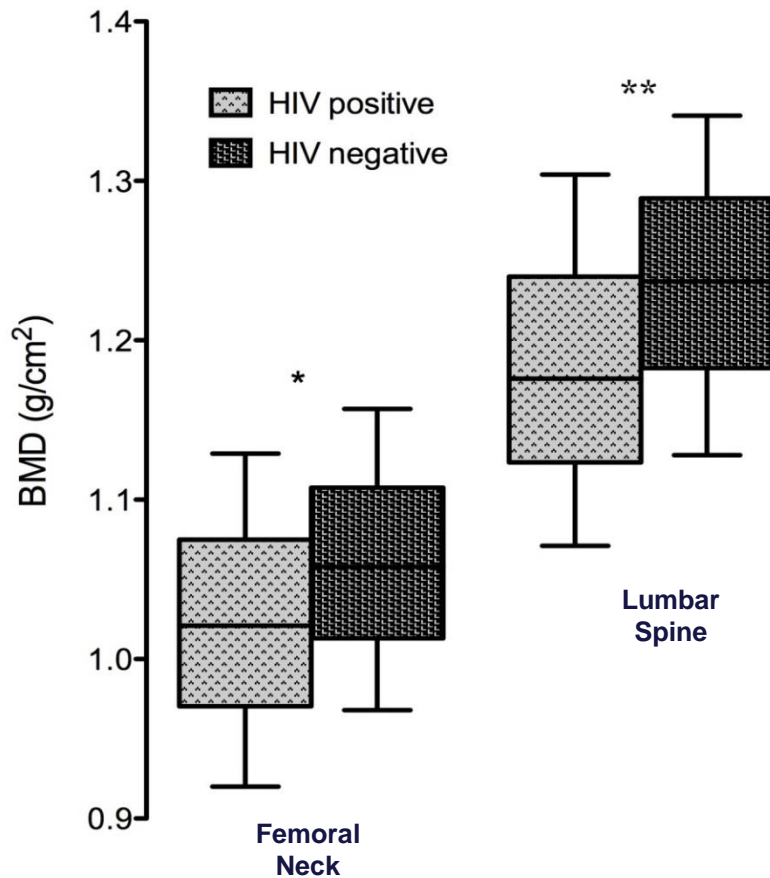
# Co-morbidities– Myths vs Reality

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- Abacavir contributes to increased risk of myocardial infarction

**Myth?**

**Reality?**

# HIV UPBEAT Study



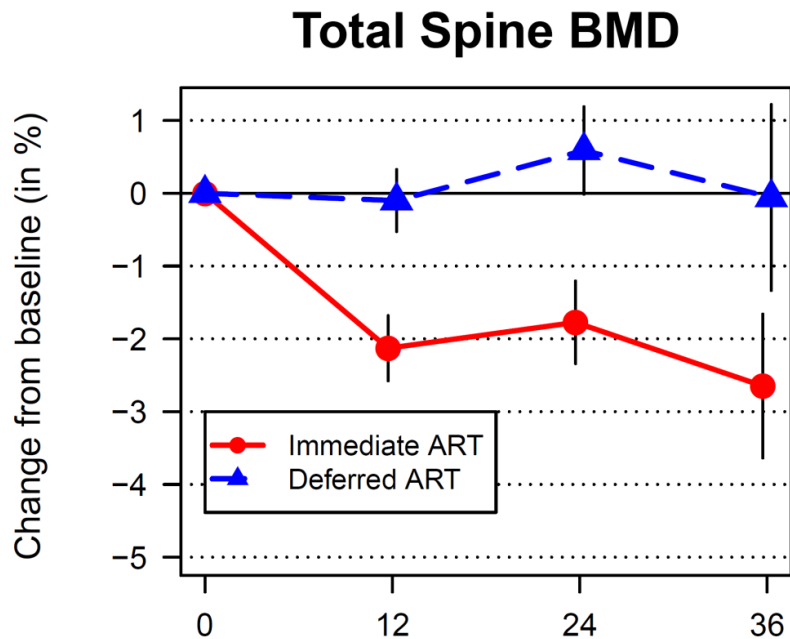
Femoral neck (FN) between group \* $P=0.003$   
 Lumbar spine (LS) between group \*\*  $P=0.001$

Low BMD by site *	HIV+ (N=210)	HIV- (N=264)	
	n (%)	n (%)	P
Femoral Neck	50 (23.8)	31 (11.7)	0.001
Lumbar Spine	51 (24.3)	33 (12.5)	0.001

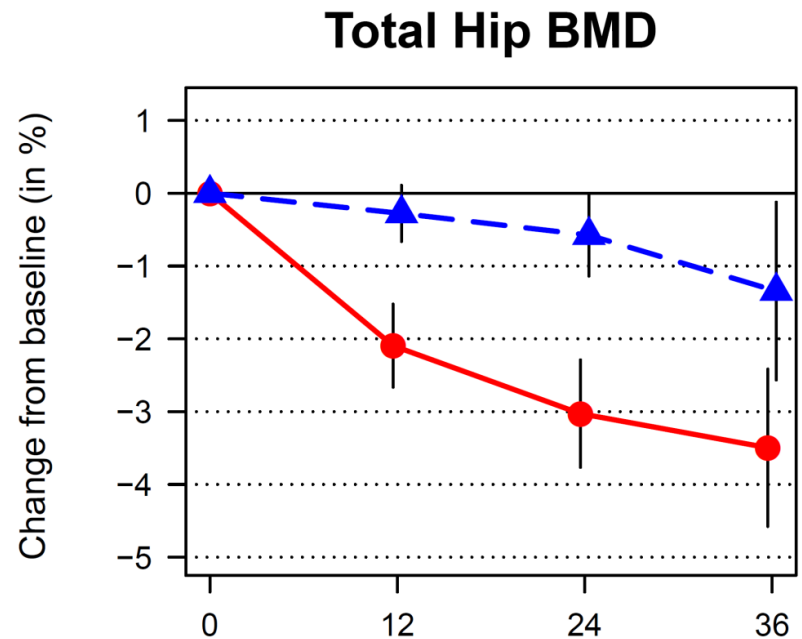
\*Z-score  $\leq -2.0$  in those aged  $<40$  years or  
 T-score of  $\leq -1.0$  in those aged  $\geq 40$  years

# Loss of BMD occurs with ART initiation

Change in bone mineral density on ART versus off ART



**Months from randomization**  
Estimated Mean Diff (95% CI)  
-2.2% (-2.8, -1.6),  $p < 0.001$

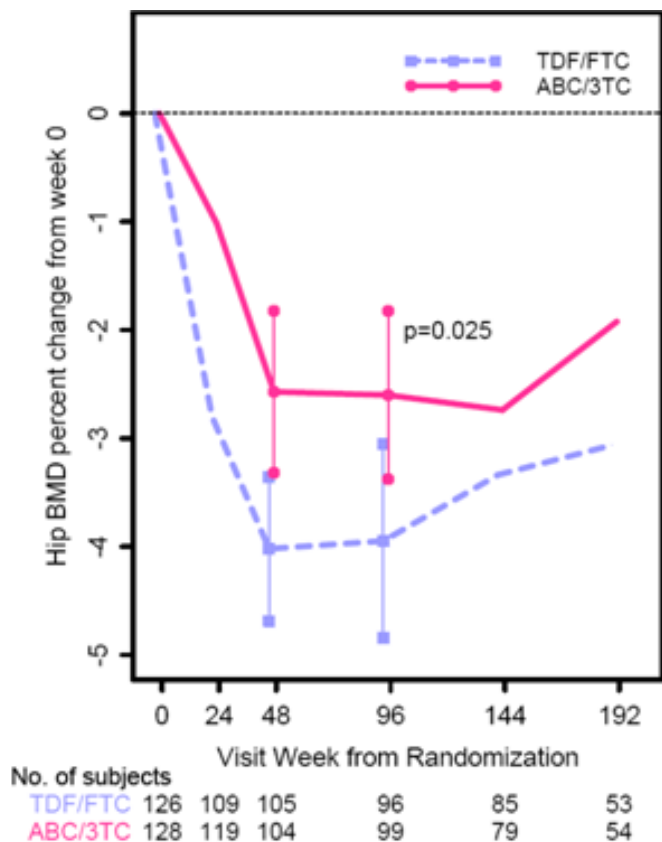


**Months from randomization**  
Estimated Mean Diff (95% CI)  
-2.1% (-2.8, -1.4),  $p < 0.001$

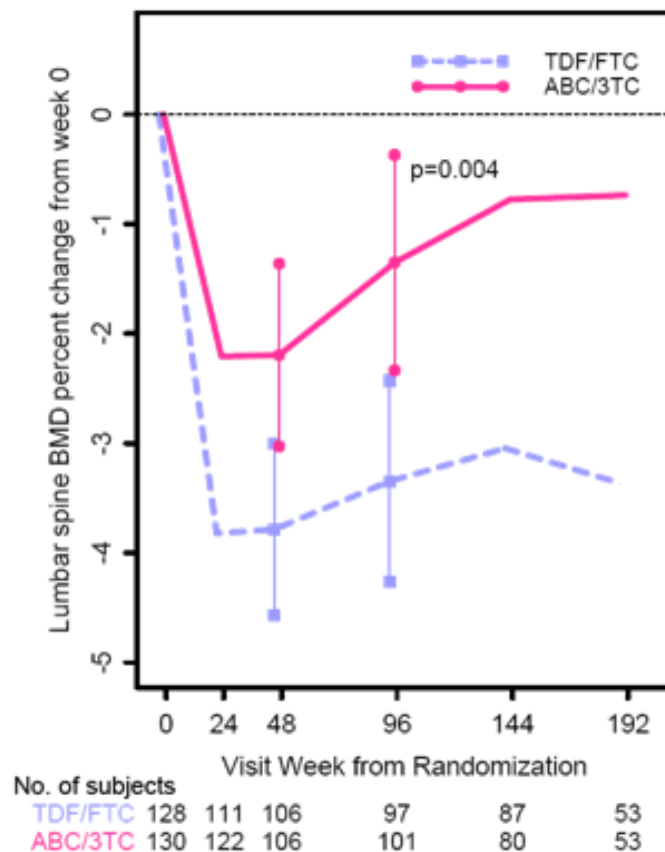
# More early bone loss occurs with TDF

## A5224s: Metabolic Substudy of A5202

### Hip



### Lumbar Spine

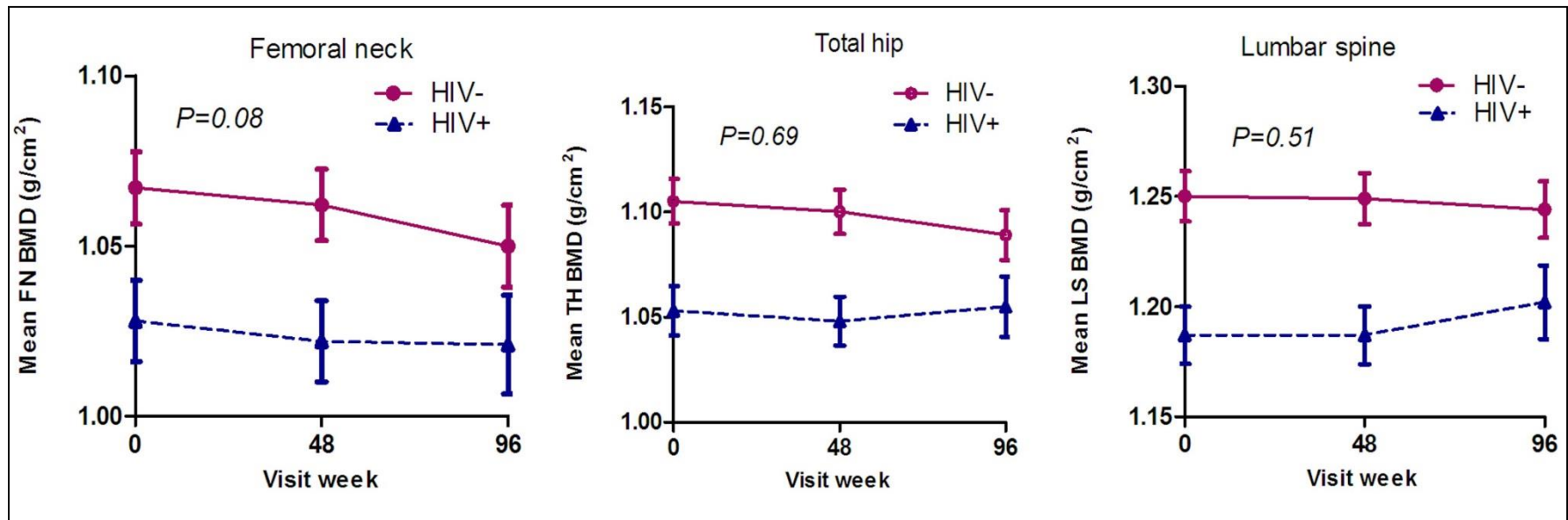


**TDF/FTC**  
**ABC/3TC**

# ART and BMD – long-term follow-up

HIV UPBEAT Study.  $N=384$ . Year 3 follow-up.

HIV+,  $N=176$ , age 39 years, 61% male, 88% on ART (83% on TDF)



**BMD loss 0.2-0.6% per year**

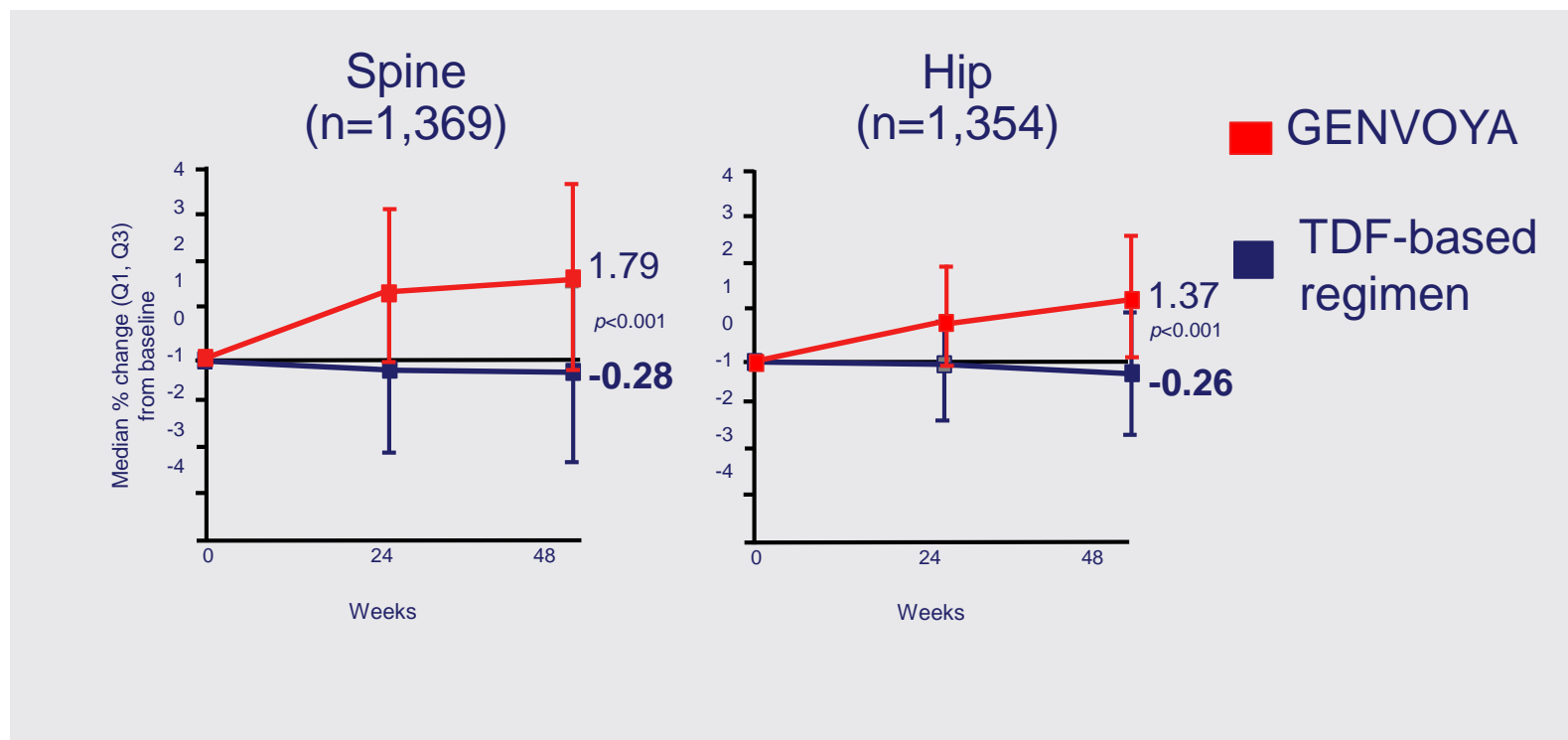
- No significant differences in rate of BMD decline in HIV+ vs HIV-
- Starting ART in previous 3/12 or not on ART both associated with greater BMD decline
- No association between specific ART (including TDF) and BMD decline

# Long-term TDF in clinical trials

GS-US-292-0109

N=1,436, 90% male, age 40 vs 41 years, on Stribild

Randomised 2:1 to switch from TDF/FTC to E/C/TAF/FTC

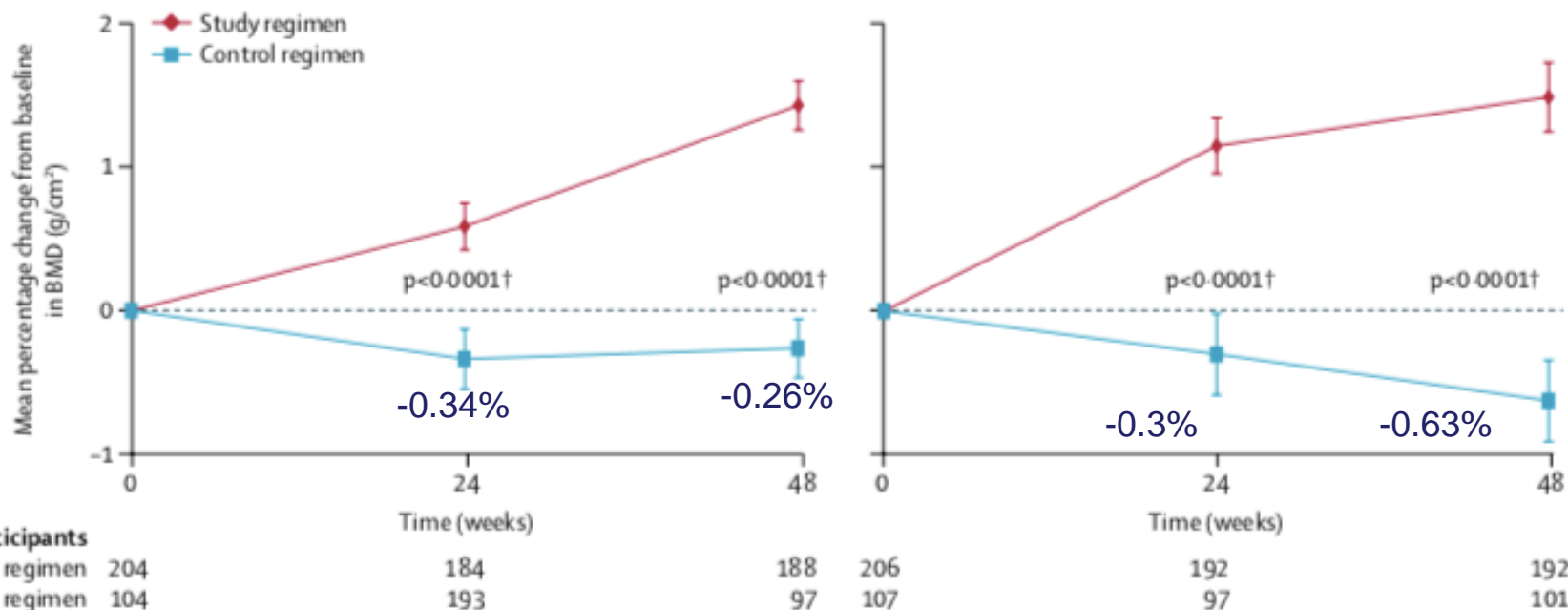


TDF, tenofovir disoproxil fumarate; BMD, bone mineral density



# Long-term TDF in clinical trials

Emerald Study, N= 1,141. An ART containing PI/b + TDF/FTC  
 Randomised 2:1 to remain on PI/b or switch to D/C/F/TAF  
 Age 46 (19-78), 82% male, 6.05 years since first starting ART



# TDF and osteoporotic fractures

French Hospital Database on HIV (FHDH – ANRS C04)

Case: control study. ART naïve, 1<sup>st</sup> fracture between 2000-2010

Matched for age, gender, calendar period and clinical centre

	<b>Controls</b>	<b>Cases</b>	<b>P</b>
N	376	254	
Age (years)	49 (42-57)	49 (42-58)	
Male (%)	65.4	66.9	
Months on ART	68.1 (21.7-123)	78.2 (34.9-119)	0.438
Previous AIDS event (%)	19.7	31.1	0.001

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Case: control study. ART naïve, 1<sup>st</sup> fracture between 2000-2010

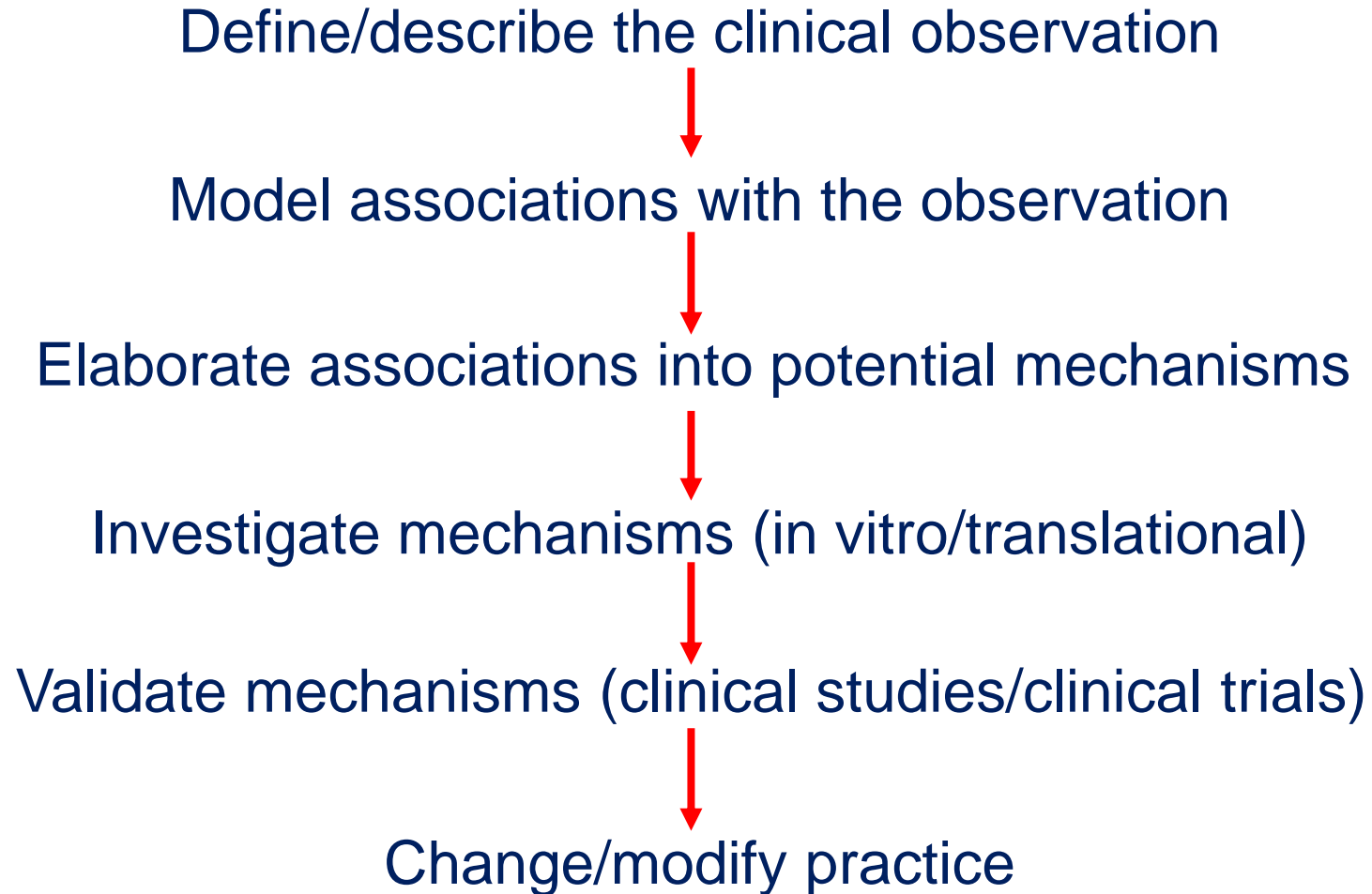
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	Controls	Cases	P
N	376	254	
Age (years)	49 (42-57)	49 (42-58)	
Male (%)	65.4	66.9	
Months on ART	68.1 (21.7-123)	78.2 (34.9-119)	0.438
Previous AIDS event (%)	19.7	31.1	0.001

	Controls	Cases	OR (95% C.I.)	P
Ever exposed to TDF (%)	44.7	48.8	1.16 (0.81, 1.66)	0.426
Duration of exposure (yrs)	1.18	1.21	0.99 (0.91, 1.09)	0.905

# Myths vs. realities – TDF and bone loss



# Co-morbidities– Myths vs Reality



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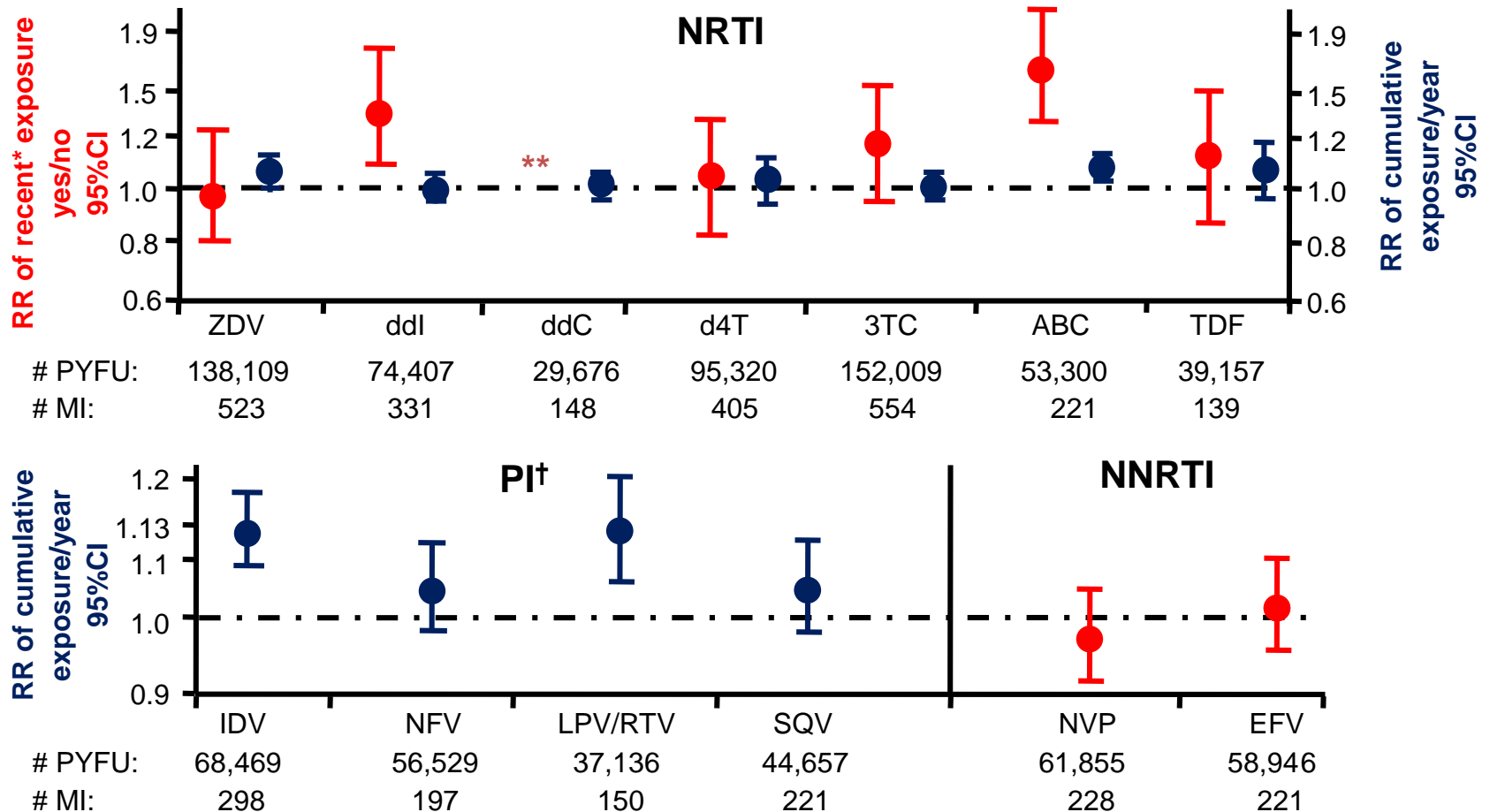
**Myth?**

**Reality?**



# Cardiovascular events: do drugs matter?

D.A.D: MI risk is associated with recent and/or cumulative exposure to specific NRTIs and PIs



\*Current or within past 6 months; †Approximate test for heterogeneity: P=0.02; \*\*not shown owing to low number of patients receiving ddC. CVD=cardiovascular disease; MI=myocardial infarction; RR=relative risk; PYFU=patient years of follow up.

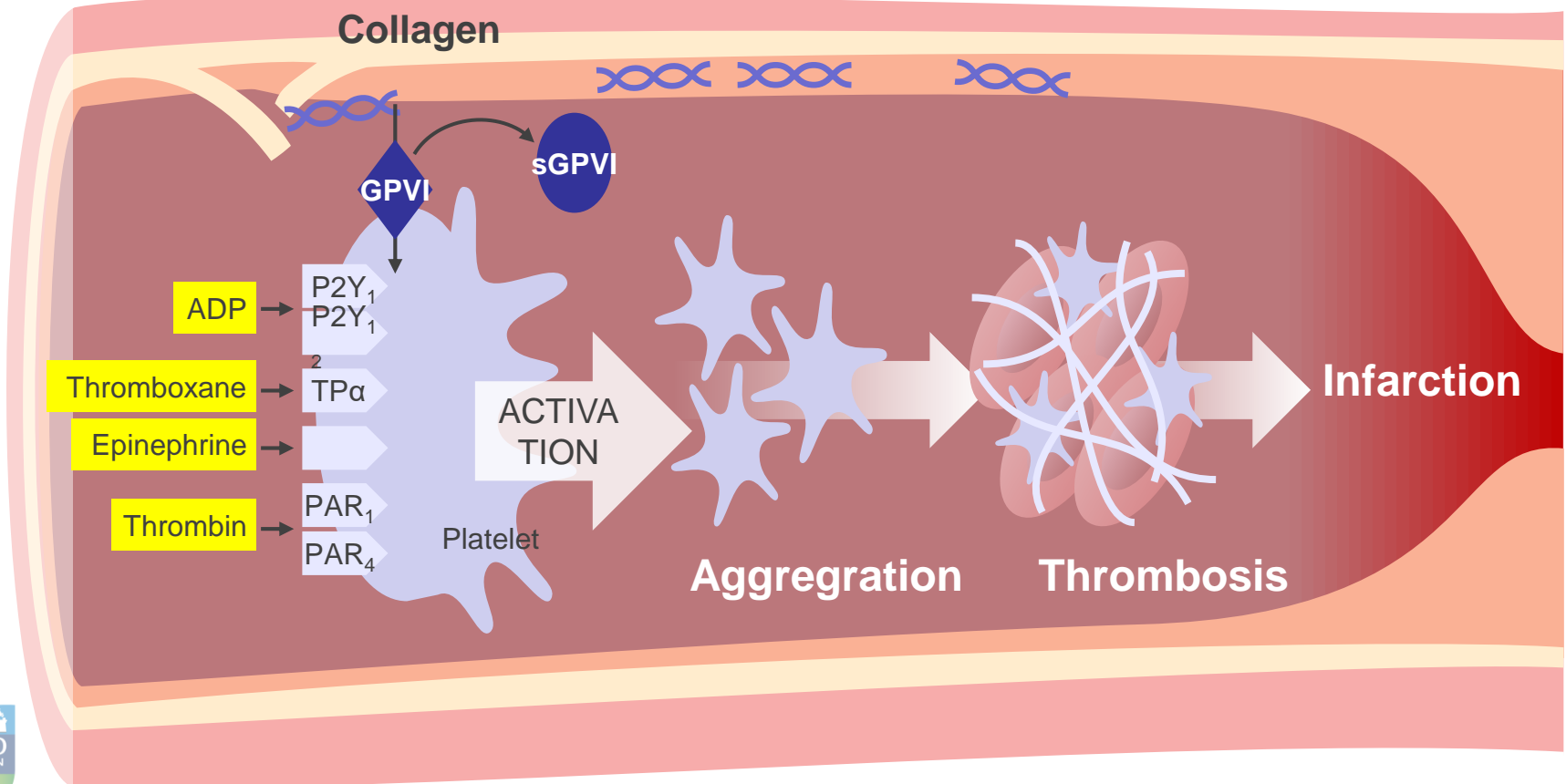
# Platelet activation, thrombosis and MI

Environmental Changes....

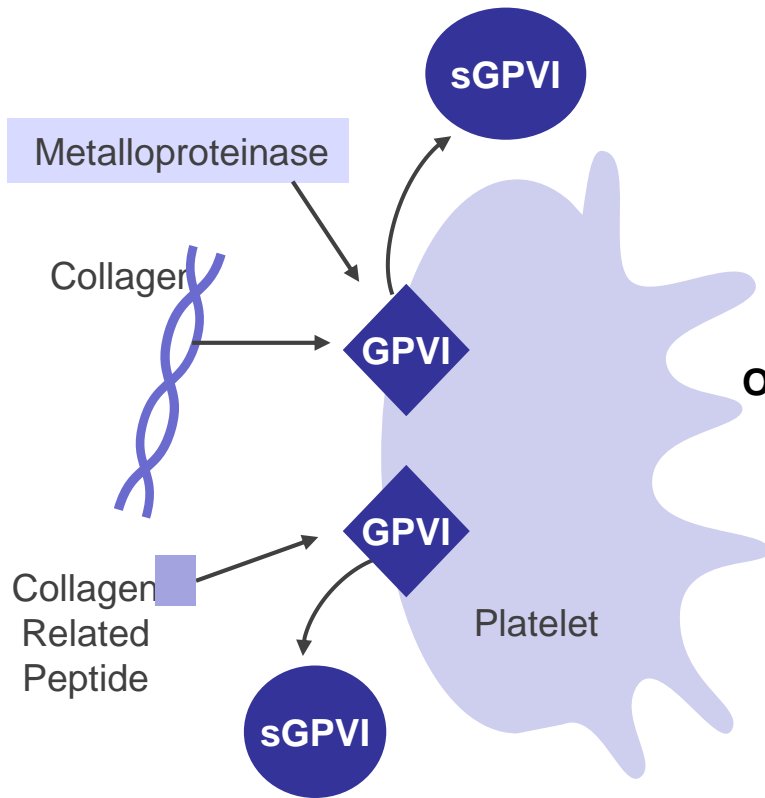
Liver

Inflammation (HIV)

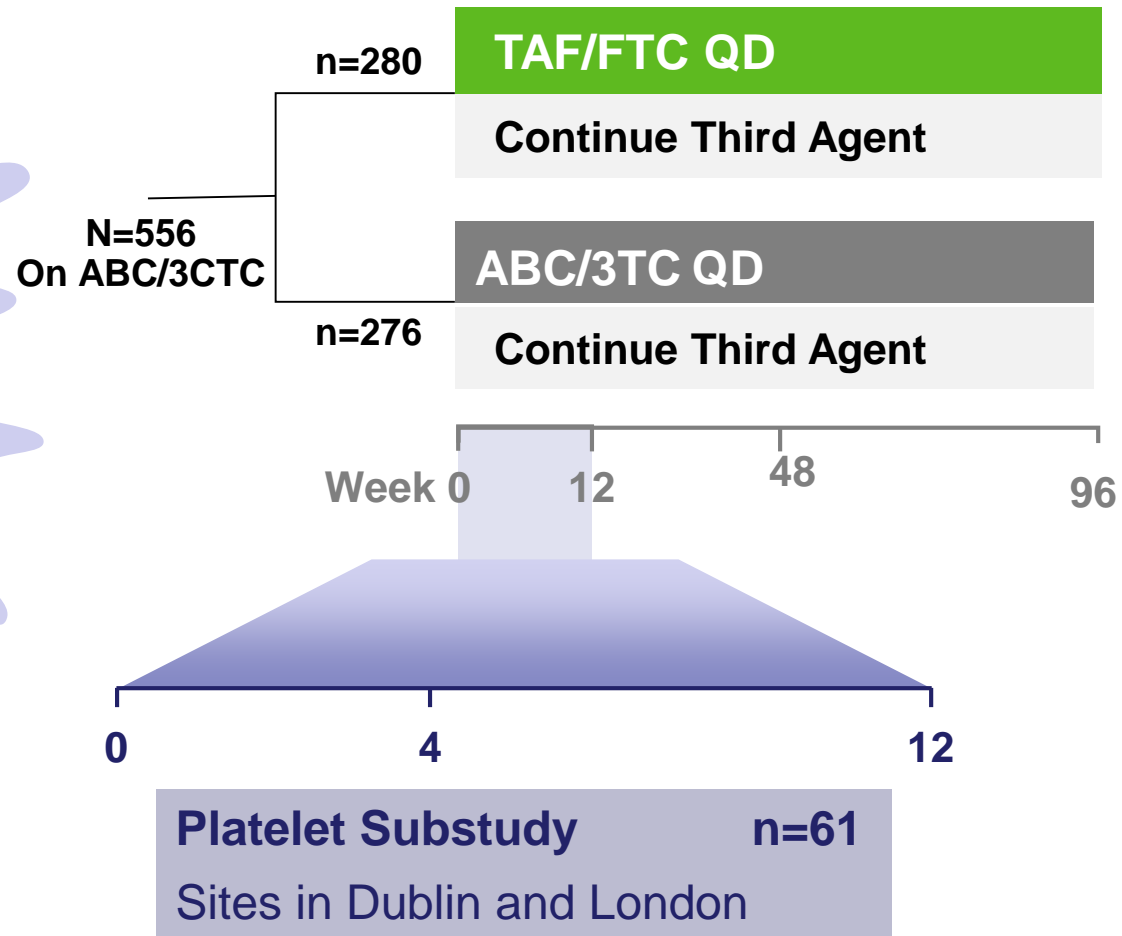
Acute Coronary Syndrome



# GPVI and CVD

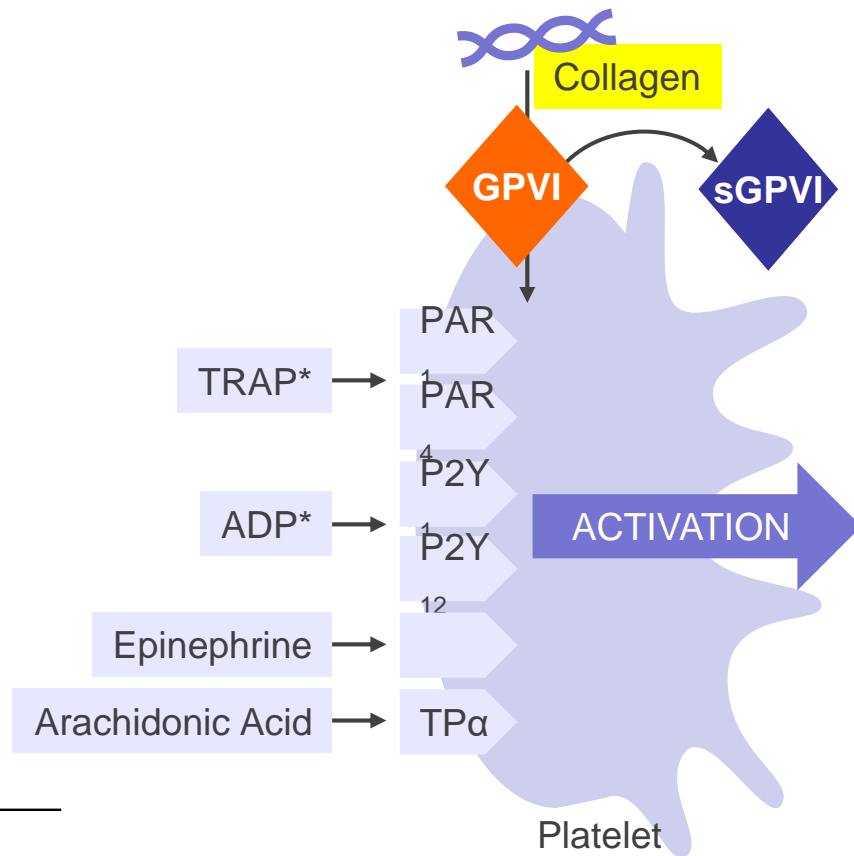
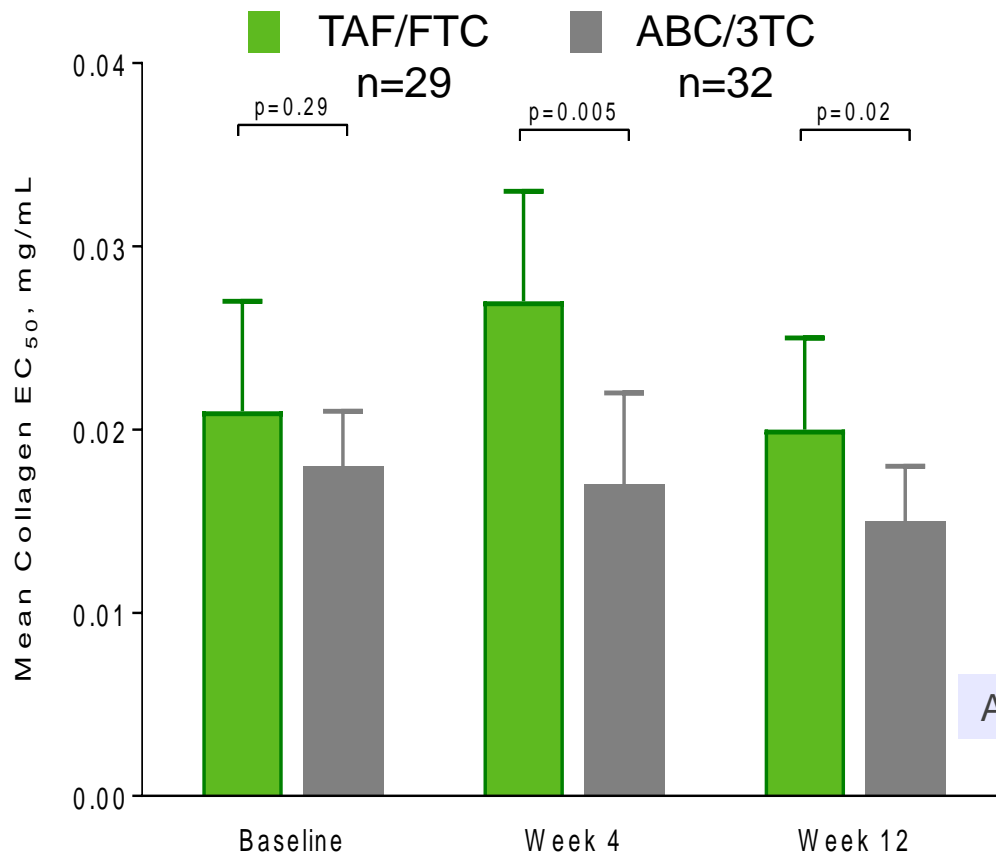


## Study 1717 - Phase 3, randomized, double-blind, active-controlled study





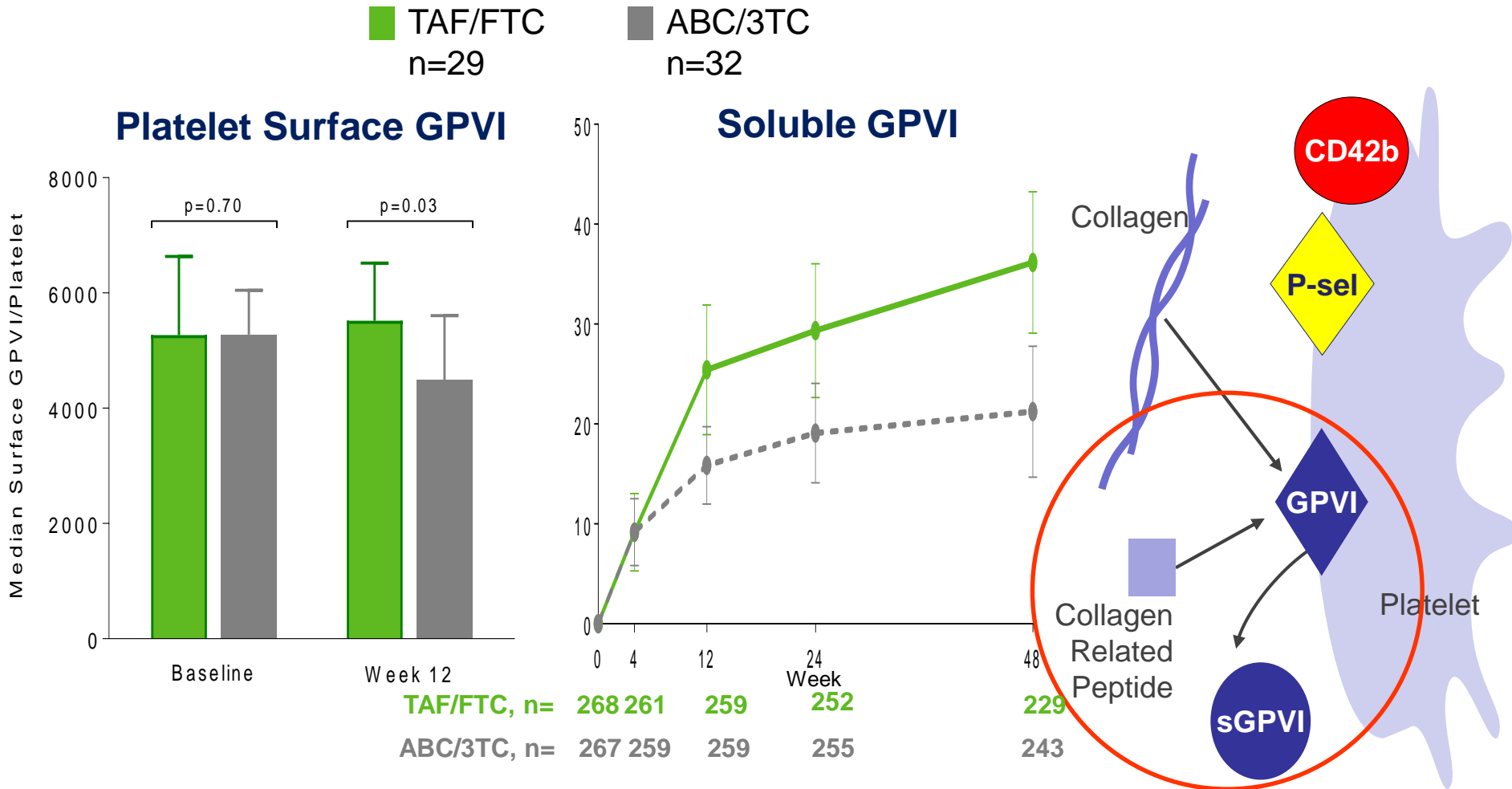
# Platelet reactivity in response to collagen



Higher collagen EC<sub>50</sub> (i.e., less reactive platelets) in TAF/FTC group at both Weeks 4 and 12

Similar results seen with TRAP and ADP but not with Epinephrine or Arachidonic Acid

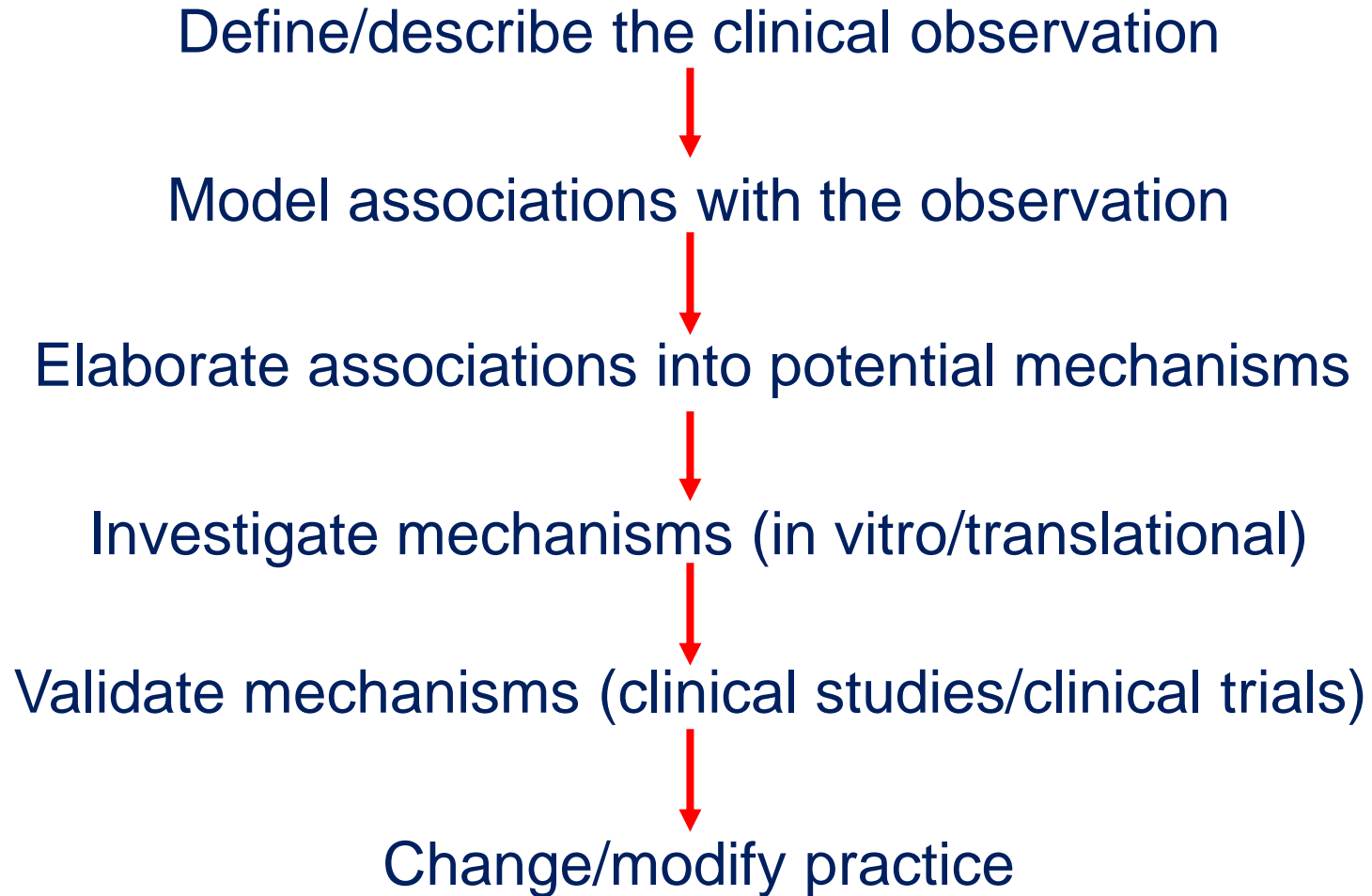
# GPVI and CVD – 1717 platelet sub-study



Higher platelet surface GPVI expression in the TAF/FTC group at week 12

Greater increases in sGPVI expression in the TAF/FTC group to week 48

# Myths vs. realities – ABC and MI



# Summary - myths vs. realities



- Some commonly held beliefs in modern HIV clinical practice do not stand up to scrutiny
- Research is the key to clarity in clinical practice
- Obligation on researchers to report findings consistently
- Never presume we know everything!

*'There are some people so addicted to exaggeration that they can't tell the truth without lying!'*

Josh Billings



# Acknowledgements

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- Dr Willard Tinago
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- Alan Macken
- Bindu Krishnanivas
- Aoife McDermott
- Aoife Lacey

