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# Disfunzione endocrino-metabolica e possibili ricadute d'organo

Una storia cominciata molti anni fa....



*AIDS* 2000, 14: 123-128

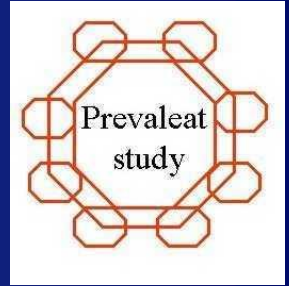
**fast track**

**Maggi P, Serio G, Epifani G, Fiorentino G, Saracino A, Fico C, Perilli F,  
Lillo A, Ferraro S, Gargiulo M, Chirianni A, Angarano G, Pastore G :**

**Premature lesions of the carotid vessels in  
HIV-1-infected patients treated with  
protease inhibitors**



# Results



	Group I	Group II	Controls
	55	47	104
Acquired lesions	29 (52.7%)	7 (14.9%)	7 (6.7%)
IMT	11	4	7
IMT + plaques	16	2	
IMT + kinking	2	1	
Normal findings	25 (45.4%)	40 (85.1)	
Kinking	1		not described

M IMT: 1.2 mm (range 1.01-3.00)

M stenosis: 41.9% (range 15-70)

# Statistical analysis / 3

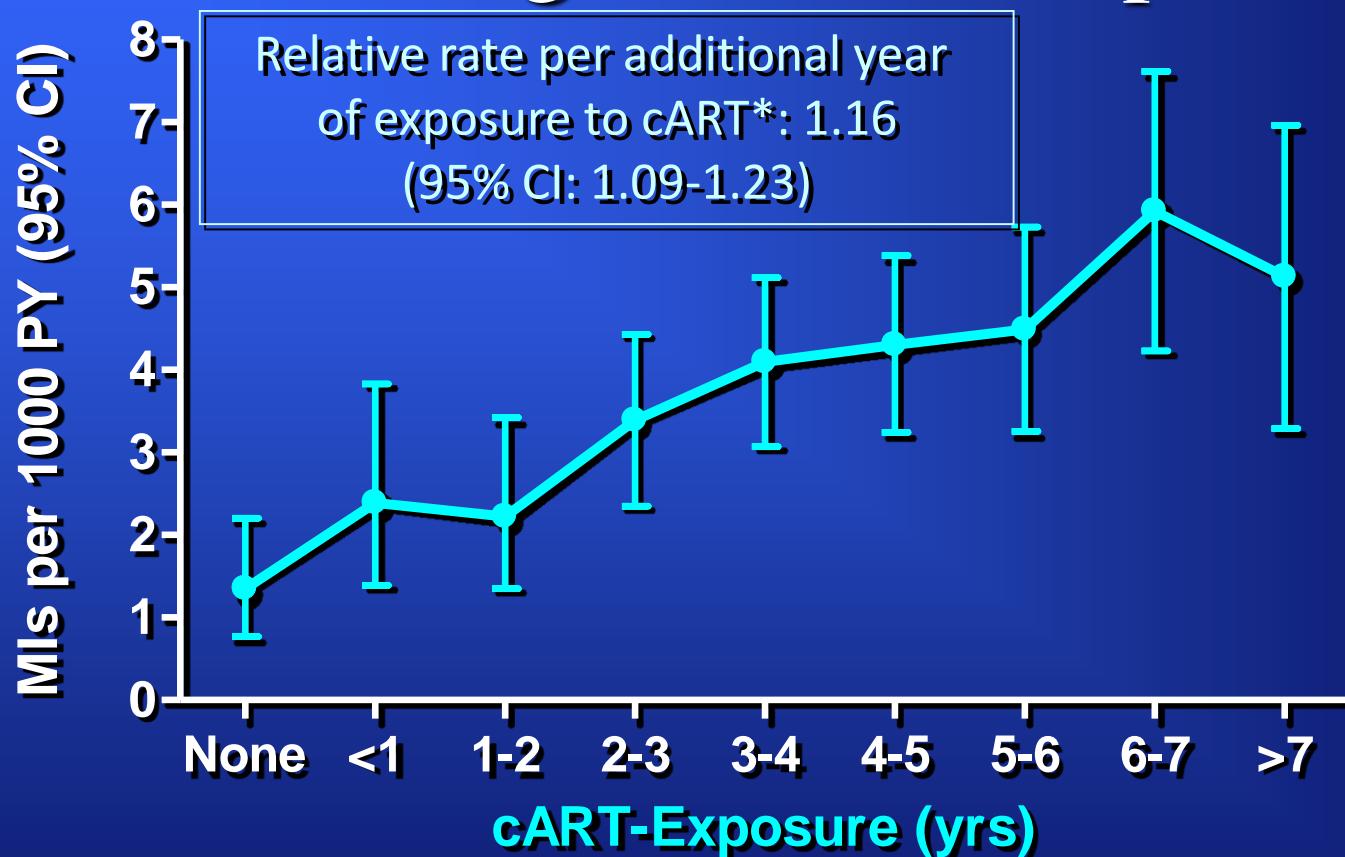
Male sex	<b>p=0.099</b>	$\chi^2$ , 2.71 RR, 2.45 95% CI, 0.826-7.275
Hypercholesterolemia	<b>p=0.085</b>	$\chi^2$ , 2.97
Age	<b>p=0.0321</b>	(lesions +: 38.5; lesions -:35.1, p=0.0321)
Cigarette smoking	<b>p=0.022</b>	$\chi^2$ , 5.27 RR, 2.9 95% CI, 1.2-7.3
Hypertriglyceridemia	<b>p=0.017</b>	$\chi^2$ , 2.71 RR, 2.83 95% CI, 1.91-6.74
$\chi^2$ Mantel Haenzsel	<b>p=0.228;</b>	<b>PI+: p=0.0044</b> $\chi^2$ 8.34
CDC stage	<b>p=0.079</b>	$\chi^2$ , 5.088
group A vs B+C	<b>p=0.011</b>	$\chi^2$ , 5.075 (Brand and Snedecor)
PI-based ARV	<b>p=0.001</b>	$\chi^2$ , 20.839
$\chi^2$ Mantel Haenzsel	<b>PI+: p=0.001</b>	$\chi^2$ , 17.049 RR, 7.9 95% CI, 2.9-21.2

# Studi prospettici: Data Collection on Adverse events of Anti-HIV Drugs

## D:A:D: Study

- Prospective multinational cohort study initiated in 1999 (Europe, USA, Australia)
- 11 cohorts; 188 clinics; 21 countries
- 23,468 patients
- 94,469 person years of follow up

# Incidence of Myocardial Infarction according to **cART** Exposure



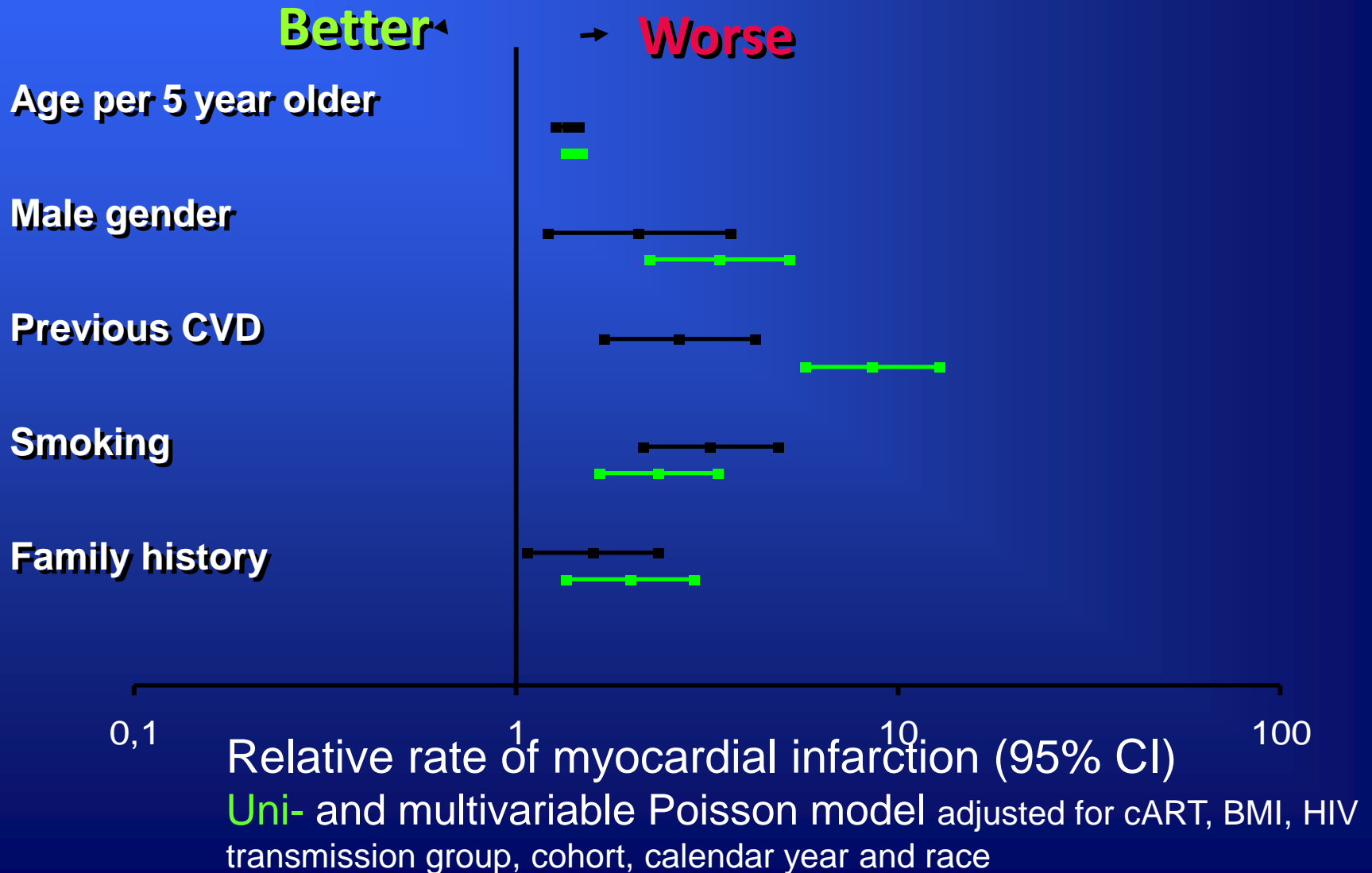
Events	16	17	20	41	61	62	51	47	30	
PYFU	11815	7105	9027	12098	14892	14394	11351	7935	5853	

*Total*

345  
94469

\*: Adjusted for conventional risk factors not influenced by cART

# Other predictors – not influenced by cART - of MI in D:A:D





# Il paradigma regge ancora?



# Multimorbidity and risk of death differs by gender in people living with HIV in the Netherlands - *the ATHENA cohort study*

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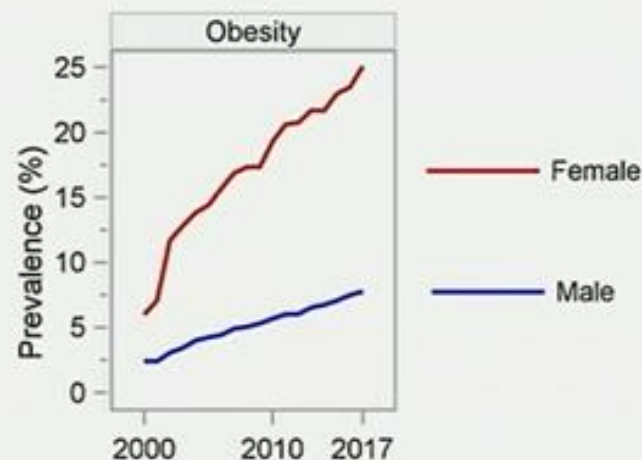
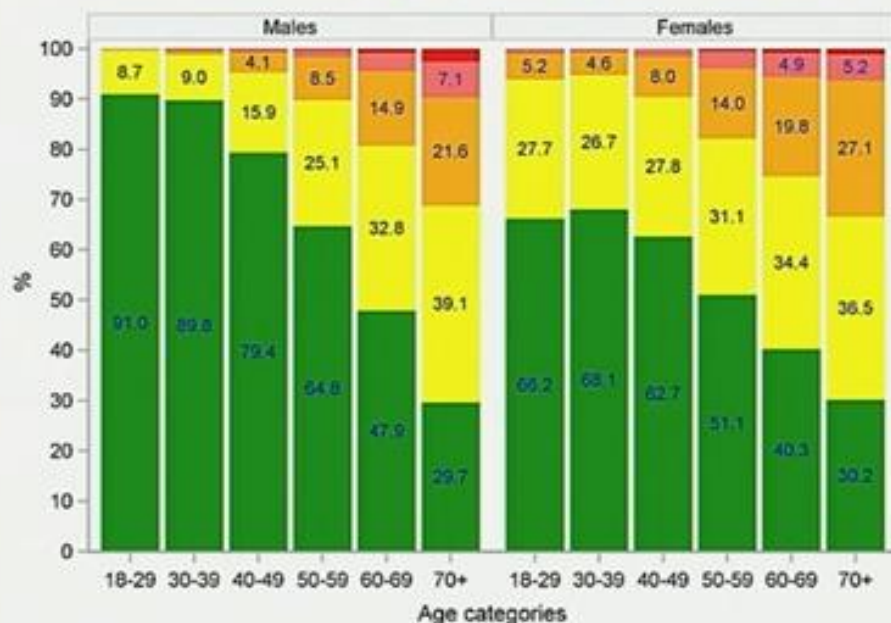
*Ferdinand Wit<sup>1,2</sup>, Marc van der Valk<sup>2</sup>, Jet Gisolf<sup>3</sup>, Wouter Bierman<sup>4</sup>, Peter Reiss<sup>1,2</sup> on behalf of the ATHENA HIV observational cohort study*

1. *Stichting HIV Monitoring, Amsterdam*
2. *Academic Medical Center, Amsterdam*
3. *Rijnstate Hospital, Arnhem*
4. *University Medical Center Groningen, Groningen  
The Netherlands*

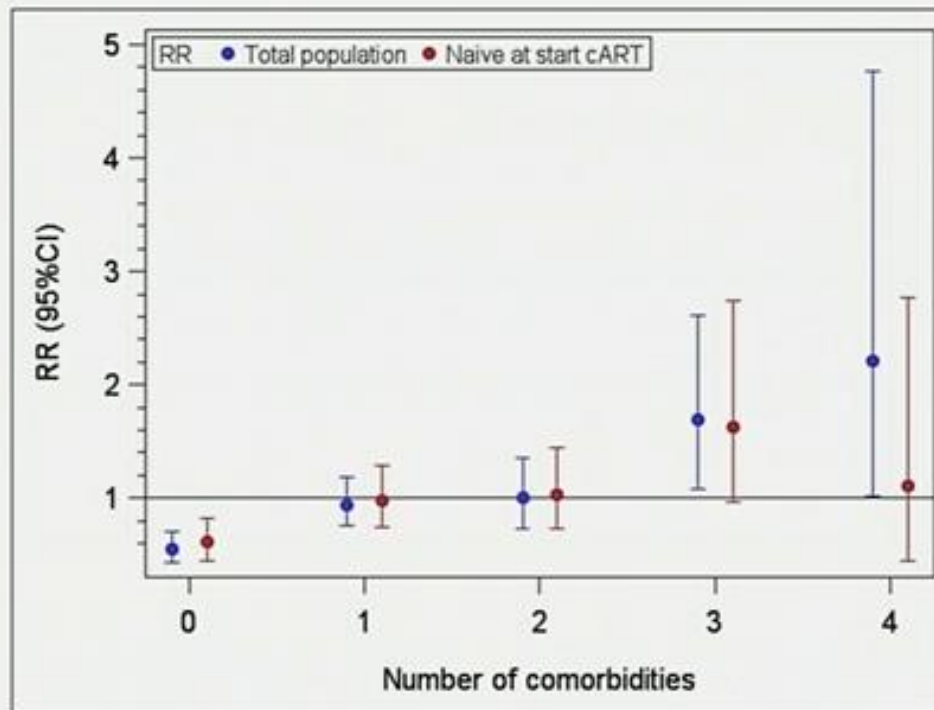


# Multimorbidity and crude mortality rates

Multimorbidity by age and gender in 2017



## Multimorbidity and mortality: women relative to men



	Total population	NRTI-pretreated excluded
0	0.55 (0.43-0.70)	0.61 (0.45-0.83)
1	0.94 (0.76-1.18)	0.98 (0.74-1.29)
2	1.00 (0.73-1.36)	1.03 (0.74-1.45)
3	1.69 (1.09-2.61)	1.63 (0.97-2.74)
4	2.21 (1.02-4.77)	1.11 (0.44-2.77)

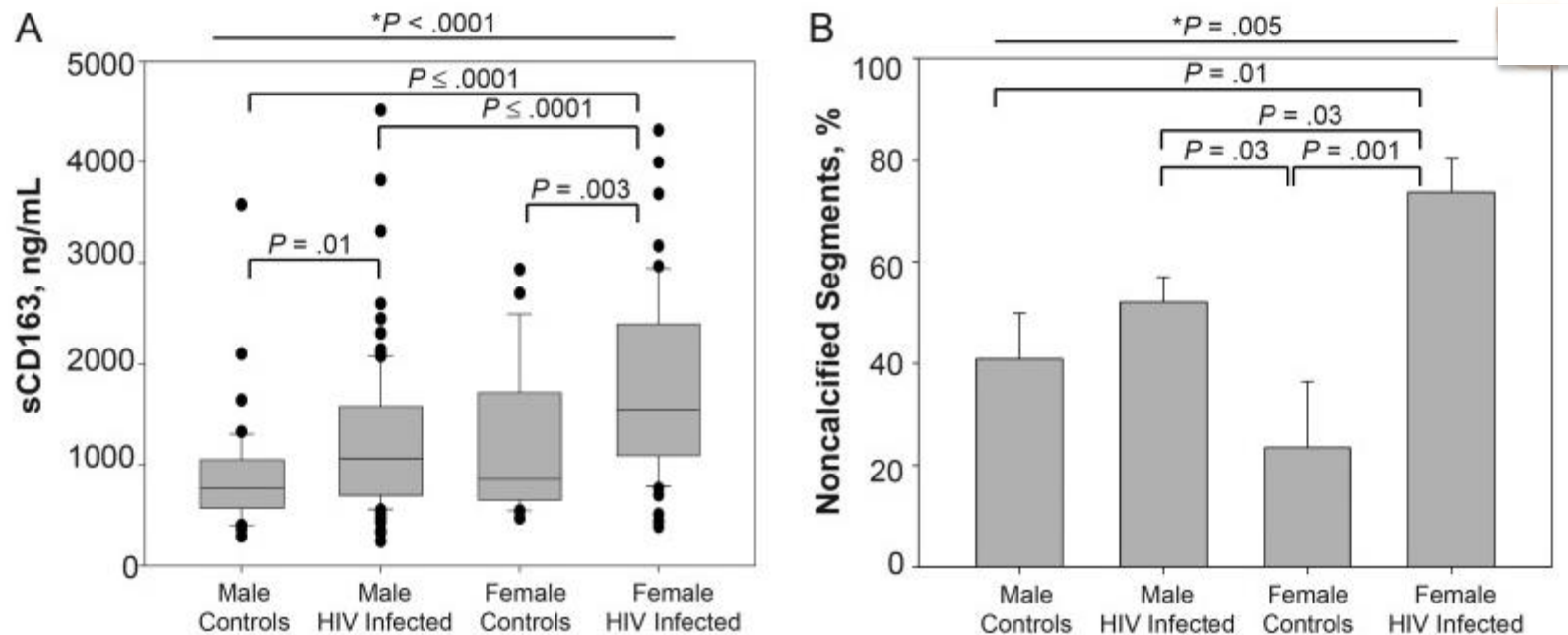
## Conclusions

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- Women have more multimorbidity at younger ages, but very similar rates after 50
  - This is mainly driven by obesity
- Multimorbidity is independently and strongly associated with mortality
- All-cause mortality is lower in women in general, but is more strongly impacted by multimorbidity than in men
- Excess risk in women with more extensive multimorbidity was most pronounced in those with prior exposure to mono and dual nucleoside analogues
  - Cave: association  $\neq$  causation



K.V. Fitch, S. Srinivasa, S. Abbara, T.E. Asher, G. Silvestri, S. Rao, *et al.*  
**Noncalcified coronary atherosclerotic plaque and immune activation in  
HIV-infected women**  
*J. Infect. Dis.*, 208 (2013), pp. 1737-1746



Young, asymptomatic, HIV-infected women, demonstrate increased noncalcified coronary plaque and increased immune activation, particularly monocyte activation. Independent effects of sex, HIV status, and aging on immune activation may contribute to cardiovascular disease in this population.

#517

# GENDER AND COINFECTIONS CONTRIBUTE TO IMMUNE ACTIVATION IN TREATED HIV INFECTION

Gowoon Son



Taken all together, **we demonstrate the contribution of gender to immune activation in virologically suppressed** individuals infected with HIV on cART (<50 copies/ml).

Furthermore, elevated immune activation markers in co- infected individuals reveal that co-infections contribute to immune activation.

## Median Values of Cytokines (pg/mL)

	Male	Female	p-value
TNF-alpha	1.948	1.989	0.6527
IL-6	0.7493	1.04	0.1404
CXCL10/IP-10	58.19	70.45	<0.0001
IL-10	0.36	0.36	0.318
CCL2/ MCP-1	86.38	90.1	0.2474
IL-1beta	1.75	1.75	0.6515
IFN-gamma	5.13	5.13	0.0711
MIP-1beta	147.9	145.8	0.5361
CD163	232233	252025	0.0001
CD25/ IL-2Ra	337.9	383.3	0.0012
CXCL9	49.98	49.98	0.5982
TNF RII	2174	2315	0.1669
IFN-alpha	0	0	0.5603



#1068

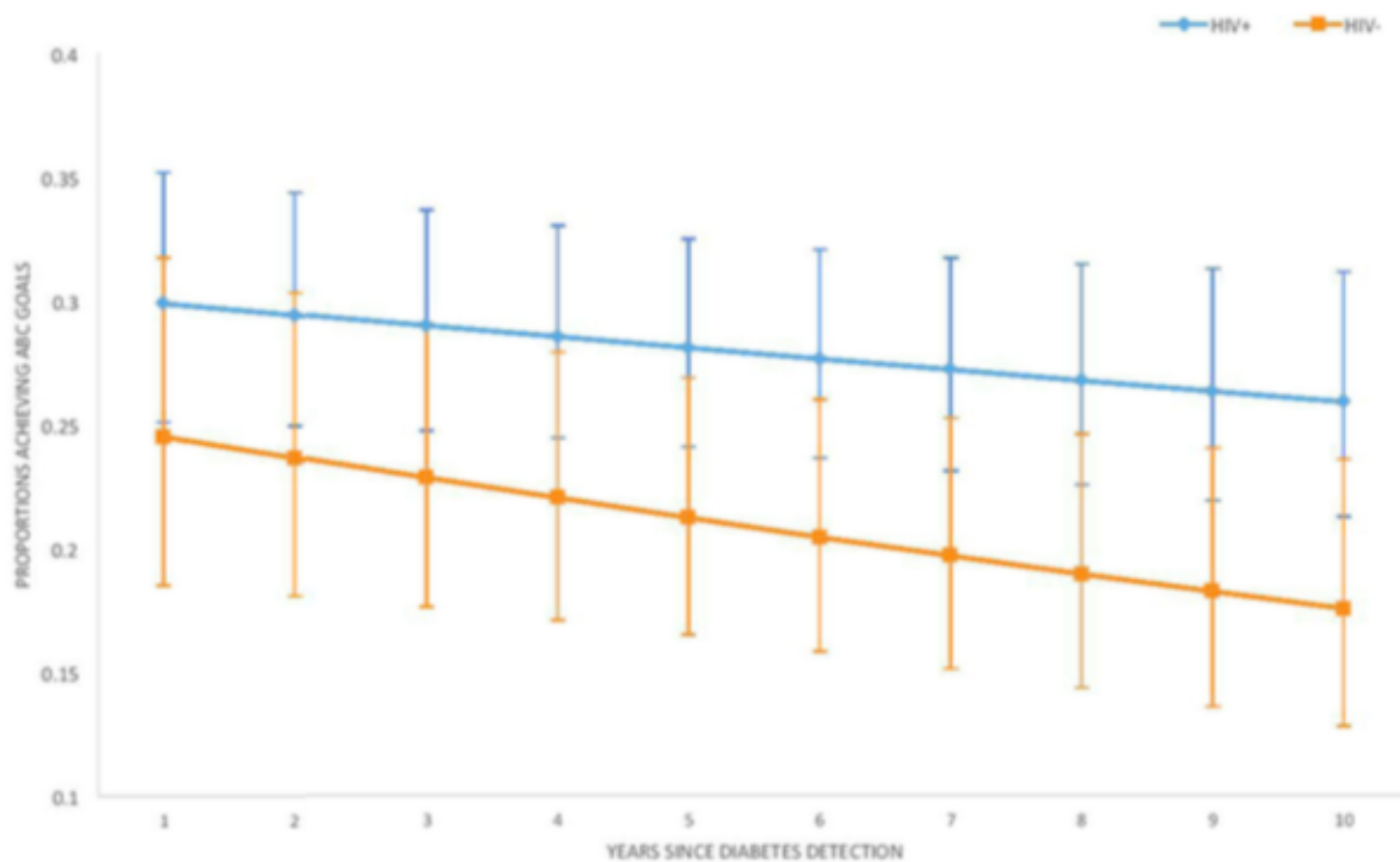
# POOR DIABETES CONTROL IN HIV+ AND HIV- WOMEN: OPPORTUNITIES FOR INTERVENTION

Karla I . Galaviz



**We noted large and growing gaps in DM care goal achievement in both HIV+ and HIV-women.** Opportunities to improve DM care are numerous; aggressive DM management interventions among HIV+ and HIV- women are needed.

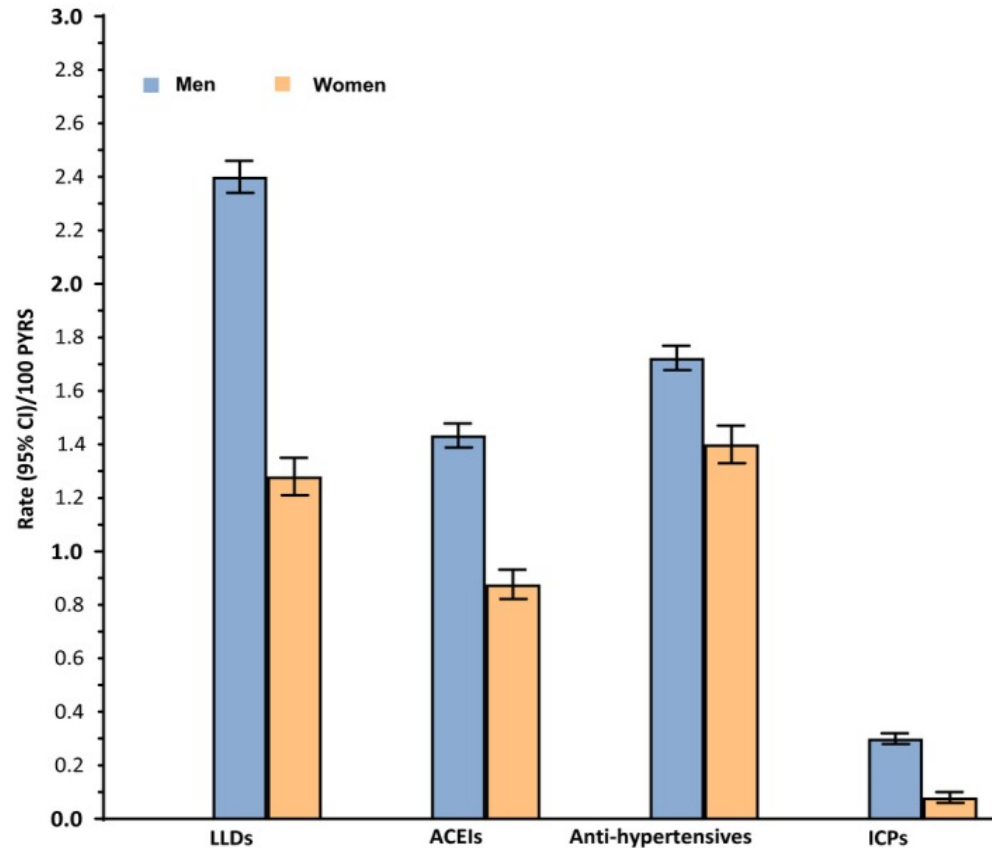
**Figure.** Adjusted probability of achieving ABC goals by HIV status.



# Gender differences in HIV-positive persons in use of cardiovascular disease-related interventions: D:A:D study

J. Int. AIDS Soc., 17

**JIAS** JOURNAL OF THE  
INTERNATIONAL AIDS SOCIETY  
Open Access



B.M. Victor, V. Teal, L. Ahedor, D.G. Karalis

## Gender differences in achieving optimal lipid goals in patients with coronary artery disease

Am. J. Cardiol., 113 (2014), pp. 1611-1615

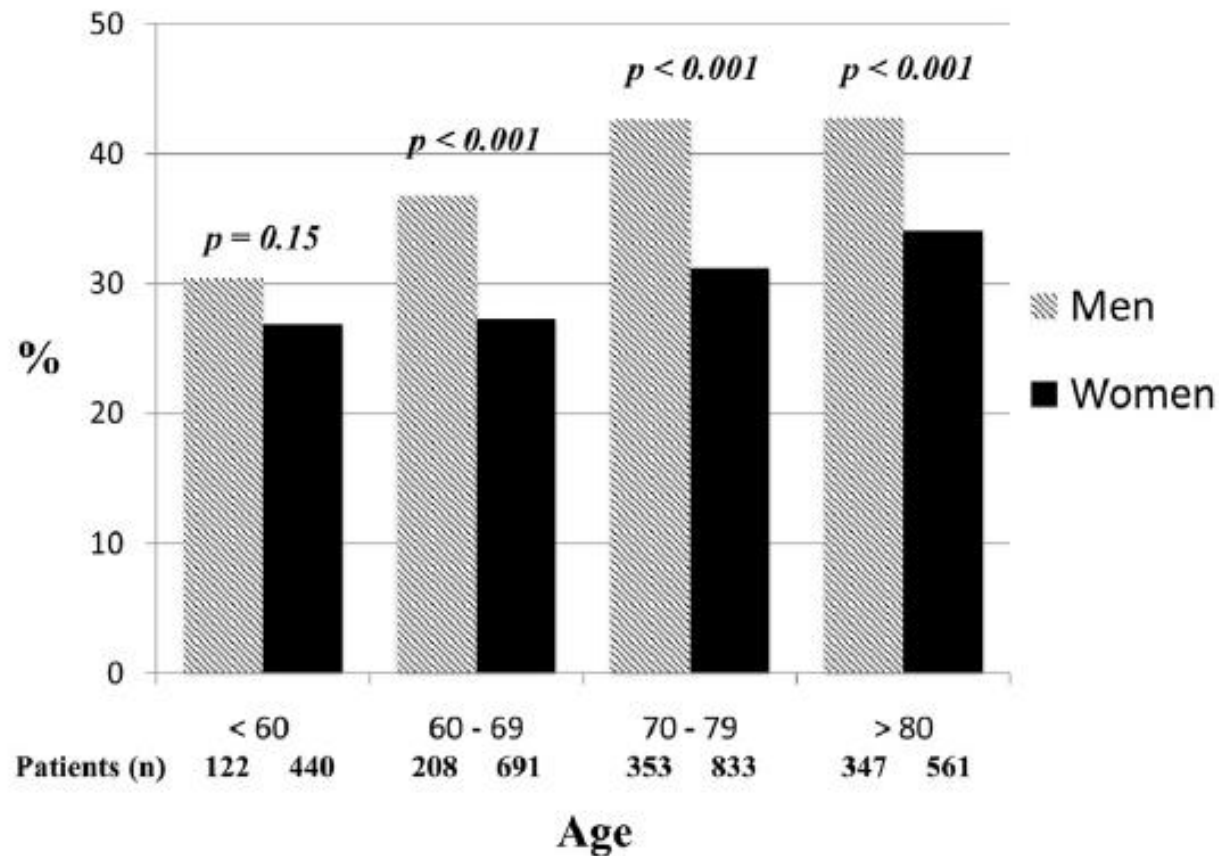
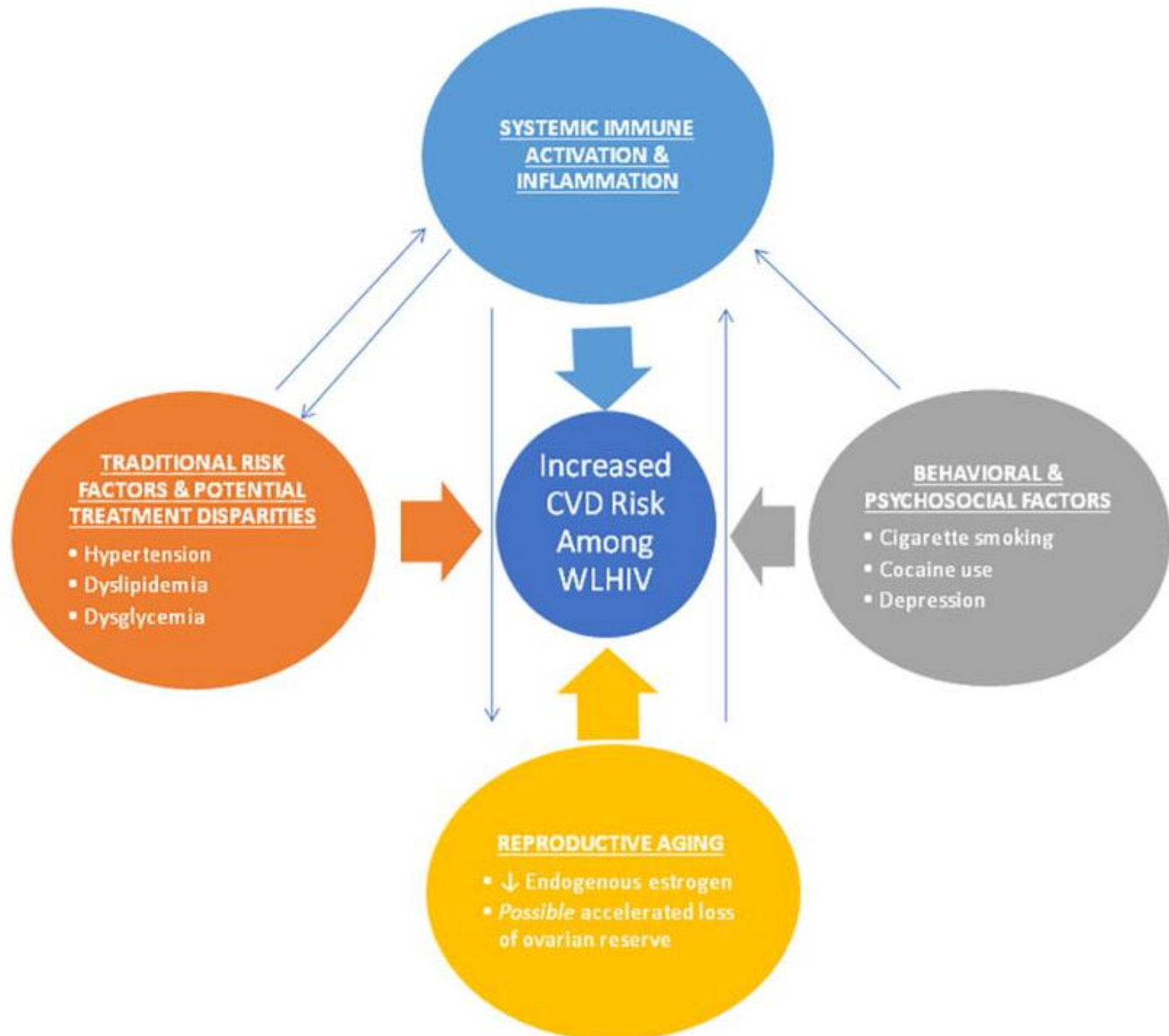


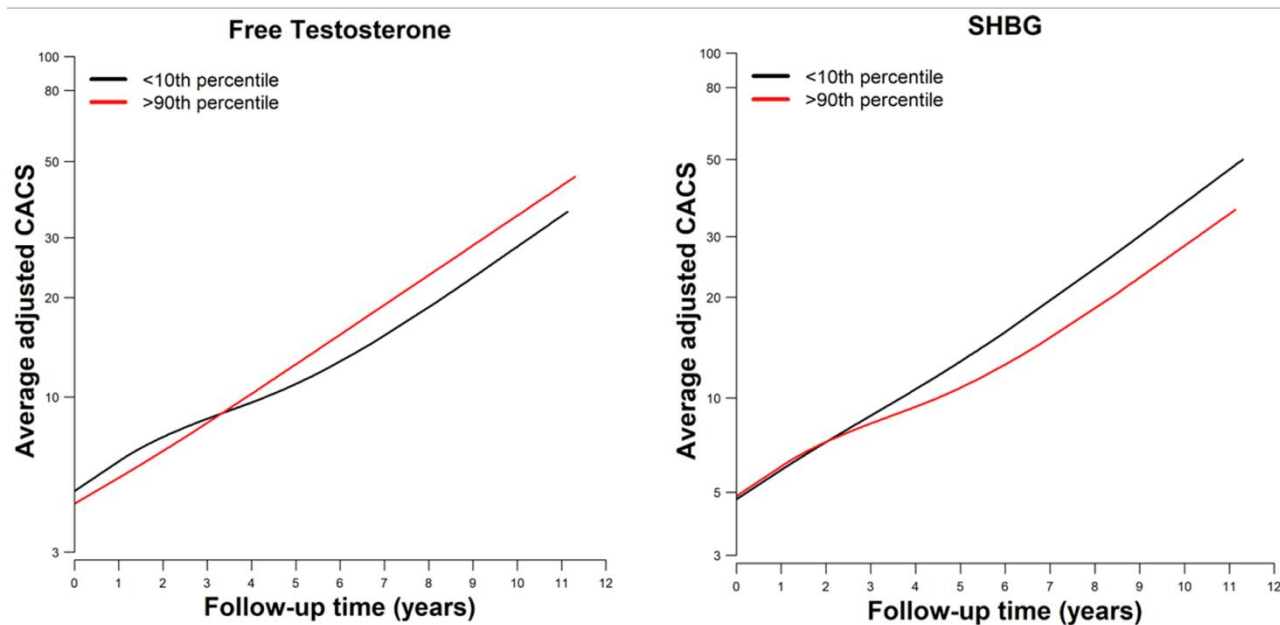
Figure 1. Likelihood of achieving an LDL cholesterol goal of <70 mg/dl in men and women based on age.



Subramanya V.

# Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA).

J Cardiovasc Comput Tomogr. 2019 Jan - Feb;13(1):41-47



**A more androgenic hormone profile** of higher free testosterone and lower SHBG **is associated with a greater CAC progression** up to 10-years in post-menopausal women. Sex hormone levels may help identify women at increased risk for CVD who may benefit from additional risk-reducing strategies

G.A. Calvet, B.G.J. Grinsztejn, M.S.B. Quintana, M. Derrico, E.M. Jalil, Cytryn, et al. Predictors of early menopause in HIV-infected women: a prospective cohort study  
Am. J. Obstet. Gynecol., 212 (765) (2015), pp. 1-13

**Early natural menopause was frequent among the HIV-infected women.**

In addition to **menarche <11 yo** and **cigarette smoking**, which are menopausal factors among women in general, **HIV-related immunodeficiency** and **chronic HCV** were additional predictors for an earlier age at natural menopause.

# MANAGEMENT OF MENOPAUSE IN HIV POSITIVE WOMEN

**Janice Rymer**

**MD FRCOG FRANZCOG FHEA**

**Vice President (Education) RCOG**

**Professor of Gynaecology**

**Guy's and St Thomas' Hospitals NHS Foundation Trust**

**King's College London School of Medicine**



# Menopause

## Full guideline

*Clinical Guideline*

*Methods, evidence and recommendations*

*23 October 2015*

*Final*

*Commissioned by the National Institute for  
Health and Care Excellence*

# Regimens



The diagram illustrates three hormone therapy regimens using horizontal bars. The top bar is entirely blue and labeled 'Oestrogen' and 'Unopposed oestrogen'. The middle bar is divided into a blue section on the left and a purple section on the right, labeled 'Oestrogen' and 'Progestogen' respectively, and 'Cyclical or Sequential'. The bottom bar is also divided into blue and purple sections, labeled 'Oestrogen' and 'Progestogen' respectively, and 'Continuous combined'.

Oestrogen

Unopposed oestrogen

Progestogen

Cyclical or Sequential

Continuous combined

# INI e weight gain



# ***Raltegravir is Associated with Greater Abdominal Fat Increases after Antiretroviral Therapy Initiation Compared to Protease Inhibitors***

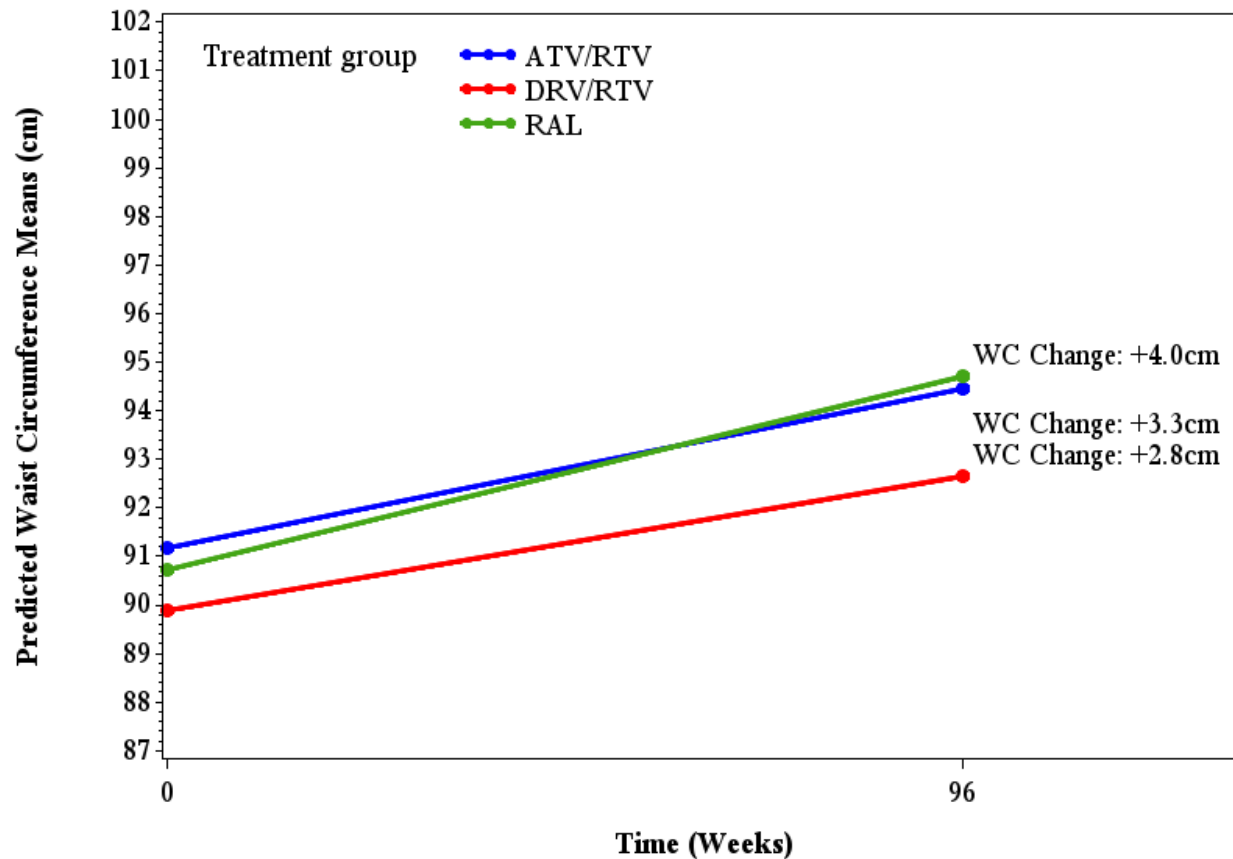
P Bhagwat, I Ofotokun, GA McComsey, TT Brown, C Moser,  
CA Sugar, JS Currier

September 12, 2016

18th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV

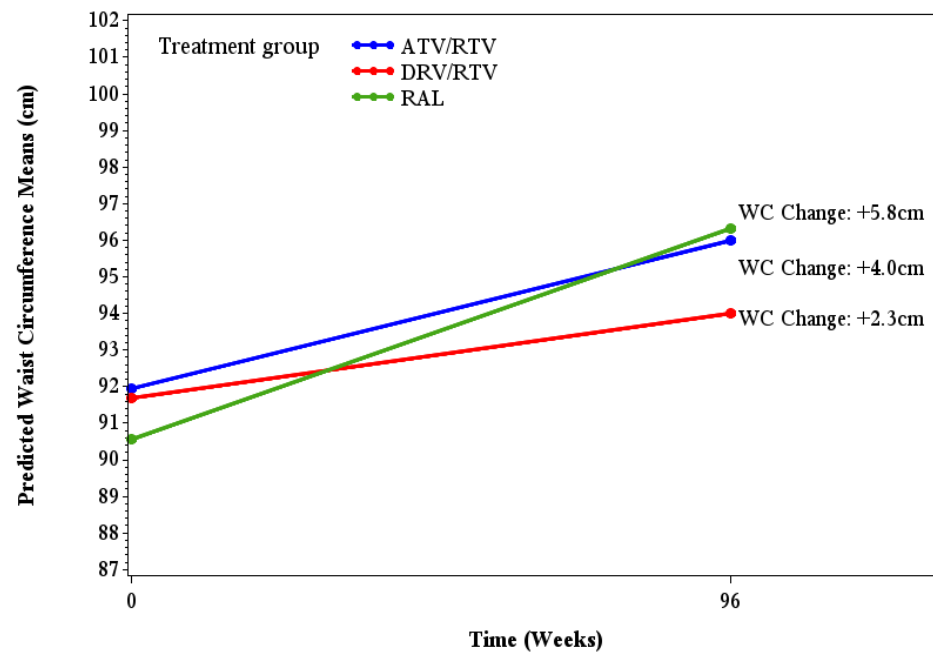
# Results: Overall Treatment Differences

Overall:  
WC Over 96 Weeks by Treatment Group

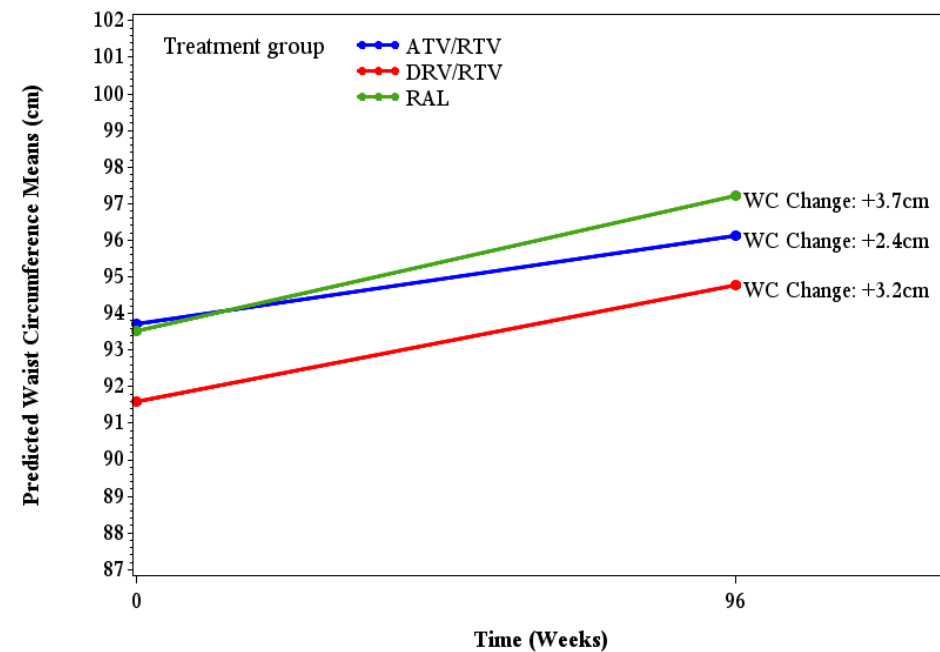


# Results: Modification by Race/Ethnicity

Black Non-Hispanic:  
WC Over 96 Weeks by Treatment Group



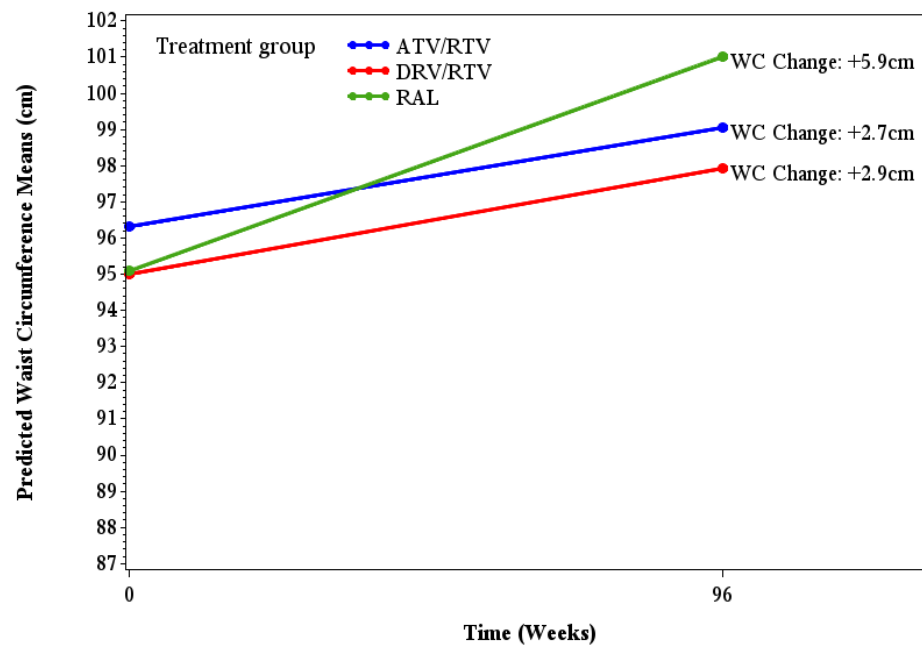
Other Race/Ethnicity:  
WC Over 96 Weeks by Treatment Group



# Results: Modification by Sex

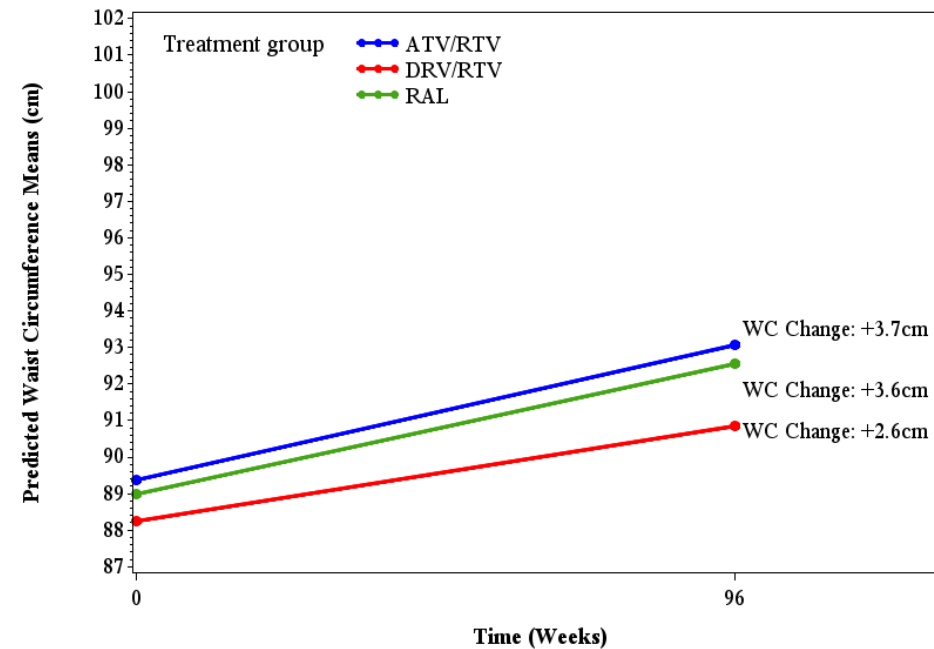
Females:

WC Over 96 Weeks by Treatment Group



Males:

WC Over 96 Weeks by Treatment Group



## WEIGHT GAIN DURING ART

Poster	Title	Author
669	RISK FACTORS FOR EXCESS WEIGHT GAIN FOLLOWING SWITCH TO INTEGRASE INHIBITOR–BASED ART	Jane A. O’Halloran
670	GREATER WEIGHT GAIN AMONG TREATMENT-NAIVE PERSONS STARTING INTEGRASE INHIBITORS	Kassem Bourgi
671	WEIGHT GAIN DURING TREATMENT AMONG 3,468 TREATMENTEXPERIENCED ADULTS WITH HIV	Grace A. McComsey
672	INTEGRASE STRAND TRANSFER INHIBITORS ARE ASSOCIATED WITH WEIGHT GAIN IN WOMEN	Anne M. Kerchberger
673	THE IMPACT OF WEIGHT GAIN AND SEX ON IMMUNE ACTIVATION FOLLOWING INITIATION OF ART	Sara H. Bares
674	Weight Gain among Virally Suppressed Persons who Switch to INSTI-Based ART, The HIV Outpatient Study	FJ Palella
675	Differential BMI changes following PI and IN-STI based ART initiation by sex and race	R Bedimo





#669

## RISK FACTORS FOR EXCESS WEIGHT GAIN FOLLOWING SWITCH TO INTEGRASE INHIBITOR- BASED ART



Jordan E . Lake

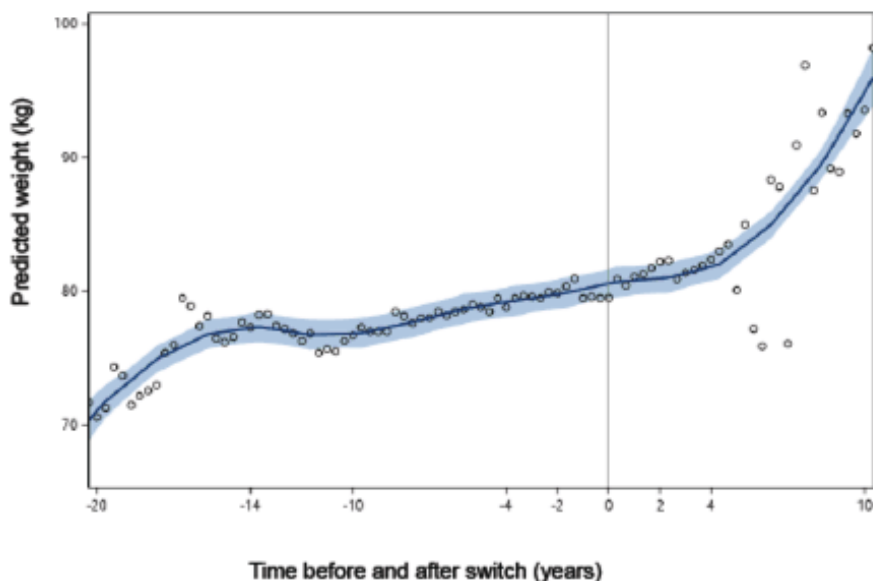
We assessed weight gain following switch to INSTI-based ART among AIDS Clinical Trials Group (ACTG) participants in ACTG protocols A5001 and A5322

Yearly weight gain increased following switch to INSTI. These increases were particularly significant for **women, blacks and persons age  $\geq 60$ .**

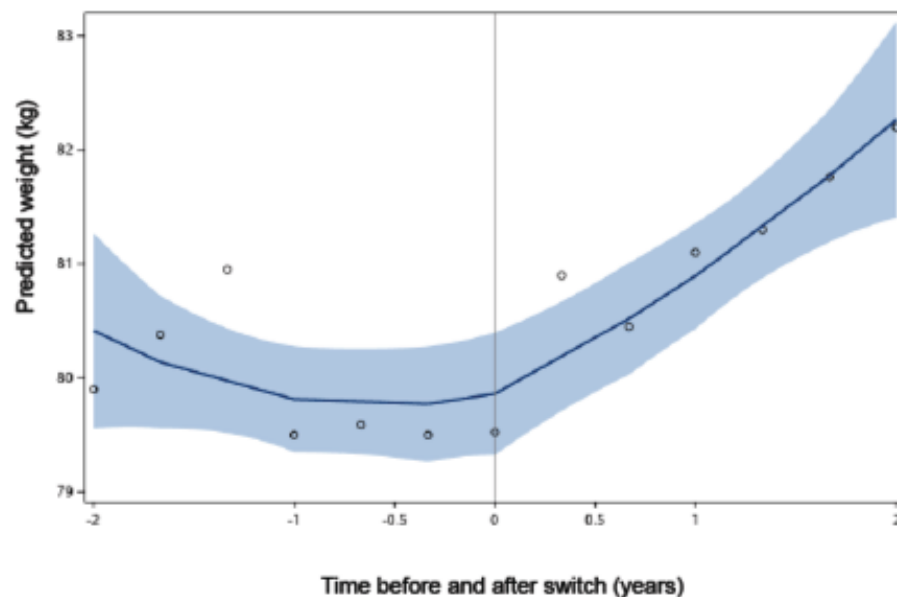
When compared to pre-switch weight changes on stable suppressive ART and given concomitant increases in waist circumference, these data suggest increases in weight/fat mass greater than expected for age. The cardiometabolic implications of increased weight gain following switch to INSTI need to be established.

# Change in weight before and after switch to INSTIs (n= 691, HIV-RNA<200c/ml)

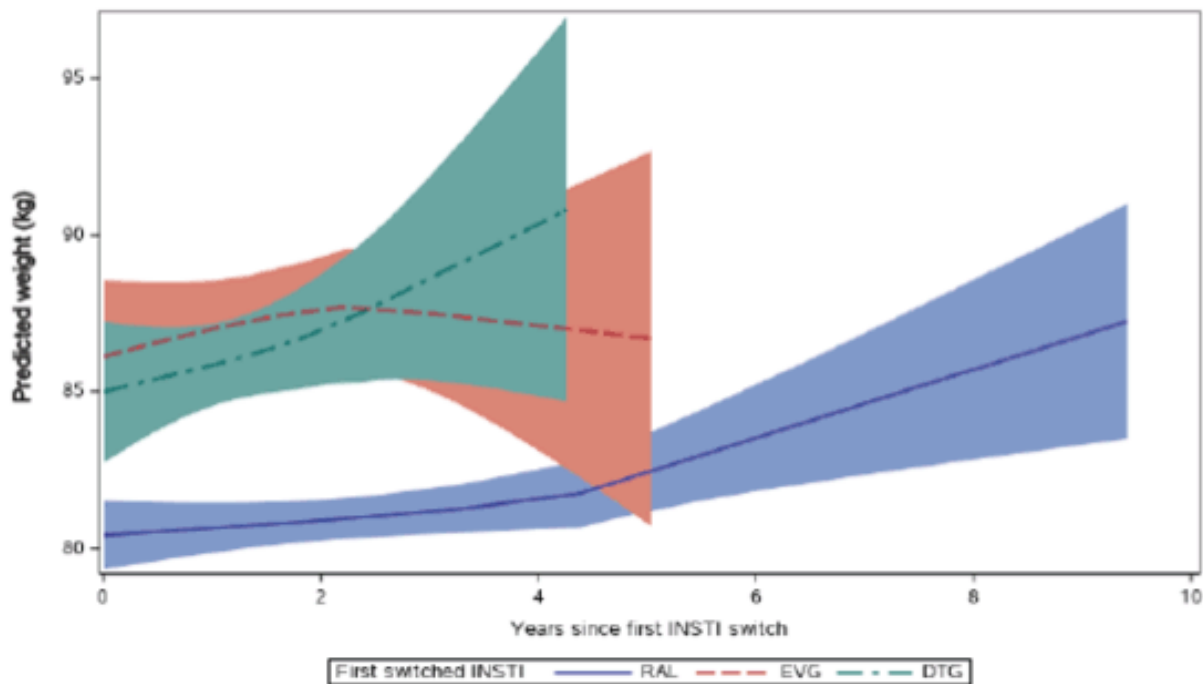
Total Duration of follow-up (includes ART initiation)



Two years of follow-up before and after switch



# Weight gain pre/post-switch to INSTIs by agent



	DTG (n=198)	EVG (n=204)	RAL (n=289)
Pre-INSTI	0.2 (0.11)	0.5 (0.008)	0.5 ( $<0.0001$ )
Post-INSTI	1.3 ( $<0.0001$ )	0.9 ( $<0.0001$ )	0.3 (0.045)
Pre-post difference	1.0 (0.0009)	0.5 (0.11)	-0.2 (0.37)
kg/year (p value)			
DTG=dolutegravir, EVG=elvitegravir, RAL=raltegravir			

# Weight change in Kg/Year (p value) for 2 years before and after switch to INSTIs (n=691)

## Adjusted annual rate of weight change by sex, race, age and BMI at switch

	Black Women	White Women	Black Men	White Men	Women age ≤40	Women Age ≥60	Men age ≤40	Men Age ≥60	Women ≥30 kg/m <sup>2</sup>
Pre-INSTI	0.4 (0.08)	0.6 (0.03)	0.4 (0.02)	0.4 ( $<0.0001$ )	1.5 (0.01)	-0.2 (0.61)	0.8 (0.009)	0.1 (0.46)	0.2 (0.54)
Post-INSTI	1.3 ( $<0.0001$ )	2.0 ( $<0.0001$ )	1.0 (0.002)	0.2 (0.09)	-1.0 (0.17)	1.8 (0.0005)	-0.1 (0.88)	0.9 (0.0008)	1.9 ( $<0.0001$ )
Pre-post Difference	0.9 (0.04)	1.4 (0.02)	0.6 (0.11)	-0.2 (0.38)	-2.5 (0.02)	2.0 (0.008)	-0.9 (0.20)	0.8 (0.04)	1.7 (0.002)

#671

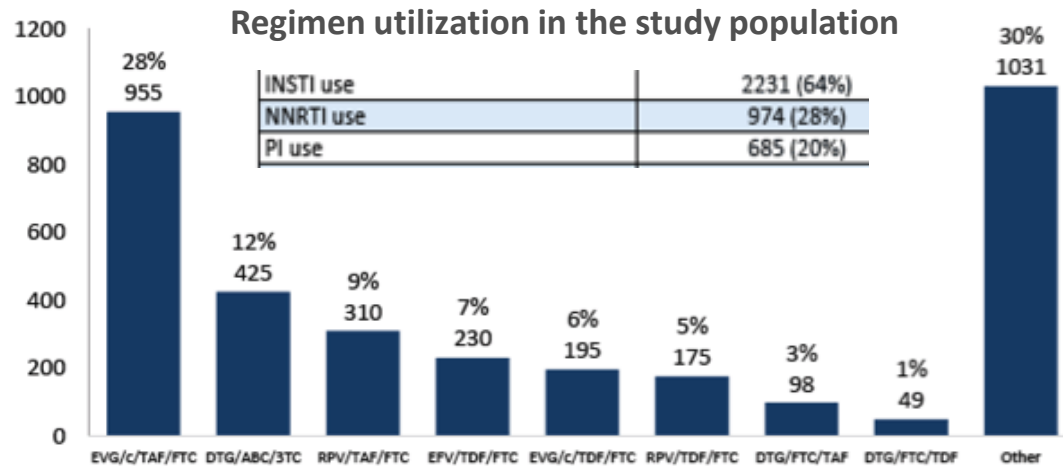
## WEIGHT GAIN DURING TREATMENT AMONG 3,468 TREATMENT- EXPERIENCED ADULTS WITH HIV

Grace A . McComsey



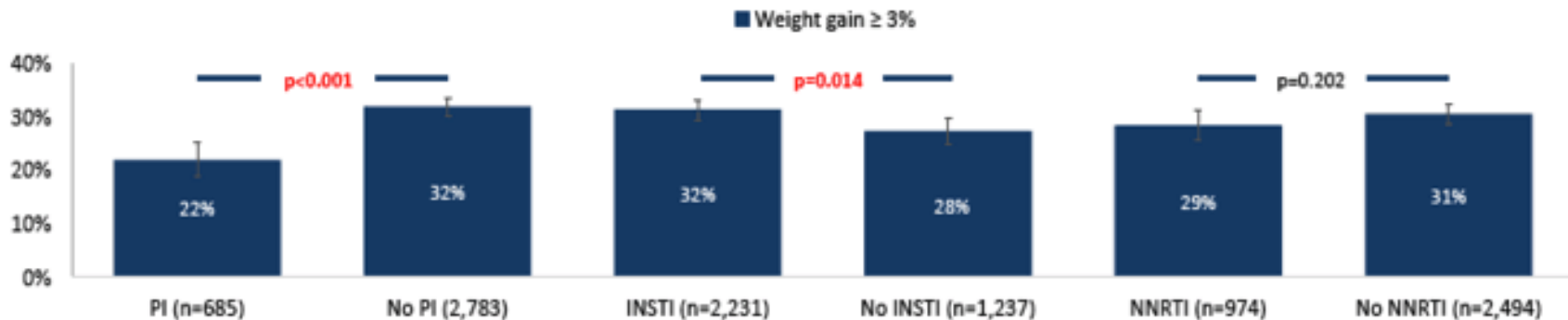
Weight gain in the treatment-experienced population with continued HIV suppression was primarily associated with **lower BMI, reduced proportion of hypogonadism**, increased proportion of **psychiatric disorders**, and non-PI-containing regimens. The association between InSTI-based ART and weight gain, which reached significance in bivariate analyses, did not remain significant in logistic regression, suggesting that in this population, **weight changes are primarily driven by other factors.**

# Weight Gain During Treatment Among 3,468 Treatment-Experienced Adults with HIV: retrospective observational study



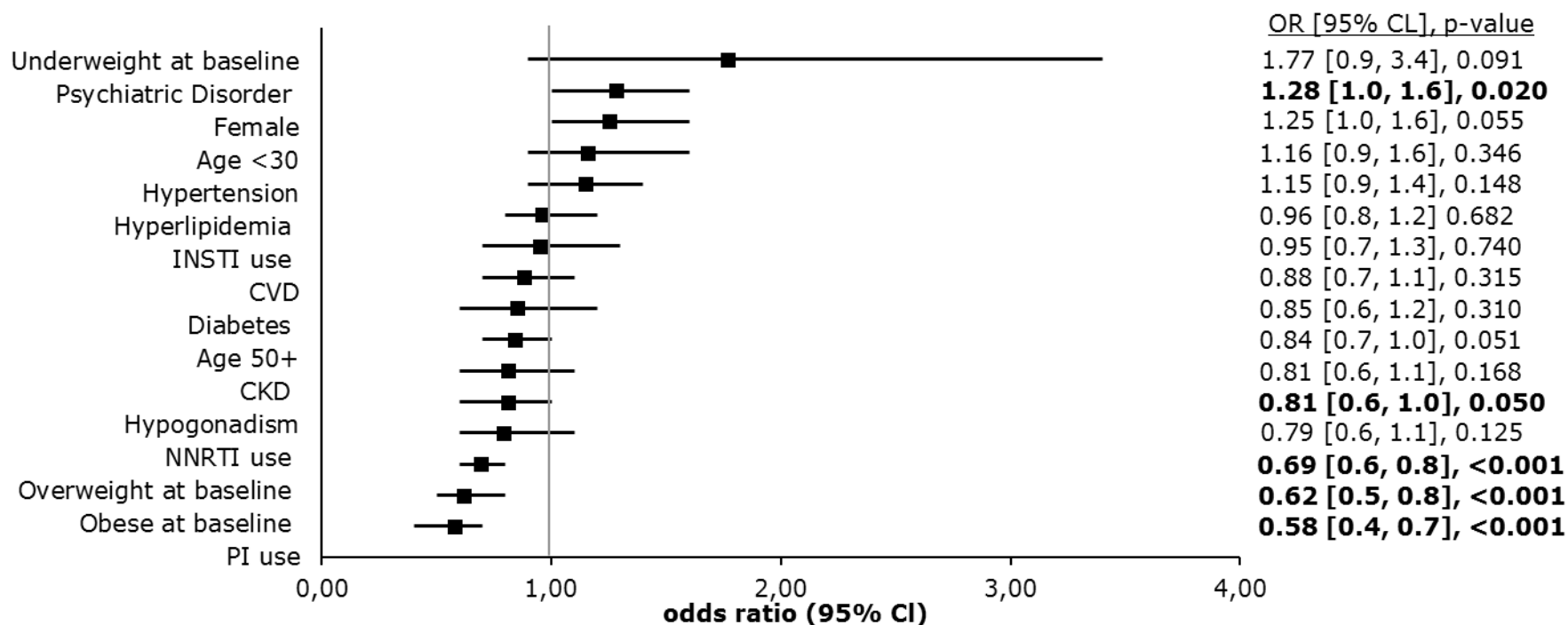
## Weight gain within regimen groups

The percentage of patients with  $\geq 3\%$  weight gain was significantly lower among those with PI vs. not treated with PI. Conversely, the percentage of patients with  $\geq 3\%$  weight gain was higher among patients treated with INSTI vs. those not treated with INSTI. There was no statistically significant difference between the NNRTI and no NNRTI groups.



# Weight Gain in ART-Experienced Adults in USA: Multivariate Analysis of Weight Gain $\geq 3\%$

- Negatively associated with weight gain  $\geq 3\%$  (logistic regression):
  - Overweight or obese at BL, hypogonadism, use of PI-based therapies
- Positively associated with weight gain (logistic regression):
  - Psychiatric disorders
- Not significantly associated with weight gain  $\geq 3\%$  (logistic regression):
  - INSTI-based ART

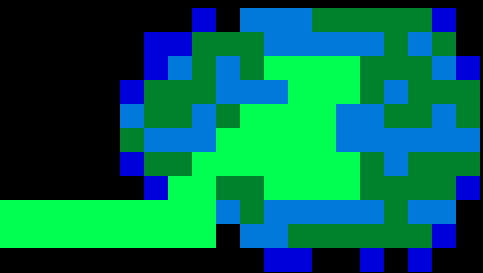


# Take home messages:



- Il paradigma del rischio CV M>F in HIV oggi non è più così solido
- In questo alcuni fattori possono giocare un ruolo fondamentale:
  - Obesità
  - Menopausa precoce
  - Difficoltà di accesso alle cure
- Futuri obiettivi:
  - affrontare studi sistematici sul rischio CV nella medicina di genere
  - migliorare l'accesso alla diagnostica e alle cure per le comorbilità nelle donne HIV
  - Personalizzare la TARV anche alle esigenze di genere





Grazie per l'attenzione