Research Letter

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Fat gain differs by sex and hormonal status in persons living with suppressed HIV switched to raltegravir/etravirine

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Fat gain is reported in integrase strand transfer inhibitors exposed persons living with HIV. We investigated in 165 persons living with HIV (117 men/48 women), included in the 96-week ANRS-163-ETRAL trial and switched to raltegravir/etravirine, the impact of sex, menopausal status and ovarian reserve (detectable anti-Müllerian hormone). From baseline to 48/96 weeks, women with ovarian reserve were protected from raltegravir/etravirine-induced weight/fat gain and associated insulin-resistance while peri/postmenopausal women increased weight, fat and insulin resistance as did men. The functional ovarian status could protect against raltegravir/etravirine-induced weight gain.

Weight/fat gain is reported in integrase strand transfer inhibitors (INSTI)-exposed patients, raising concerns on possible deleterious clinical outcomes [1,2]. An increased incidence of obesity was observed in antiretroviral therapy (ART)-naïve young Black-African patients living with HIV (PLWH) who initiated dolutegravir than in those who initiated an efavirenz-based treatment with higher weight gain in women than men [3]. In switch situations of ART-controlled PLWH, not all retrospective studies, including mainly men and white subjects, reported weight gain with INSTI [4,5]. Nevertheless, women and persons over 50 years experienced greater weight gain after vs. before switch to an INSTI [6]. In the Women's Interagency HIV Study (WIHS), women who switched to or added an INSTI to ART experienced greater increase in body weight compared with women who did not [7].

The 96-week ANRS 163 ETRAL study (NCT02212379) evaluating the efficacy and safety of raltegravir (400 mg twice-daily)/etravirine (200 mg twice-daily) in individuals over 45 years on a protease inhibitor-containing regimen, demonstrated durable efficacy [8]. We analyzed evolution of weight/fat and insulin sensitivity according to sex, and, in women, according to ovarian activity ($n = 40$, detectable level of the anti-Müllerian hormone, AMH, ELISA, Beckman-Coulter) [9] and menopausal status (12-month spontaneous amenorrhea). Body composition (total, trunk and limb mass, lean body mass) was measured using dual X-ray absorptiometry as previously published [8]. Insulin sensitivity was evaluated by the HOmeostasis Model Assessment of Insulin Resistance (HOMA-IR) index, sex steroids by mass spectrometry [10].

Baseline values and percentage changes from baseline were compared between groups using Mann–Whitney and Kruskal–Wallis tests and Wilcoxon paired test for the change within group. Correlation between parameters used the Spearman test. Chi^2 test was performed to compare categorical variables between groups.

There was no baseline difference between men ($n = 117$) and women ($n = 48$) in terms of personal and HIV-related parameters, except for race (35% Black-African women vs. 6% men) and $CD8^+$ cell count (Supplemental Digital Content-1, http://links.lww.com/QAD/B795).

At baseline, BMI did not differ between men and women and increased similarly at 48 and 96 weeks, with a 1.5 and 2.8% increase in men ($P < 0.0001$) and a 1.6 and 1.8% increase in women ($P = 0.04$ and 0.01), respectively (Table 1). Both men and women experienced increases in total, trunk and limb fat. Fat gain affected both peripheral (limbs) and central (trunk, waist, hip) areas.

AMH was detectable in 12 women, indicating functional ovarian activity (group 1, 46 years), six nonmenopausal women had undetectable AMH (perimenopausal, group 2, 47 years) and 22 were postmenopausal (group 3, 54 years). Evolution of BMI, total and trunk fat differed between the three groups (Table 1) with no variation in group 1, contrasting with increased BMI, total and trunk fat in the perimenopausal and postmenopausal groups leading to homogeneous fat gain. BMI variation did not differ between white and Black-African women.

Regarding the level of the main sexual steroids at baseline and 48 weeks (Supplemental Digital Content-2, http://links.lww.com/QAD/B795), estrogen and progesterone levels markedly differed, as expected, between groups. Conversely, there was no difference in the levels of testosterone, Δ-4-androstenedione and dehydroepiandrosterone between groups at baseline and 48 weeks, and no association with BMI changes.

The variation in BMI was negatively associated with the AMH level at 48 weeks ($R = -0.361$, $P = 0.02$) with the

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Table 1. Anthropometric parameters and insulin resistance in men and women, and in women according to their ovarian activity/menopausal status, at baseline, and 48 and 96 weeks after switch.

	n	Baseline	% Change at W48	% Change at W96	*P* value BL vs. W48	*P* value BL vs. W96
BMI (kg/m^2)						
Men	117	24.1 (22.5–25.7)	1.5 (−1.3–5.3)	2.8 (0–6.5)	**<0.0001**	**<0.0001**
Women	48	24.9 (22.5–29.2)	1.6 (−1.9–4.6)	1.8 (−1.8–6.8)	**0.043**	**0.010**
P value between groups		0.094	0.758	0.510		
Total fat (kg)						
Men	71	16.7 (11.9–22)	1.8 (−2.7–21.6)	11.8 (0–22.5)	**0.001**	**<0.0001**
Women	22	25.7 (17–38.1)	6.4 (0.6–18.1)	6.8 (−2.5–21.9)	**0.025**	**0.023**
P value between groups		**<0.0001**	0.539	0.492		
Trunk fat (kg)						
Men	71	10.4 (7.2–14.3)	2.8 (−1–22.1)	11.8 (−0.9–22.8)	**<0.0001**	**<0.0001**
Women	22	14.5 (8.9–19.2)	9.4 (−1.3–20.1)	8.7 (−2.3–23.3)	**0.050**	**0.035**
P value between groups		**0.008**	0.899	0.600		
Limb fat (kg)						
Men	71	6.3 (4.3–7.9)	0 (−3.3–21.2)	8.2 (0–26.45)	**0.008**	**<0.0001**
Women	22	11.9 (7.4–19.6)	3.9 (0.65–16.9)	6.2 (−1.6–20.4)	**0.019**	**0.021**
P value between groups		**<0.0001**	0.458			
WC cm						
Men	86	92 (86–98)	1.15 (−1.2–4.8)	2.4 (−1.05–6.9)	**0.003**	**<0.0001**
Women	34	93 (81–102)	1.6 (−1.25–3.9)	4.0 (0.95–8.2)	0.089	**0.001**
P value between groups		0.889	0.793	0.246		
WHR						
Men	86	0.98 (0.92–1.04)	0.00 (−2.8–3.5)	1.9 (−1.9–5.8)	0.684	**0.004**
Women	34	0.90 0.84–0.92)	0.6 (−1.25–4.1)	1.0 (−1.8–5.3)	0.360	0.197
P value between groups		**<0.0001**	0.568	0.654		
Total lean (kg)						
Men	71	49.8 (45–54.9)	0.6 (−0.7–3.5)	0.00 (−1.3–2.9)	**0.014**	0.228
Women	22	40.2 (34–42.8)	0.8 (−1.3–3.2)	−0.5 (−3–3.4)	0.357	0.821
P value between groups		**<0.0001**	0.807	0.594		
HOMA-IR						
Men	117	1.7 (1.2–2.4)	1.6 (−17.2–43.6)	15.2 (−12.8–59.4)	**0.017**	**<0.0001**
Women	48	1.9 (1.2–3.2)	13.7 (−28.7–80.9)	3.5 (−25.4–32.4)	**0.025**	0.731
P value between groups		0.450	0.442	0.074		
BMI (kg/m^2)						
Women with functional ovarian activity	12	27.75 (23.6–34.1)	−0.2 (−1.7–0.4)	−1.0 (−5.5–3)	0.333	0.594
Perimenopausal	6	26.1 (20.1–30.8)	7.7 (4–9.8)	5.7 (0–12.2)	**0.028**	0.068
Postmenopausal	22	24.65 (22.8–27.7)	1.6 (−1.8–3.9)	2.1 (−1.1–5.2)	0.126	**0.033**
P value between groups		0.568	**0.006**	0.110		
Total fat (kg)						
Women with functional ovarian activity	5	36.5 (30.6–39.3)	0.6 (−6–1.5)	−2.6 (−8.9 to −2.1)	0.893	0.500
Perimenopausal	3	32.3 (12.1–40.4)	16.3 (3.2–18.1)	16.8 (7.35–17.9)	0.109	0.109
Postmenopausal	9	23.4 (17.9–34.5)	17 (5.9–25.25)	24.4 (0.6–31.6)	**0.028**	**0.051**
P value between groups		0.629	0.067	0.107		
Trunk fat (kg)						
Women with functional ovarian activity	5	19 (15.05–19.2)	−2.6 (−14.7 to −1.1)	−6.9 (−12.9 to −2.3)	0.225	0.225
Perimenopausal	3	21.8 (6.4–24.3)	15.7 (3–20.1)	18.8 (10.3–25.3)	0.109	0.109
Postmenopausal	9	12.4 (8.9–17.4)	19 (10.95–29.8)	21.3 (6–39.4)	**0.038**	**0.021**
P value between groups		0.501	**0.050**	0.053		
Limb fat (kg)						
Women with functional ovarian activity	5	17.5 (15.5–20.1)	3.4 (0.65–3.9)	−2.9 (−5.8–1.9)	0.500	0.686
Perimenopausal	3	8 (5.7–18.6)	15.8 (3.9–16.9)	6.7 (−1.6–16.9)	0.109	0.285
Postmenopausal	9	12 (7.3–16.6)	12.8 (2.5–20)	10.9 (0–28.2)	0.086	0.110
P value between groups		0.321	0.319	0.374		
WC cm						
Women with functional ovarian activity	7	99 (84–107)	1.4 (−5.95–9.35)	2.7 (−4.8–6.5)	0.600	0.398
Perimenopausal	6	88 (77–107)	2.6 (1.9–3.9)	4.2 (2.8–15.85)	**0.027**	**0.028**
Postmenopausal	17	92 (83–100)	−1 (−1.7–7.7)	6.5 (1.1–8.2)	0.379	**0.006**
P value between groups		0.675	0.402	0.324		
WHR						
Women with functional ovarian activity	7	0.91 (0.77–0.96)	0.1 (−5.3–1.9)	−3.4 (−4.6 to −1.2)	0.866	**0.028**
Perimenopausal	6	0.89 (0.87–0.91)	2.4 (0.4–6.1)	0.0 (−1.4–10.5)	0.173	0.600
Postmenopausal	17	0.90 (0.83–0.96)	0.3 (−1.25–3.3)	1.85 (−1.2–5.3)	0.619	0.113
P value between groups		0.908	0.383	0.079		
Total lean (kg)						
Women with functional ovarian activity	5	41.8 (41.4–50.1)	2.3 (1.1–5)	−1.35 (−1.9–1.1)	0.225	0.686
Perimenopausal	3	35.3 (29.7–39.5)	4.9 (0.5–5.6)	5.8 (2–8.1)	0.109	0.109
Postmenopausal	9	41.8 (40–42.9)	−1.3 (−2.6–1)	−3 (−4.1–2.9)	0.441	0.314
P value between groups		0.165	0.092	0.107		
HOMA-IR						
Women with functional ovarian activity	12	3 (1.8–4)	−42.6 (−61 to −0.1)	−40.2 (−54.4 to −1.6)	0.239	0.084
Perimenopausal	6	1.9 (0.5–2.4)	93.1 (40.8–184.1)	21.8 (−6.2–74.3)	**0.046**	0.173
Postmenopausal	22	1.7 (1.1–2.8)	25.3 (−8.6–67.7)	6.25 (1.1–33.25)	**0.021**	0.054
P value between groups		0.143	**0.006**	**0.014**		

BL, baseline; HOMA-IR, HOmeostasis Model Assessment of Insulin Resistance; WC, waist circumference; WHR, waist to hip ratio. *P*-values indicated in bold are those equal or less than 0.05

same trend at baseline ($R = -0.274$, $P = 0.08$); 75% of women with detectable AMH at 48 weeks had stable or decreased BMI. Conversely, 71% of peri/postmenopausal women had increased BMI (Chi^2 $P = 0.0065$). The results obtained with baseline AMH were almost similar. This suggests that functional ovarian activity could protect against raltegravir/etravirine-induced weight gain.

HOMA-IR did not differ between men and women at baseline and increased at 48 weeks in men and in peri/postmenopausal women and at 96 weeks in men.

BMI and HOMA-IR variations between baseline and 96 weeks were corelated both in men ($R = 0.348$, $P < 0.001$) and women ($R = 0.413$, $P = 0.004$), in favor of increased insulin resistance partly resulting from weight gain.

We observed here that men increased weight/fat after switching to raltegravir/etravirine. This weight variation appears different from that related to aging in PLWH. In the Multicenter AIDS Cohort Study [11], BMI steadily increased between 40 and 60 years by 0.05 kg/m^2/year (0.2%/year) and stabilized over 60 years, far less than the 1.5%/year observed in ETRAL men. While initiation of INSTI has been associated with weight gain in men [3], most studies on patient switched to INSTI were retrospective and report no or a mild weight gain [4–6] contrasting with the ETRAL results.

Women from the general population experience progressive fat mass increase with chronological aging, whereas changes in body composition with central fat distribution are primarily due to ovarian aging, reflected by the AMH level [12]. However, PLWH from the WIHS aged 40–60 years undergoing the menopausal transition increased steadily annually their BMI by 0.06 kg/m^2/year (0.2%) [11]. The rate of fat gain was not increased during/after menopause by contrast to HIV-negative women who experienced increased BMI and waist circumference [13]. In our study, postmenopausal women experienced an 2.1% increased BMI and 6.5% increased waist circumference after 96 weeks, far more than expected according to the data from the WIHS [11], further stressing for a global weight/fat gain related to raltegravir/etravirine, in addition to the hormonal status. Accordingly, specific weight gain related to switching to an INSTI has been reported in white and Black women from the AIDS Clinical Trials Group A5001/A5233 studies more than 50 years but not less than 40 years [6]. In the WIHS [7], INSTI-treated women experienced a 2.4-kg increased body weight vs. 0.2 kg in the group receiving conventional ART. Weight gain was higher for women more than 50 years, again stressing for a possible role of the menopausal status in women switched to an INSTI. This contrasts with the INSTI-induced weight gain observed in young women initiating ART [3]. This discrepancy remains to be addressed. Regarding ethnicity, we did not find differences between white or Black-African women, as observed in the ACTG follow-up study [6]. Discrepant results have been reported regarding variations in insulin resistance after switching to an INSTI, with raltegravir either decreasing (SPIRAL) or increasing (ETRAL) insulin resistance.

Limitations are the single-arm design of study and the relatively small number of women included. Modifications in the dietary habits or exercise levels were not recorded.

Overall, men and women gained weight/fat when receiving raltegravir/etravirine. However, these changes differed markedly according to the women's hormonal status Functional ovarian activity prevented fat gain or higher insulin resistance. These findings might be important for the clinical management of these women.

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Conflicts of interest

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