NOVEDADES EN VIH

25 DE JUNIO DE 2020

Controversias relacionadas con el tratamiento ARV Aumento de peso, comorbilidades, embarazo, inflamación.

Dr. Antonio Ocampo
Hospital Álvaro Cunqueiro

Conflicto de intereses

He recibido honorarios como ponente, así como la fundación Galicia Sur a la que pertenezco, ha recibido compensaciones económicas producto de ensayos clínicos o ayudas para la investigación, o la sociedad SOGASIDA la que se presido, de:

Abbvie

Bristol-Myers Squibb

Gilead

Janssen

MSD

ViiV

Carezco de ningún conflicto de interés

Gestación

- Con TAR: Tasas cercanas a cero
- No controversias conaplicación de las guías: Raltegravir + truvada/kivexa
- No estudios en biterapia: posiblemente no necesarios

Controversia con dolutegravir y gestación.

Nuevos datos en Botswana y Brasil: Tsepamo
Analiza 119.000 partos, 2014 -2019
Defectos de tubo neural
1.700 mujeres con DTG**: 0,3%,** *vs* **0,1%** otros tratamientos antirretrovirales.

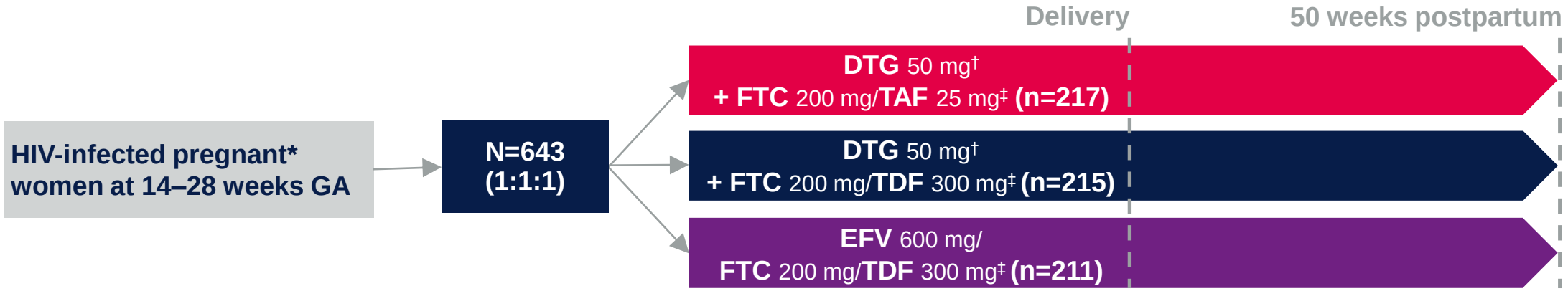
Dolutegravir recomendado por la **OMS en** mujeres

Estudio IMPAACT:
Eficacia viral y EA

Estudio fase 3.
Eficacia de DTG/FTC+ TAF o TDF *vs* Atripla
Seguridad (embarazo, gestante, neonatal)

IMPAACT 2010: study design[1,2]

- **IMPAACT 2010 (NCT03048422):** a Phase III study conducted in nine countries to investigate the virologic efficacy and safety of DTG- versus EFV-containing ART regimens in HIV-1-infected pregnant women and their infants



- **Primary efficacy analysis:** the combined DTG-containing arms were compared with the EFV arm for virologic non-inferiority (–10% margin), then superiority, with regard to maternal delivery HIV-1 RNA <200 c/mL
- **Safety outcomes:** comparison between all arms for:
  - Composite adverse pregnancy outcome – PTD (<37 weeks), SGA (<10th percentile), SB or SAB
  - Maternal Grade ≥3 AE through 14 days postpartum
  - Neonatal Grade ≥3 AE through 28 days
  - NND (≤28 days)

*ART-naïve at screening. Defined as having not received prior ART therapy other than those received during prior pregnancies or prior periods of breastfeeding (i.e., receipt of any single, dual, or triple ARV regimen during prior time-limited periods of pregnancy and breastfeeding was permitted). Receipt of up to 14 days of ARVs during the current pregnancy was permitted. †Oral, once daily. ‡Oral, once daily, fixed-dose combination tablet

AE, adverse event; **ART**, antiretroviral therapy; **DTG**, dolutegravir; **EFV**, efavirenz; **FTC**, emtricitabine; **GA**, gestational age; **NND**, neonatal death; **PTD**, pre-term delivery **SAB**, spontaneous abortion; **SB**, stillbirth; **SGA**, small for gestational age; **TAF**, tenofovir alafenamide; **TDF**, tenofovir disoproxil fumarate

1. IMPAACT 2010. Available from: https://clinicaltrials.gov/ct2/show/NCT03048422. Accessed Feb 2020
2. Chinula L, et al. Abstract 4585. CROI. March 8–11, 2020. Boston, MA, USA

Gestación entre 14-28 semanas
Aceptable media de recuento de CD4 y carga viral

IMPAACT 2010: Baseline characteristics and antepartum follow-up

	Total randomised patients (N=643)
Baseline median	
GA, weeks	21.9
HIV-1 RNA, c/mL	903
CD4 count, cells/μL	466
ART prior to entry, % (days)	83 (6)
Antepartum median follow-up, weeks	17.4

Adapted from Chinula L, et al. Abstract 4585. CROI. March 8–11, 2020. Boston, MA, USA

IMPAACT 2010: Primary efficacy outcome – maternal virologic efficacy results

	DTG + FTC/TAF + DTG + FTC/TDF n/N (%)	EFV/FTC/TDF n/N (%)	Estimated risk difference % (95% CI)‡	P-value‡,§
Delivery HIV-1 RNA <200 c/mL, ITT*,†	395/405 (97.5)	182/200 (91.0)	6.5 (2.0, 10.7)	**0.005**
Delivery HIV-1 RNA <200 c/mL, PP*,†	389/399 (97.5)	171/187 (91.4)	6.0 (1.6, 10.3)	**0.008**

*Primary pre-specified outcome for non-inferiority analysis. †Two-sample test of the difference in binomial proportions.
‡Adjusted for multiple interim analyses. §Test for superiority for secondary analysis

CI, confidence interval; **ITT**, intention-to-treat; **PP**, per protocol

Adapted from Chinula L, et al. Abstract 4585. CROI. March 8–11, 2020. Boston, MA, USA

Menor EA: DTG/TAF vs 2 ramas
Mayor partos prematuros DTG/TAF *vs* EFV
Mayor ganancia de peso: DTG/TAF *vs* 2 ramas

IMPAACT 2010: Pregnancy and maternal/neonatal safety outcomes

	Treatment arm estimates, n/N (%)			P-value		
	DTG + FTC/TAF	DTG + FTC/TDF	EFV/ FTC/TDF	DTG + FTC/TAF vs DTG + FTC/TDF	DTG + FTC/TAF vs EFV/FTC/TDF	DTG + FTC/TDF vs EFV/FTC/TDF
Any adverse pregnancy outcome*,†	52/216 (24.1)	70/213 (32.9)	69/211 (32.7)	0.043	0.047	0.97
PTD (<37 weeks)†,‡,§	12/208 (5.8)	19/202 (9.4)	25/207 (12.1)	0.16	0.023	0.38
SGA (<10th %-ile)†,§	33/202 (16.3)	45/200 (22.5)	41/200 (20.5)	0.12	0.28	0.63
SB (≥20 weeks)†,¶,‖	8/216 (3.7)	11/213 (5.2)	4/211 (1.9)	0.46	0.26	0.067
SAB (<20 weeks)	0	0	0			
Maternal Grade ≥3 AE‖,**	45/217 (20.7)	56/215 (26.0)	47/211 (22.3)	0.27	0.58	0.59
Neonatal Grade ≥3 AE‖,**	29/208 (13.9)	33/202 (16.3)	43/207 (20.8)	0.51	0.069	0.25
NND‖,**	2/208 (1.0)	3/202 (1.5)	10/207 (4.8)	0.63	0.019	0.053
Average maternal weight gain per week, kg§,††	0.378	0.319	0.291	0.011	<0.001	0.19

*Primary pre-specified outcome for non-inferiority analysis; †Two-sample test of the difference in binomial proportions
‡Preterm births in live born neonates. §Secondary outcome; ¶Post-hoc test; ‖Log-rank test
**Partial follow-up for primary or secondary safety outcome; ††Generalised estimating equations

Adapted from Chinula L, et al. Abstract 4585. CROI. March 8–11, 2020. Boston, MA, USA

Tasa de transmisión < 1%
% de mortalidad perinatal y nacidos muertos: similar

IMPAACT 2010: Additional results

- Two infants were diagnosed with HIV at ≤14 days
  - One each in DTG + FTC/TAF and DTG + FTC/TDF arms (maternal delivery HIV-1 RNA: 58,590 and <40 c/mL, respectively)
- Combined SB or NND rates were similar by arm (post-hoc analysis)
- At least one Grade ≥3 AE occurred in 148 (23%) women and 105 (17%) infants (all by-arm p-values ≥0.05)

Mayor % control viral: DTG TFC/TAF-TDF vs 2 EFV
Menos E.A en la gestación con DTG/TAF/FTC
Similar EA: maternal o neonatal

IMPAACT 2010: Conclusions

- **DTG-containing ART** initiated in pregnant women with HIV at GA 14–28 weeks had superior virologic efficacy (HIV-1 RNA <200 c/mL) at delivery compared with EFV/FTC/TDF
- **DTG + FTC/TAF** had the lowest composite frequency of adverse pregnancy outcomes
- Maternal and neonatal AE outcomes **were similar by study arm**

Comentario
- Practica clínica ir a pautas con mas experiencia
- Tercer mundo abala su prescripción la OMS
- DTG buena eficacia y escasos EA
- Los defectos del tubo neuronal y DTG se desvanecen poco a poco
- Esperar futuros datos

WHO — First-line Treatment Guidelines

Preferred	Alternative	Special Circumstances only
TDF/XTC/DTG	TDF/XTC/EFV400	TDF/XTC/EFV600 ZDV/3TC/EFV600 TDF/3TC/PI/r TDF/3TC/RAL **TAF/3TC/DTG*** ABC/XTC/DTG

***TAF may be considered for patients with established osteoporosis and/or impaired renal function**

World Health Organization. WHO 2019 Treatment Guidelines. https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf.

ART Metabolic and CV impact

Controversias con alteraciones cardiovasculares

- VIH: su papel aterogénico
- El paciente VIH edad y sus hábitos de vida
- TAR y aumento de lípidos (ritonavir)
- Abacavir y riesgo cardiovascular ¿?
- Papel protector ¿? de ciertos ATR: nevirapina..tenofovir disoproxil (TDF)

Actualidad:

Aumento de peso con ciertas integrasas…el papel **del TAF**

Como diagnosticarlas o predecirlas: Cribaje, aplicación de test, base de datos

…enfermería y factor tiempo

Otros factores…. Otras estrategias de control

Predicted 10-Year Risks **of Diabetes and Cardiovascular** Disease in the **ADVANCE Trial**

Andrew Hill,[1] Kaitlyn McCann,[2] Ambar Qavi,[2] Bryony Simmons,[2] Victoria Pilkington,[2] Michelle Moorhouse,[3] Godspower Akopmiemie,[3] Simiso Sokhela,[3] Celicia Serenata,[3] Alinda Vos,[4] Francois Venter[3]

[1]Liverpool University, Pharmacology, Liverpool, UK; [2]Imperial College London, Faculty of Medicine, London, UK; [3]Ezintsha, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; [4]University Medical Center Utrecht, Epidemiology, Utrecht, Netherlands

Conference on Retroviruses and Opportunistic Infections; March 8-11, 2020; Boston, MA

IMC< 30: Riesgo de la obesidad: patologías especificas y reducción de la esperanza de vida

Potential Risks From Clinical Obesity (BMI >30)

- Type II diabetes
- Cardiovascular disease: myocardial infarction/death
- Alzheimer's disease
- Obstetrics/birth outcomes: gestational diabetes, pre-eclampsia, venous thromboembolism, maternal death, birth defects
- Cancer
- Reductions in life expectancy

Mensaje:

- Identificación y cuantificación de casos
- Actuar sobre los factores modificables
- Profilaxis primaria del riesgo C.V.
- **El TAR** es modificable

Research Questions

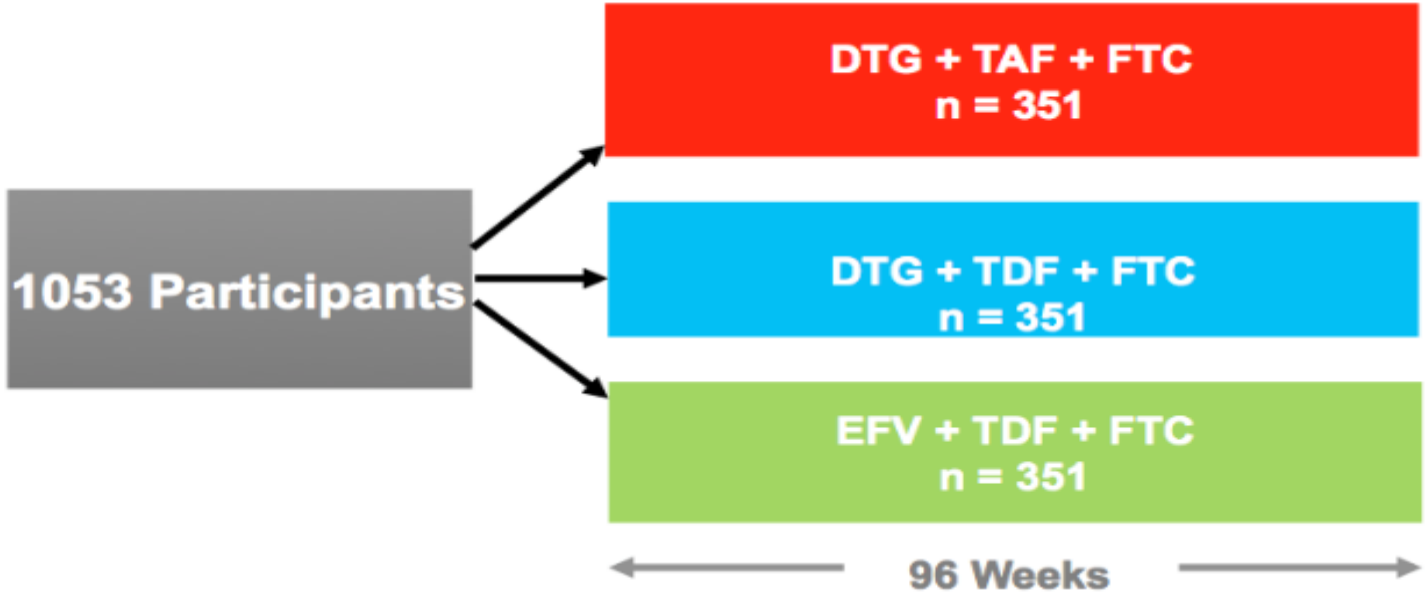
1- Cambios en marcadores de riesgo cardiovasculares y de diabetes tras TAR.
2- Son útiles las ecuaciones de riesgo

- In the **ADVANCE** trial of treatment **naive** patients in South Africa:
  1. What changes are seen in markers of cardiovascular risk and diabetes?
  2. Can we use risk equations to predict the risk of cardiovascular disease or diabetes from these changes?
- Non-parametric tests used throughout analysis, given strong positive skew. Results repeated using log10 transformation and parametrics, with similar results
- Bonferroni corrections used to adjust for multiple testing (p=0.017, three pairwise comparisons)

1- Pacientes naives
2- Tres ramas con o sin: DTG o TAF

ADVANCE Study: Trial Design

- **Inclusion criteria:**
  - **Treatment-naive,** HIV-1 RNA level >500 copies/mL in the last 60 days



- Open-label, 96-week study in Johannesburg, **South Africa**
- Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84 and 96

1- Alto porcentaje de mujeres
2- Aceptable estado inmunológico

Baseline Characteristics

Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Age, mean (SD), years	33 ± 8	32 ± 8	32 ± 7
Female	61%	59%	57%
Black	99%	100%	100%
Baseline HIV-1 RNA			
≤100,000 copies/mL	78%	80%	77%
>100,000 copies/mL	22%	20%	23%
CD4+ cell count, mean (SD), cells/mm^3	349 ± 225	323 ± 234	337 ± 222

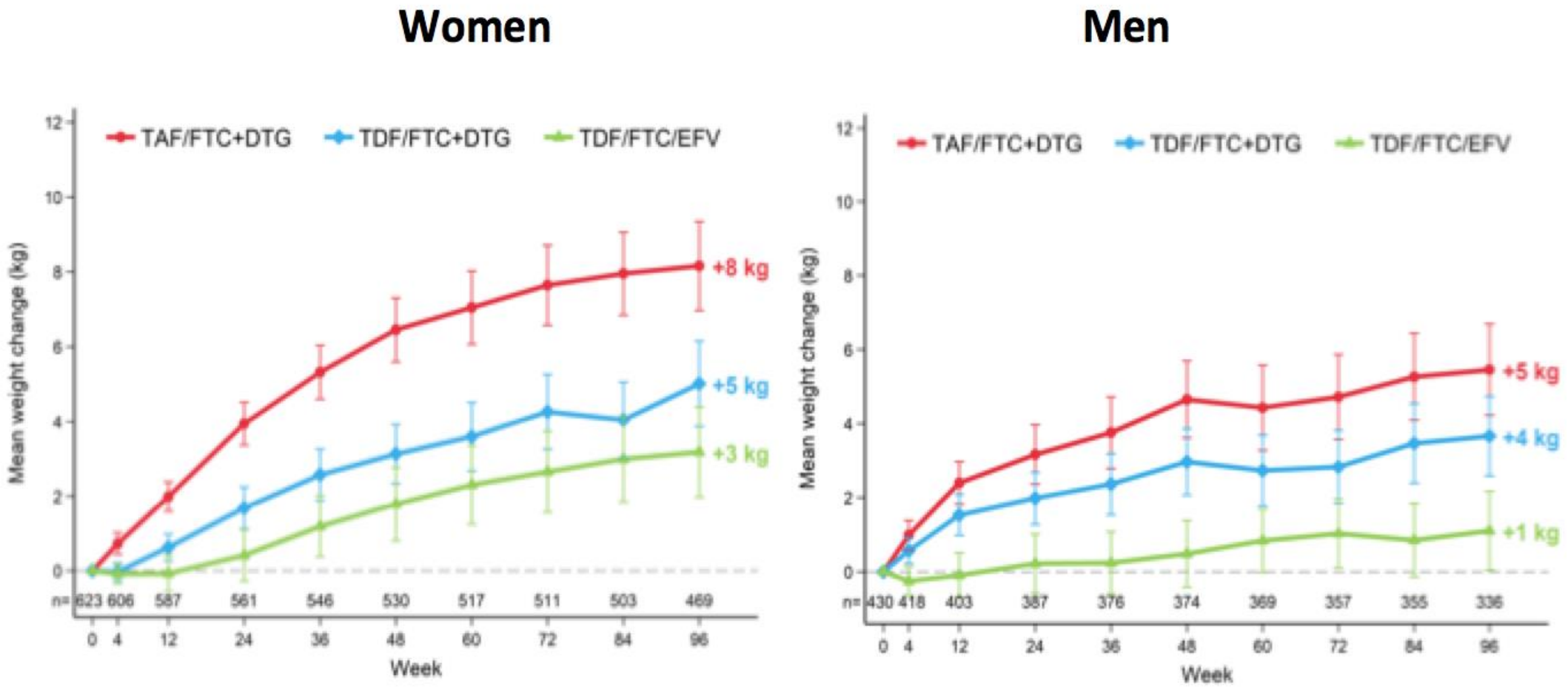
1- Un 12% de obesos y 10 % de bajo peso
2- > IMC y peso en mujeres

Baseline Characteristics (cont)

Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Weight, mean (kg)			
Male	67.9	67.1	67.3
Female	68.8	69.5	70.2
BMI, mean (kg/m²)			
Male	21.7	21.6	21.8
Female	25.6	26.1	26.1
Categories of BMI, n (%)			
Underweight (< 18.5)	42 (12%)	35 (10%)	37 (11%)
Normal (18.5-25)	177 (51%)	190 (54%)	193 (55%)
Overweight (25-30)	96 (27%)	78 (22%)	77 (22%)
Obese (> 30)	35 (10%)	48 (14%)	44 (13%)

1- Mayor ganancia de peso con DTG y TAF
2- Mayor ganancia en mujeres

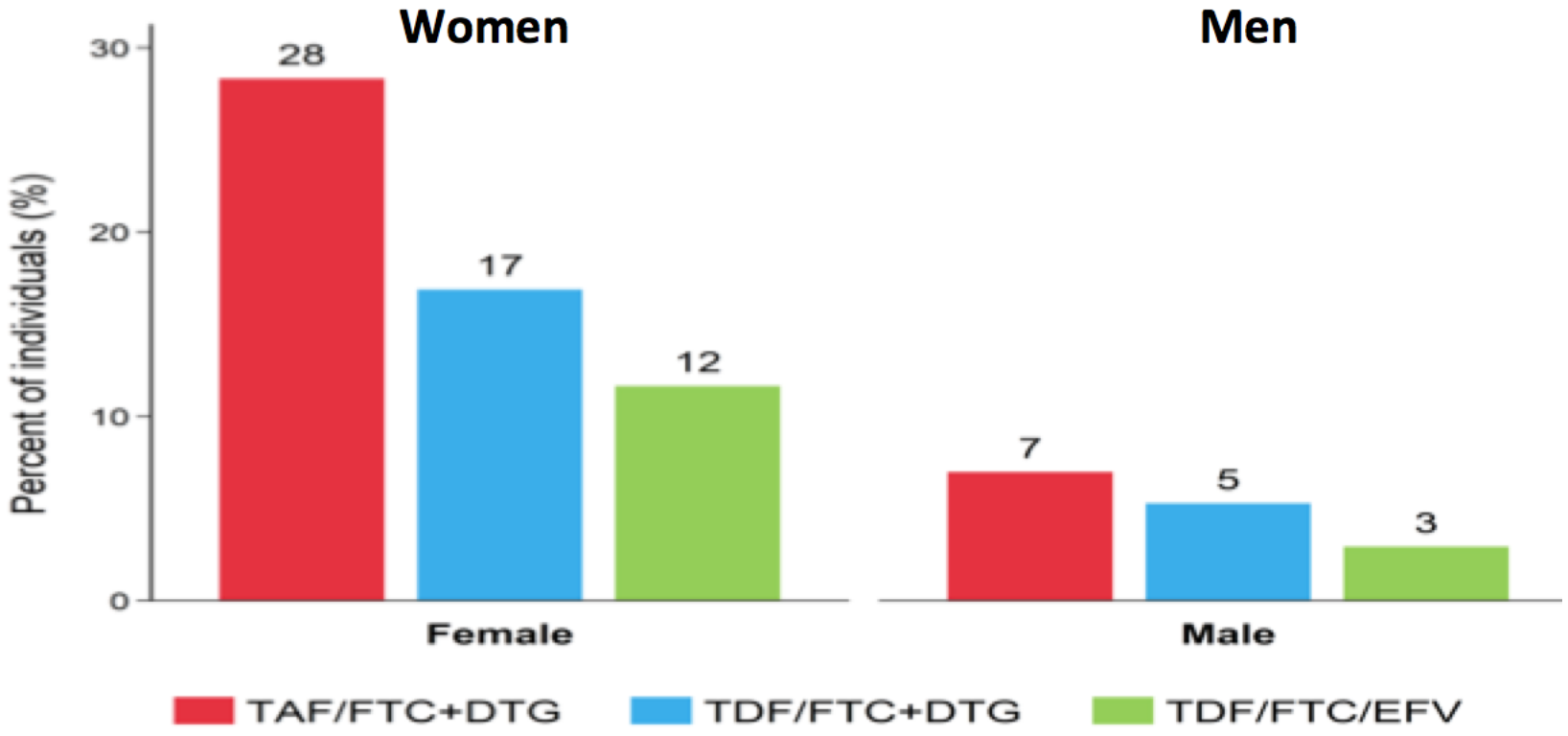
Mean Change in Weight (kg) to Week 96



Hill et al. CROI 2020; Boston, MA. Slides 81.

Treatment-Emergent Obesity to Week 96

1- Mayor % de obesidad con DTG y > > con **TAF**
2- Mayor % de obesidad en mujeres



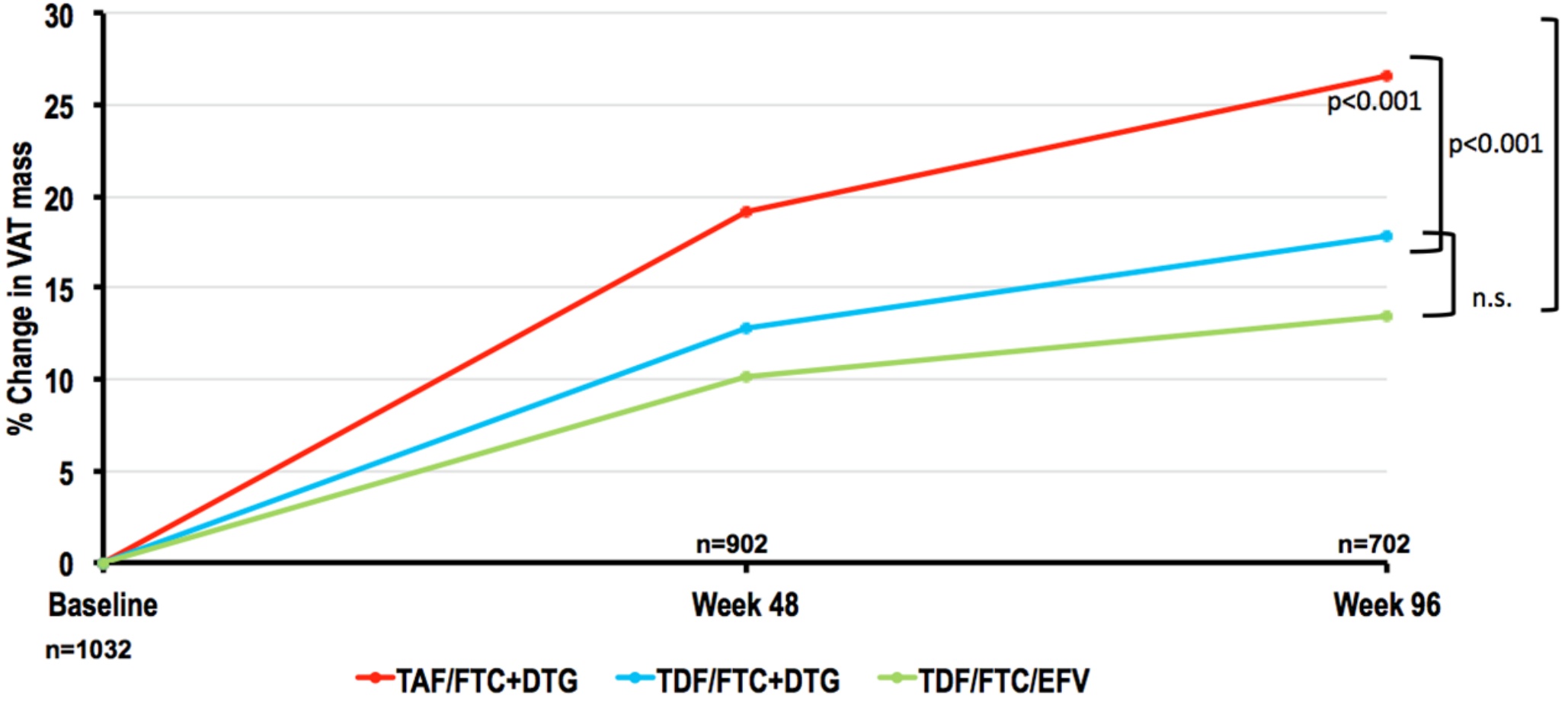
Hill et al. CROI 2020; Boston, MA. Slides 81.

Changes in Lab Parameters to Week 96, Median (IQR)

	TAF/FTC+DTG (n=185)	TDF/FTC+DTG (n=187)	TDF/FTC/EFV (n=191)			
Week 96				Group 1 vs. 3	Group 1 vs. 2	Group 2 vs. 3
Total cholesterol (mg/dL)	10.4 (-5.4, 24.0)	1.5 (-13.1, 19.7)	13.1 (-1.9,33.3)	P=0.022	p=0.007	p<0.001
LDL (mg/dL)	8.5 (-6.2, 20.5)	2.3 (-10.8, 12.4)	6.2 (-5.0 , 22.0)	p=0.82	p=0.007	P=0.013
HDL (mg/dL)	4.6 (-2.3, 12.0)	3.9 (-2.3, 12.0)	9.7 (2.3, 19.3)	p<0.001	p=0.73	p<0.001
Fasting glucose (mg/dL)	19.3 (7.7, 34.8)	19.3 (0.00, 34.8)	27.1 (11.6, 42.5)	0.0049	p=0.21	p<0.001
Systolic BP (mmHg)	3.0 (-7.0,11.0)	-1.0 (-12.0,8.0)	0.50(-9.0 8.0)	p=0.19	p=0.030	p=0.35

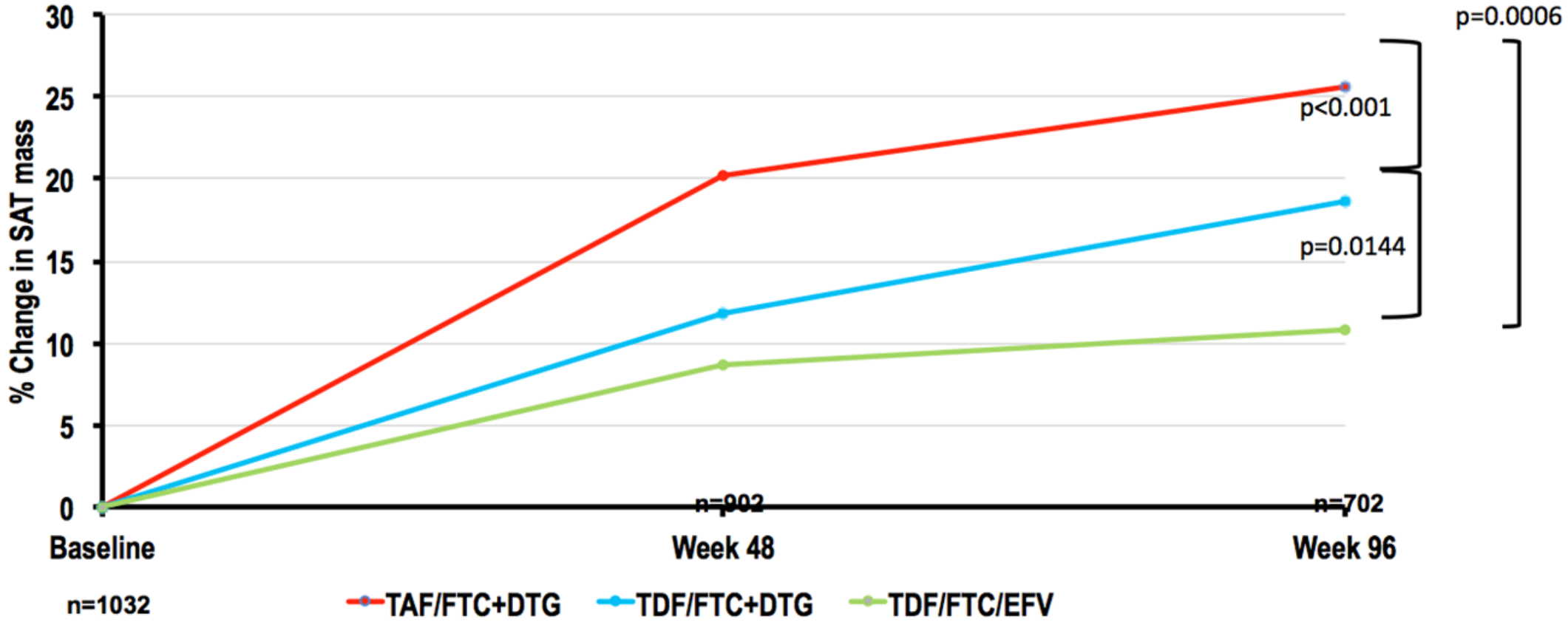
Median % Change in Visceral Adipose Tissue (VAT) From Baseline to Week 96 (DXA)

1- mayor % de grasa visceral con DTG y TAF a las 96 semanas. **No meseta**



1- mayor % de grasa subcutánea con DTG y TAF a las 96 semanas. No meseta
2- Menor con EFV/TDF/FTC

Median % Change in Subcutaneous Adipose Tissue (SAT) From Baseline to Week 96 (DXA)



Metabolic Syndrome: Definition

- Assessed using the **International Diabetes Federation Definition** (IDF) definition:
  - **Clinical obesity (BMI >30 kg/m^2)**
  - **AND** any **two** of the following factors

Raised triglycerides	≥150 mg/dL (1.7 mmol/L) *OR* on treatment for this lipid abnormality
Reduced HDL cholesterol	Males: ≤40 mg/dL (1.03 mmol/L) Females: ≤50 mg/dL (1.29 mmol/L) *OR* on treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥130 mmHg Diastolic BP ≥85 mmHg *OR* on treatment for previously diagnosed hypertension
Raised fasting glucose	≥100 mg/dL (5.6 mmol/L) *OR* diagnosis of Type 2 diabetes

Mensaje:

- Identificación de los casos: IMC. TA…
- Cuantificación de casos
- **Actuación**: Consejo dietético + ejercicio ± fármacos …El TAR?.
- No todo es TAR

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Hill et al. CROI 2020; Boston, MA. Slides 81.

1- Mayor % de síndrome metabólico con DTG/TAF/FTC vs EFV/TDF/FTC

Metabolic Syndrome at Week 96

	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
Baseline prevalence	16/351 (5%)	21/351 (6%)	14/351 (4%)
Treatment-emergent metabolic syndrome			
Week 96	20/259 (8%)	15/258 (6%)	8/242 (3%)

Statistically significant differences between **TAF/FTC+DTG and TDF/FTC/EFV** at Week 96 (p=0.031)

Framingham Risk Equation

- Estimates **10-year risk** of myocardial infarction or coronary death
- https://reference.medscape.com/calculator/Framingham-cardiovascular-disease-risk
- Variables included in equation:
  - Age
  - Sex
  - Systolic BP
  - Total cholesterol
  - HDL cholesterol
  - On hypertension medication
  - Smoking status
  - Diabetes

No diferencias entre las tres ramas

Framingham Risk Equation Results

- **Predicted results over time**:

Treatment arm / 10-year risk	Baseline	Median change to:	
		Wk 48	Wk 96
TAF/FTC+DTG:	2.37%	0.00%	+0.43%
TDF/FTC+DTG:	2.53%	-0.06%	+0.22%
TDF/FTC/EFV:	2.24%	-0.08%	+0.28%

- No significant differences between arms at Week 96

QRISK Equation

- Estimates **10-year risk of developing a heart attack or stroke**
- https://qrisk.org/three/
- Variables included in equation
  - Age (25-84)
  - Sex
  - Ethnicity (Black African included)
  - Cholesterol ratio
  - Systolic BP
  - BMI
  - Family history of heart attack/angina*
  - Smoking status
  - Diabetes
  - Chronic kidney disease (stages 3, 4, or 5)
  - Atrial fibrillation
  - Migraines
  - Rheumatoid arthritis
  - Systemic lupus erythematous (SLE)
  - Severe mental illness (schizophrenia, bipolar disorder, moderate/severe depression)
  - On treatment for hypertension
  - On atypical antipsychotic medication
  - On regular steroid tablets
  - Erectile disfunction

*Information not available.

QRISK Equation Results

- Predicted results over time:

Treatment arm / 10-year risk	Baseline	Median change to:	
		Wk 48	Wk 96
TAF/FTC+DTG:	0.60%	+0.10%	+0.20%
TDF/FTC+DTG:	0.60%	+0.10%	+0.20%
TDF/FTC/EFV:	0.50%	0.00%	+0.10%

- Borderline significant differences between TAF/FTC+DTG and TDF/FTC/EFV at week 96 (p=0.027)

QDIABETES Equation

- Website/reference: http://qdiabetes.org
- Estimates the **10-year risk of developing diabetes**
- Variables included in equation:
  - Age (25-84)
  - Sex
  - Ethnicity (Black African included)
  - Fasting blood glucose
  - HBA1c*
  - BMI
  - Smoking status
  - Family history of diabetes*
  - On treatment for hypertension
  - Heart attack/angina/stroke/TIA
  - Learning disabilities
  - Manic depression/schizophrenia
  - On regular steroid tablets
  - On statins
  - On atypical antipsychotic medication
  - Polycystic ovaries
  - Gestational diabetes

*Information not available.

Mayor con DTG y TAF vs TDF
Menor con DTG y TDF vs EFV

QDIABETES Equation Results

- Predicted results over time:

Treatment arm / 10-year risk	Baseline	Median change to:	
		Wk 48	Wk 96
TAF/FTC+DTG:	0.30%	+0.70%*	+0.90%*
TDF/FTC+DTG:	0.40%	+0.40%	+0.50%
TDF/FTC/EFV:	0.30%	+0.60%**	+0.70%**

*TAF/FTC+DTG risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.008) and Week 96 (p=0.004)

**TDF/FTC/EFV risk significantly higher than TDF/FTC+DTG at Week 48 (p=0.047) and Week 96 (p=0.005)

No significant differences between TAF/FTC/DTG and TDF/FTC/EFV at Week 48 or 96

Limitations of the Current Analysis

- **The ADVANCE** population is young (median 31 years), when the risk of MI and diabetes is relatively low
- Among women treated with **TAF/FTC+DTG**, weight is continuing **to ris**e to Week 96, with no sign of a plateau. The predictive models to not account for additional weight gain after week 96
- **ADVANCE** is in treatment naive patients; increases in weight could be partly a **"return to health"** effect. However, this does **not explain** the higher weight gains for TAF/FTC/DTG versus TDF/FTC/DTG
- Other NCDs need to be evaluated: Cancer, Alzheimer's, adverse birth outcomes

Conclusions

- **In the ADVANCE trial**, TAF/FTC+DTG was associated with a significantly higher risk of:
  - **Clinical obesity**
  - **Metabolic syndrome**
  - **Rises in VAT and SAT**
  - **Predicted risk of diabetes**
- The predicted risk of MI from these changes is not significant. However, there is a predicated increase in the risk of diabetes ─ 4 cases per 1000 people treated with TAF/FTC+DTG versus TDF/FTC+DTG. Additional risks for TDF/FTC/EFV as well
- These analyses should be repeated for other studies evaluating TAF/FTC and integrase inhibitors in other patient populations and lines of treatment

These analyses should **be repeated** for other studies **evaluating TAF/FTC** and integrase inhibitors in other patient populations **and lines** of treatment

- El papel de TAF en los resultados
- Estudios en biterapia sin TAF
- Aumento de peso un efectos de clase de ciertos I. I.
- **Clínico:** la justa valoración del aumento de peso y la modificación de los factores de riesgo
- Estrategias**: detección, del consejo, test y fármacos:** exige colaboración enfermería y clínico

Factor genético?

Conference on Retroviruses and Opportunistic Infections; March 8-11, 2020; Boston, MA

CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz

Rulan Griesel, Gary Maartens, Simiso Sokhela, Godspower Akpomiemie, Francois Venter, Michelle Moorhouse, Phumla Sinxadi

Background

Polimorfismo: asociado a concentración de EFV
Un 20% de metabolizadores lentos en África
Estos polimorfismos explicarían el aumento del peso tras cambio de EFV a II?
O un potencial efecto del EFV?

- *CYP2B6* polymorphisms are associated with higher EFV concentrations
- *CYP2B6* slow metabolisers are common in Africa (~20%)[1]
- *CYP2B6* slow metabolisers gained more weight when switched from EFV to INI-based ART,[2] suggesting that high EFV concentrations could impair weight gain
- Potential mechanisms of **impaired weight gain on EFV**:
  - Toxic to **mitochondri**a and adipocytes[3]
  - Less **limb** fat gain versus PIs[4]
  - Chronic **neuropsychiatric** toxicity could impair appetite

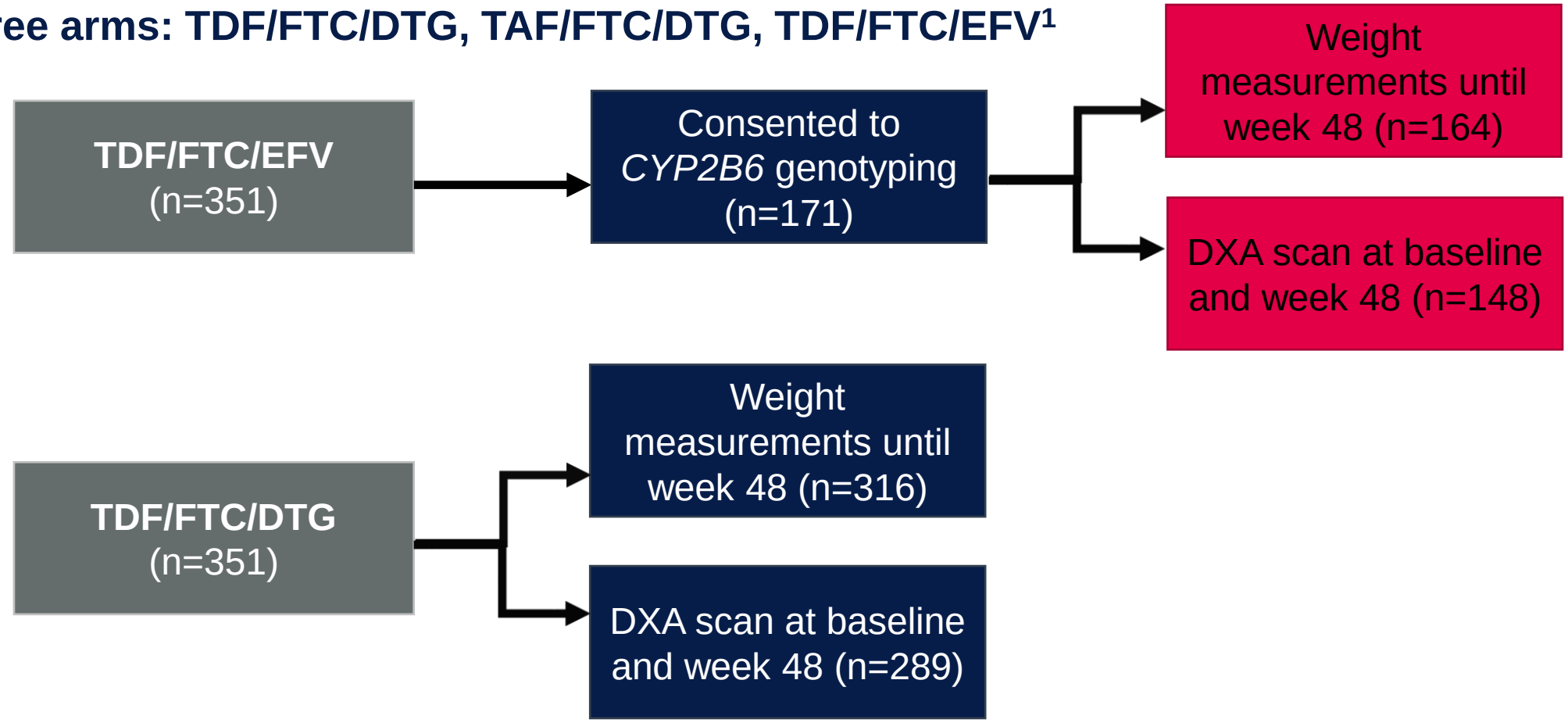
PI, protease inhibitor

1. Barret J, et al. Int J Clin Pharmacol Ther 2002; **2.** Leonard M, et al. CROI 2019
3. Moure R, et al. Antiviral Research 2016; **4.** de Waal R, et al. Plos one 2013

ADVANCE: *CYP2B6* Weight Gain Sub-study

ADVANCE RCT in ART-naïves in South Africa

Three arms: TDF/FTC/DTG, TAF/FTC/DTG, TDF/FTC/EFV[1]



DXA, Dual-energy X-ray absorptiometry; **FTC,** emtricitabine

1. Venter WDF, et al. NEJM 2019

Methods

- *CYP2B6* genotyping:
  - *CYP2B6* 516G→T (rs3745274)
  - *CYP2B6* 983T→C (rs28399499)
  - *CYP2B6* 15582C→T (rs4803419)
- Metaboliser genotype groups for *CYP2B6* SNPs were categorised as **extensive, intermediate, or slow**
- Weight measured at baseline, Weeks 4, 12, 24, 36, and 48
- Percentage change from baseline to Week 48 of limb and trunk fat was estimated **with DXA**

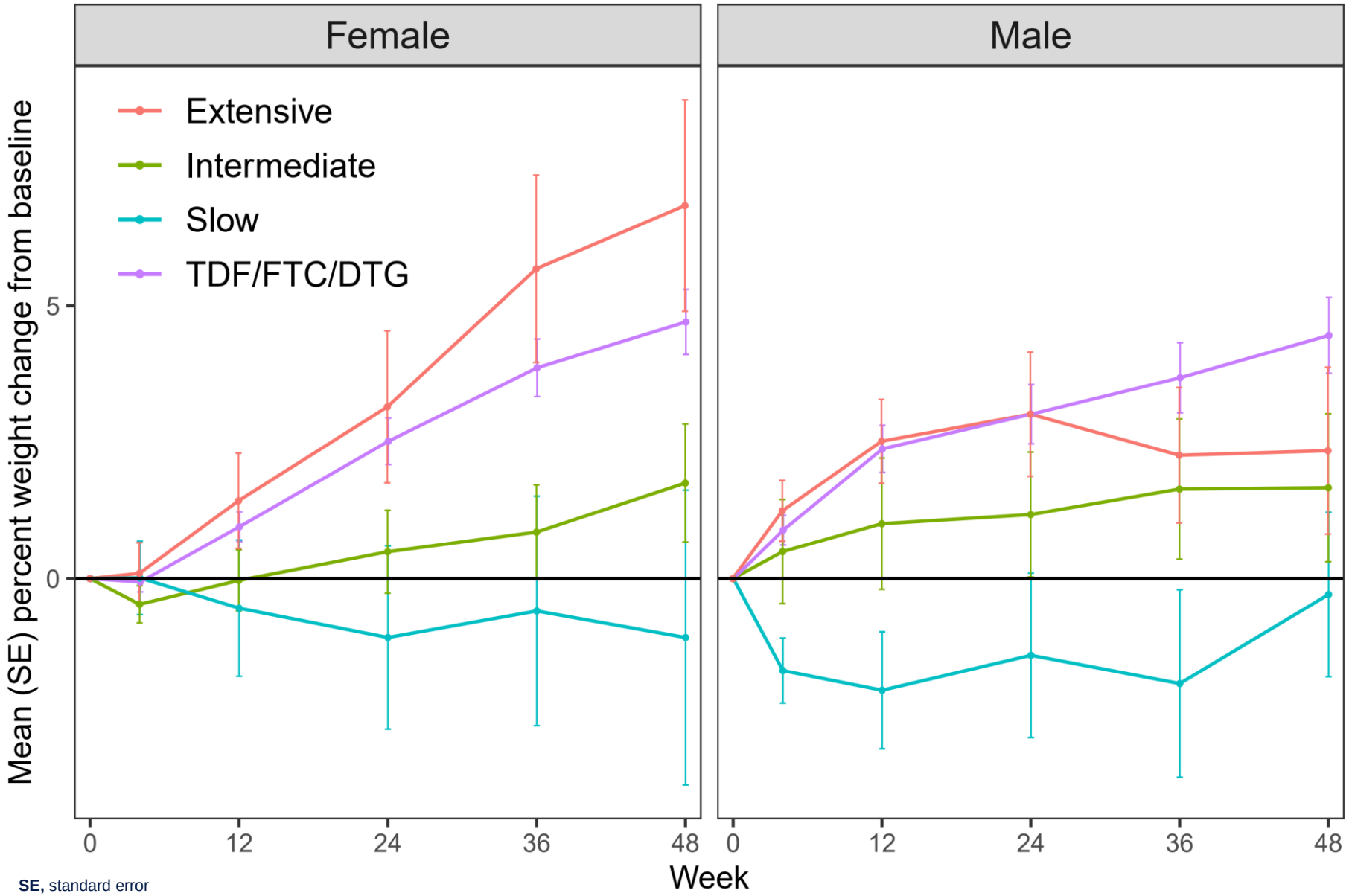
SNP, single nucleotide polymorphism

Baseline Characteristics

	TDF/FTC/EFV by *CYP2B6* metaboliser genotype			
	Extensive (n=51)	**Intermediate (n=74)**	**Slow (n=46)**	**TDF/FTC/DTG (n=351)**
Age (years) median (IQR)	31 (26–37)	31 (27–36)	32.5 (29–37)	32 (26–37)
Sex (female) n (%)	**27 (52.9)**	**47 (63.5)**	**23 (50)**	208 (59.3)
BMI (kg/m^2) median (IQR)	21.4 (19.7–25.5)	24.4 (21.4–28.3)	24.1 (20.4–27.5)	22.9 (20.0–26.8)
CD4 count (cells/μL) median (IQR)	290 (181–400)	303 (176–417)	268 (159–384)	275 (163–427)
HIV-1 RNA (log$_{10}$) median (IQR)	4.4 (3.8–4.8)	4.3 (3.5–5.1)	4.6 (4.0–5.1)	4.4 (3.8–4.9)

IQR, interquartile range

Weight Change from Baseline by Sex & *CYP2B6*



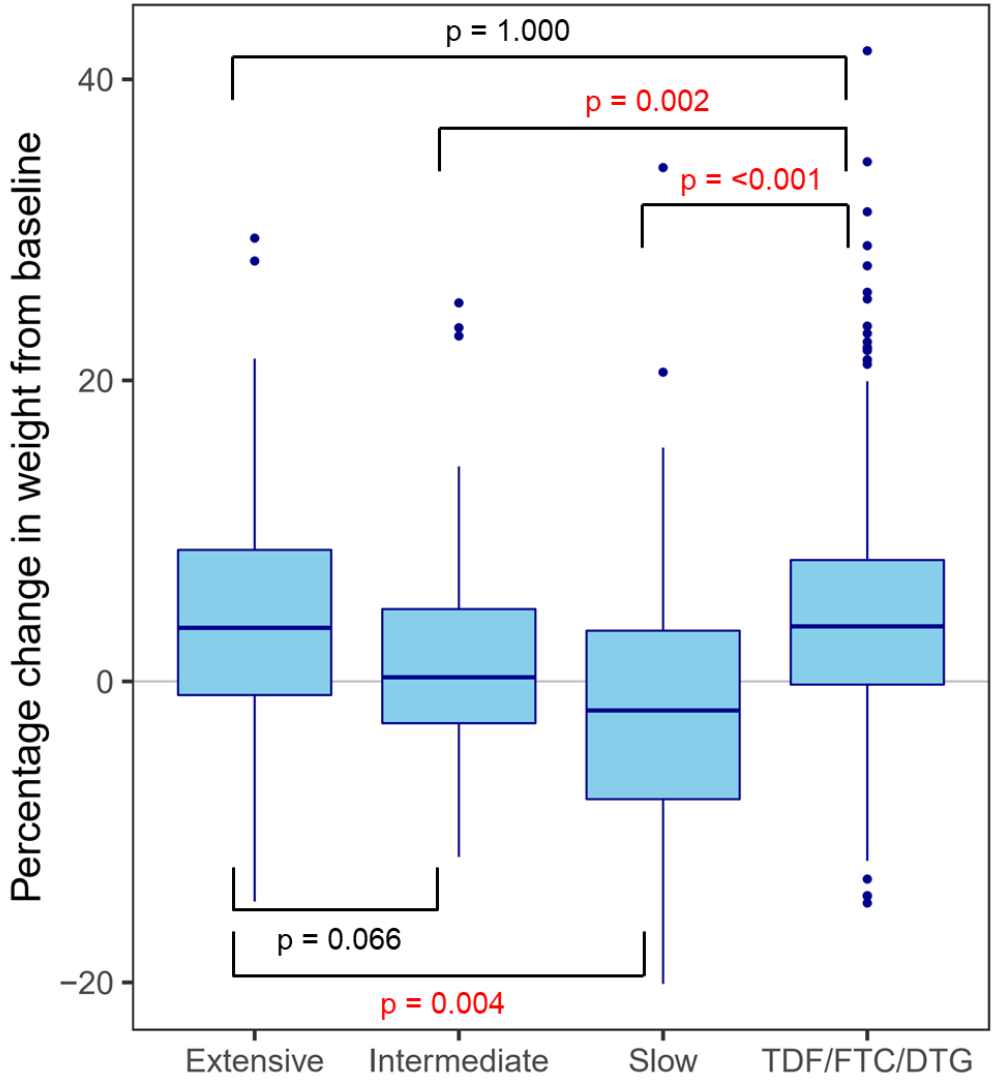
SE, standard error

Mayor aumento en mujeres

EFV: relación con los polimorfismos

DTG; se comporta igual que los metabolizadores rapidos

Weight Change from Baseline to Week 48



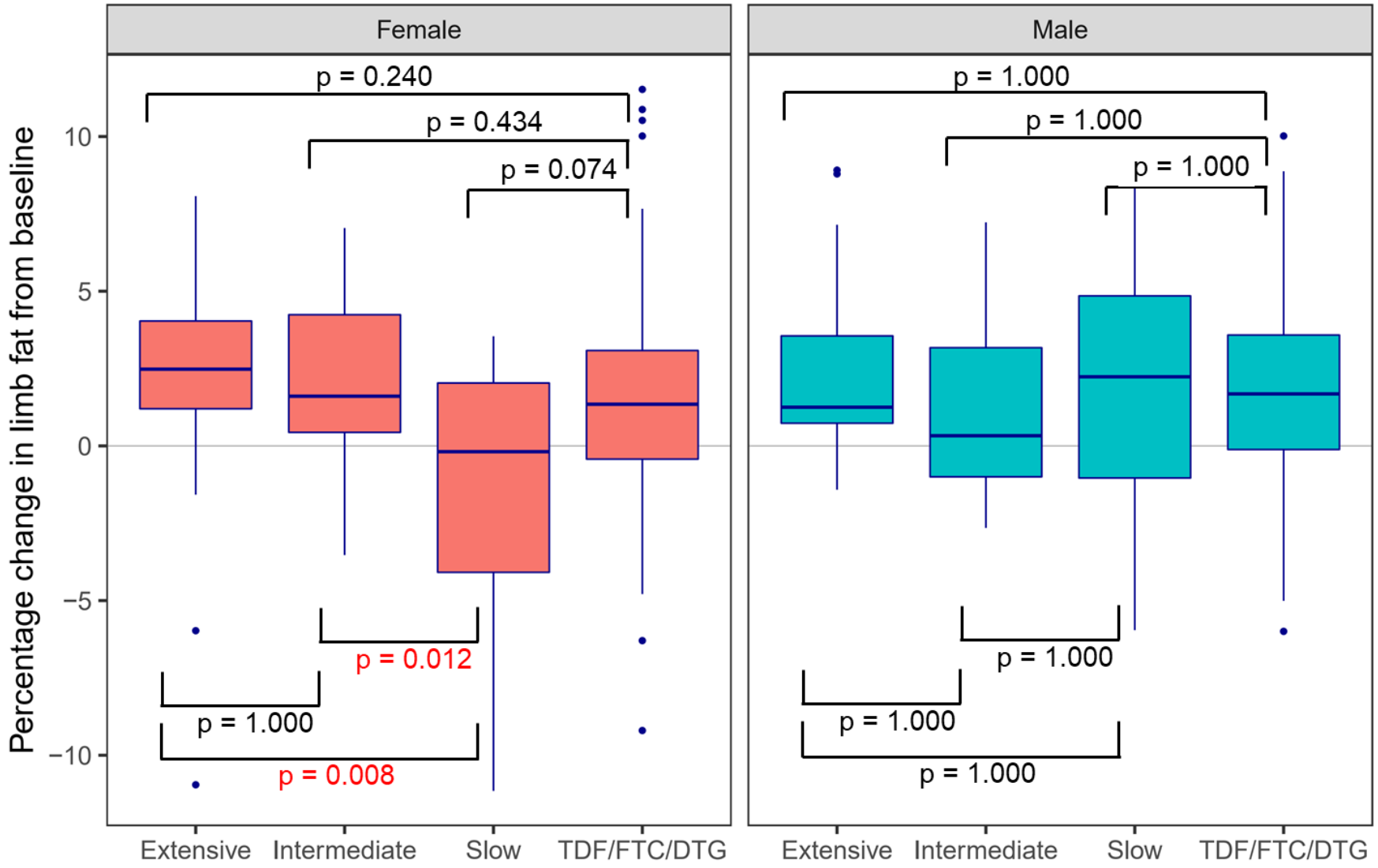
Metabolizadores lentos o intermedios menor ganancia de peso en **mujeres** en hombres ocurre con lentos vs rápidos

Con TDF/FTC/DTG: se asemeja al metabolizadores rápidos.

Comentario:

- El no aumento de peso con EFV depende de ciertos polimorfismos.
- Explicaría todo?

Change in Limb Fat from Baseline to Week 48 by Sex



Dexa de grasa en extremidades:

- En hombres no diferencias
- Si en mujeres en relación a polimorfismos

Otras variables:

CD4 y carga viral: un > aumento de peso beneficioso?¿.

Linear Regression:
Weight Change from Baseline to Week 48 in the TDF/FTC/EFV Arm

Variable	Multivariate associations	
	Estimate (95% CI)	p-value
Age (per 5 years)	–0.760 (–1.768, 0.247)	0.138
Sex		
Female	Reference group	
Male	–1.888 (–4.661, 0.884)	0.181
Baseline CD4 count (per 50 cells/µL)	–0.390 (–0.739, –0.041)	0.029
Baseline HIV-1 RNA (per 1 $\log_{10}$)	2.215 (0.643, 3.788)	0.006
***CYP2B6* metaboliser genotype**		
Extensive	Reference group	
Intermediate	–2.926 (–5.752, –0.099)	0.043
Slow	–5.564 (–9.351, –1.777)	0.004

CI, confidence interval

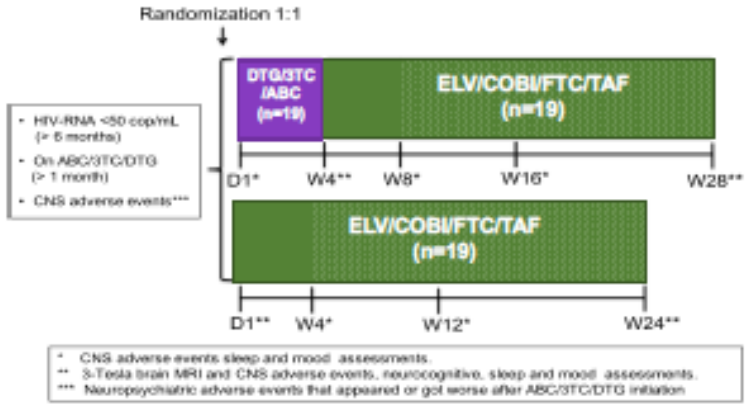
Conclusions

- ***CYB2B6* intermediate and slow** metabolisers gained **less** weight over 48 weeks than extensive metabolisers in the EFV arm
- ***CYP2B6* extensive** metabolisers in the TDF/FTC/EFV arm and participants in the TDF/FTC/DTG arm had **similar weight gains over 48 weeks**
- **Female *CYB2B6* slow** metabolisers **gained less** limb fat over a 48-week period compared with extensive metabolisers
- ***CYP2B6* metaboliser genotype, and baseline viral load and CD4 count** were independent predictors of weight change in the EFV arm
- Our findings suggest **that weight differences** between **EFV and DTG** are driven by impaired weight gain in PHIV likely to **have high EFV concentrations**

NEUROCOGNITIVE AND VOLUMETRIC CHANGES AFTER 24 WEEKS OF DTG/3TC/ABC DISCONTINUATION I. Pérez Valero et al.

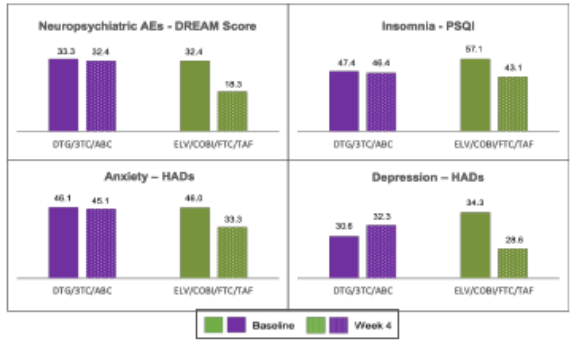
Las alteraciones el SNC se relacionan con ciertos I.I.
Que ocurre tras el cambio a otra integrasa **Elvitegravir**.

STUDY DESIGN



DIFFERENCES IN THE CHANGE OF CNS SCORES BETWEEN STUDY ARMS

We observed significant differences in changes of all neuropsychiatric scores, at week 4, among patients switched to ELV/COBI/FTC/TAF and those remaining on DTG/3TC/ABC



- **Mejoría de los parámetros del SNC:**
- Sueño, depresión, ansiedad

CHANGES IN CNS ADVERSE EVENTS

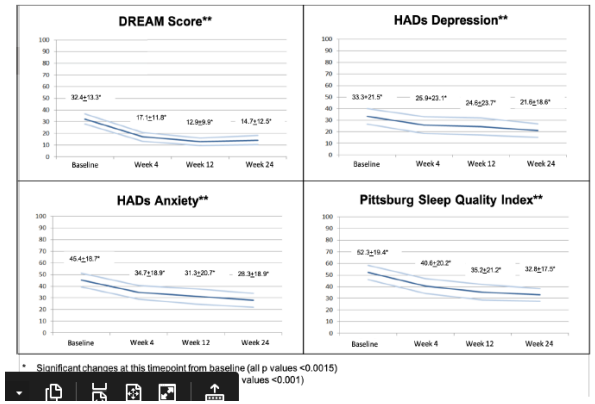
The proportion of participants reporting grade II-III neuropsychiatric adverse events decreased after switching DTG/3TC/ABC to ELV/COBI/FTC/TAF.

	BASELINE (n=38)	WK 4 (n=38)	WK 12 (n=38)	WK 24 (n=37)
Insomnia, (%)	73.7	34.2*	18.4*	8.1*
Abnormal dreams, (%)	31.6	13.2*	5.3*	8.1*
Impaired concentration, (%)	57.9	21.1*	13.2*	16.1*
Nervousness or irritability, (%)	47.4	15.8*	10.5*	10.8*
Asthenia or fatigue, (%)	55.3	26.3*	21.1*	24.3*
Symptoms of anxiety, (%)	42.1	18.4*	7.9*	10.8*
Symptoms of depression, (%)	34.2	18.4*	5.3*	13.5*
Suicidality, (%)	8	0	0	0

* Significant differences from baseline.

CHANGES IN CNS SCORES

We observed significative changes in all neuropsychiatric scores 24 weeks after switching to ELV/COBI/FTC/TAF.



- **N=19** pacientes
- Seleccionan los que no mejoran en un mes.
- Desconozco si el cambio fue inmediato.
- Efecto cambio/aprendizaje

NEUROCOGNITIVE AND VOLUMETRIC CHANGES AFTER 24 WEEKS OF DTG/3TC/ABC DISCONTINUATION I. Pérez Valero et al.

Las alteraciones el SNC se pueden cuantificar método de imagen?

CHANGES IN COGNITIVE PERFORMANCE

After switching to ELV/COBI/FTC/TAF we observed significant improvements in the global NC function (mean±SD GDS change: 0.12±0.32; p=0.029) and in the speed of processing (-0.26±0.86; p<0.001), delayed recall (-0.33±0.8; p=0.019) and motor (-0.51±0.85; p=0.001) domains.

COGNITIVE SCORES	day 1 *mean±SD*	week 24 *mean±SD*	P value
Attention, mean (SD)	0.03 (0.81)	0.19 (0.78)	0.119
Executive functioning, mean (SD)	0.23 (0.74)	0.47 (0.63)	0.068
Speed of processing, mean (SD)	0.49 (0.66)	0.79 (0.68)	<0.001
Learning, mean (SD)	-0.13 (1.18)	0.11 (0.95)	0.100
Delayed Recall, mean (SD)	-0.06 (1.04)	0.25 (1.1)	0.019
Verbal Fluency, mean (SD)	0.21 (0.92)	0.32 (1.03)	0.184
Motor, mean (SD)	-0.55 (1.3)	-0.02 (1.22)	<0.001
GDS, mean (SD)	0.33 (0.4)	0.2 (0.26)	0.029

CHANGES IN BRAIN VOLUMES

After FDR adjustment, only the changes in the right frontal pole, a cerebral region involved in information processing, emotion and motivated behaviors, remained significant (p<0.03).

LEFT BRAIN REGIONS	Volume at day 1 *mean±SD*	Volume at week 24 *mean±SD*	P value	RIGHT BRAIN REGIONS	Volume at day 1 *mean±SD*	Volume at week 24 *mean±SD*	P value
Cuneus	3.81±0.48	3.9±0.5	p=0.004	Cuneus	4.3±0.52	4.37±0.55	p=0.02
Calcarine	3.38±0.54	3.52±0.66	p=0.01	Calcarine	3.5±0.51	3.64±0.59	p=0.004
Inferior occipital gyrus	5.66±0.59	5.74±0.59	P=0.02	Inferior occipital gyrus	5.95±0.68	6.02±0.64	p=0.02
Cerebellar vermal lobules I-V	1.72±0.19	1.8±0.19	p=0.004	Cerebellar vermal lobules I-V	1.53±0.16	1.6±0.17	p=0.003
Basal cerebrum and forebrain	0.7±0.09	0.72±0.08	p=0.03	Inferior frontal angular gyrus	3±0.43	2.96±0.42	p=0.004
Lingual gyrus	7.4±0.89	7.54±0.83	P=0.03	Frontal pole	3.17±0.42	3.09±0.4	P<0.001
Accumbens	0.43±0.07	0.44±0.06	p=0.006	Caudate	2.94±0.46	2.96±0.46	p=0.008
Central operculum	4.01±0.61	4.04±0.56	P=0.04	CSF	0.15±0.04	0.13±0.04	p=0.006

- Desconozco metodología y reproductibilidad de estos resultados.
- El rendimiento cognitivo y los test: efecto aprendizaje
- Diferencias mínimas con significación estadística.

- La afectación del SNC, es un hecho, pero se produce en un bajo porcentaje.
- Tienden a desparecer en las primeras semanas
- En ocasiones obliga a un cambio: la elección de un fármaco sin tal efecto
- La retirada se relaciona en una disminución del los síntomas a nivel neurocognitivo
- Existe un porcentaje de pacientes con alteraciones previas: selección
- Desconozco clínica de métodos de imagen para diagnosticar tal efecto

Otras comorbilidades del ART en la actualidad

- Relacionadas con las interacciones
- Relacionadas con hábitos de vida
- Función renal/ósea: ok
- Envejecimiento + fragilidad: prematura
- Toxicidad a largo plazo de nucleósidos
- Neurocognitivo
- El control del inflamación ¿?

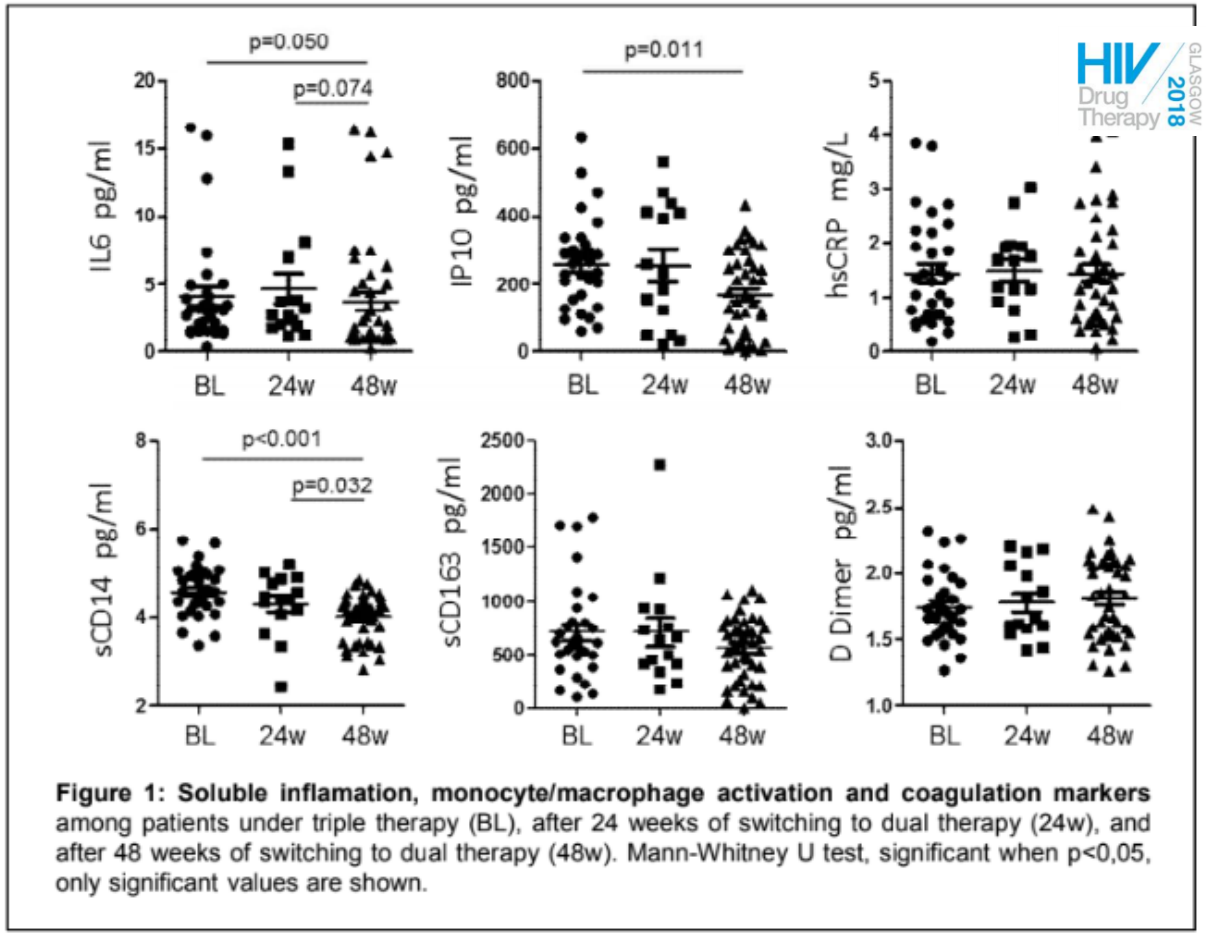
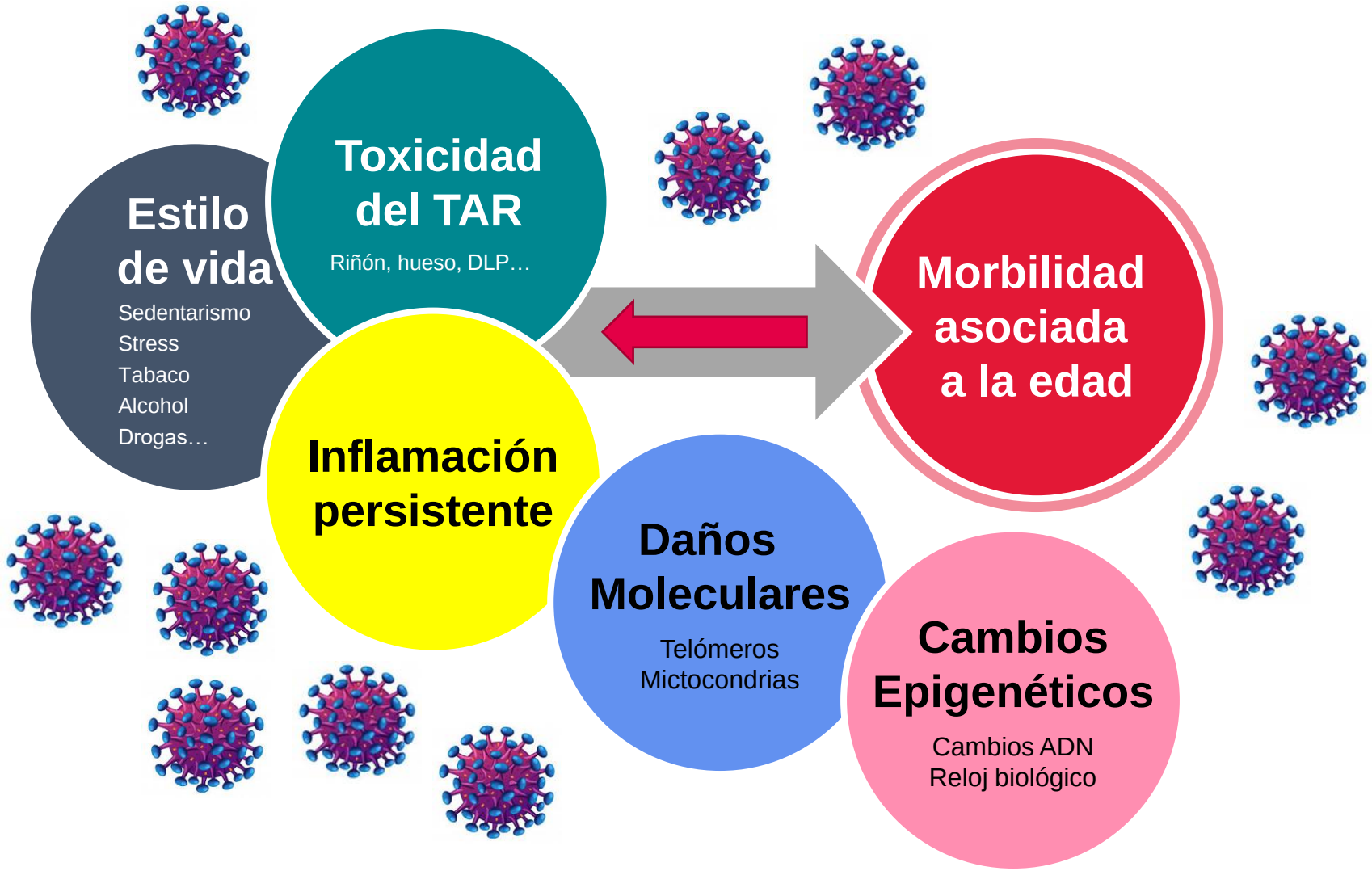


Figure 1: Soluble inflamation, monocyte/macrophage activation and coagulation markers among patients under triple therapy (BL), after 24 weeks of switching to dual therapy (24w), and after 48 weeks of switching to dual therapy (48w). Mann-Whitney U test, significant when p<0,05, only significant values are shown.

Moreover, **significant lower levels of IL6 and sCD14** levels were found in patients on dual therapy. Hence, dual therapy might be a useful strategy for the management of patients with increasing age and comorbidities.

Factores implicados en la morbilidad en personas mayores infectados por el VIH



Deeks SG. et al. BMJ 2009;338:a372

A todos los que estabais ahí…
Y en memoria de los que ya no están..