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Dolutegravir monotherapy and body weight gain in antiretroviral naïve patients

The start of antiretroviral therapy (ART) in naïve patients is often associated with an increase in body weight [1]. In the first years of ART, weight gain was often seen as a 'return to health' condition [2]; however, in recent years, the steady increase in BMI of HIV-infected patients on ART has been associated with overweight and obesity [3] and with cardiovascular and metabolic disorders [4].

Some studies have suggested that integrase inhibitors (INSTIs), and particularly dolutegravir, administered with a nucleoside/nucleotide backbone, are associated with greater increases in BMI in naïve or antiretroviral-switched suppressed patients compared with other antiretroviral drugs [5–7]. Only the MONODO study has shown weight gain in experienced patients on dolutegravir monotherapy [8].

Two years ago, we described the efficacy of dolutegravir monotherapy in a selected cohort of 20 highly adherent antiretroviral naïve patients with a zenith HIV-RNA below 100 000 copies/ml [9], and we have now conducted a retrospective evaluation of body weight changes at 12 months of treatment in 23 patients (including those described in [9]) who started dolutegravir monotherapy 50 mg once daily between June 2015 and October 2017. The patients (18 men, five women; 22 whites, one Black African) had a mean age of 43.6 years (range 28–76). At baseline the mean T $CD4^+$ cell count was 396.48/μl (range 1–785) and the mean HIV-RNA was 33 420 copies/ml (range 1400–96 600 copies/ml). Only one patient was hypertensive (on cholesterol-lowering therapy) at baseline and no one had diabetes. Most patients achieved virologic suppression within 1 month of starting therapy.

Baseline BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–25 kg/m^2), overweight (25–29.9 kg/m^2) or obese (≥30 kg/m^2). The mean BMI before ART initiation was 24.21 kg/m^2 (range 20.96–28.15), with a mean weight of 73.78 kg (range 57.5–96.5). No patients were under weight or obese at baseline; 14 patients had normal weight (60.9%), whereas nine were overweight (39.1%).

We compared numerous outcome variables [BMI, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, $CD8^+$ cell count and $CD8^+$%, $CD4^+/CD8^+$ ratio] at baseline and at month 12 using a paired sample *t* test (the results are reported in Table 1), and we evaluated the association between different variables using Pearson's correlation coefficient. A two-tailed *P* value of less than 0.05 was considered statistically significant.

After 12 months of dolutegravir monotherapy, the mean BMI was 25.49 kg/m^2, with a mean increase of 1.28 kg/m^2 ($P < 0.001$). The mean weight increased to 77.6 kg (range 62–99), with a mean rise of 3.82 kg ($P < 0.001$). Five of the 14 patients with a normal weight at baseline were overweight at month 12. The nine overweight patients at baseline remained so at month 12. No patients were obese or underweight at month 12. Among those with normal weight at baseline, the mean BMI increased from 22.78 to 24.09 kg/m^2, with a mean rise of 1.31 kg/m^2. Among those patients who were overweight at baseline, the mean BMI increased from 26.44 to 27.68 kg/m^2, with a mean rise of 1.24 kg/m^2. The BMI rise in baseline normal weight vs. overweight patients was not statistically significant ($P = 0.77$).

Table 1. Changes in body weight and laboratory parameters between baseline and at 12 months of dolutegravir monotherapy.

	Baseline	12 Months	Difference (95% CI)	*P*
Weight (kg)	73.78	77.6	3.82 (−1.56 to 9.20)	**<0.001**
BMI (kg/m^2)	24.21	25.49	1.28 (0.01 to 2.55)	**<0.001**
Total cholesterol (mg/dl)	164.61	183.3	18.7 (−2.31 to 39.71)	**0.014**
LDL cholesterol (mg/dl)	102.78	111.74	8.96 (−8.68 to 26.60)	0.14
HDL cholesterol (mg/dl)	44.22	50.04	5.83 (−2.18 to 13.82)	**0.012**
Triglycerides (mg/dl)	98.96	107.61	8.65 (−17.87 to 35.17)	0.33
$CD4^+$ cell count (cells/μl)	396.48	643.91	247.43 (120.45 to 374.41)	**<0.001**
$CD4^+$%	22	30.17	8.17 (3.78 to 12.56)	**<0.001**
$CD8^+$ cell count (cells/μl)	876.57	921.52	44.96 (−167.44 to 257.34)	0.48
$CD8^+$%	50.20	43.16	−7.04 (−14.09 to 0.01)	**<0.001**
$CD4^+/CD8^+$ ratio	0.48	0.78	0.3 (0.07 to 0.53)	**<0.001**

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Bold values indicate statistical significance ($P < 0.05$).

No patients developed hypertension or diabetes during the period examined and no one started cholesterol-lowering therapy. TC ($P = 0.014$) and HDL cholesterol ($P = 0.012$) increased significantly after 12 months of treatment, while LDL cholesterol and triglycerides did not.

The mean $CD8^+$ cell count increased from 876.6/μl at baseline to 921.5/μl at month 12 ($P = 0.47$), whereas the mean $CD8^+$ percentage decreased from 50.2% to 43.2% ($P < 0.001$). The mean $CD4^+/CD8^+$ ratio increased from 0.48 to 0.78 ($P < 0.001$).

The patients who gained more weight were more likely to be females (mean increase of 1.88 kg/m^2 in women vs. 1.12 kg/m^2 in men, $P = 0.004$) and to have a higher HIV-RNA level at baseline (Pearson's correlation coefficient 0.55, $P = 0.006$). No significant associations were found between weight gain and age, $CD4^+$ cell count or BMI at baseline.

Our study in naïve patients on dolutegravir monotherapy confirms the association between treatment with this INSTI and body weight gain [3,5–7,10] as well as the correlation between body weight gain and baseline HIV-RNA level [7,11,12] or female sex [1,7,11]. A longer follow-up and higher numbers of patients are needed to establish possible higher incidence of cardiometabolic diseases which were not found in our limited study.

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Conflicts of interest

There are no conflicts of interest.

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Perinatal HIV and response to vaccination

I read with interest the exhaustive review of Flynn and Abrams [1] regarding the challenging health issues of the growing perinatally HIV-infected (PHIV) population worldwide.

One major issue is, however, not covered in their review: response to vaccines administered routinely during childhood.

PHIV patients underwent frequent treatment interruptions [2]. Uncontrolled viral replication in PHIV children has been associated with expansion of abnormal B cells subsets and defective follicular helper T cells functions that are critical in the induction of long-lived vaccine responses [3].

Lower seronconversion rates and a shorter duration of seroprotection has been reported in PHIV children for most of the vaccine administered in childhood [4].

As an example, the immune response following measles–mumps–rubella (MMR) vaccine has been well documented in PHIV in both developed and developing countries [5]. Although, in HIV-uninfected children, one