

Reduction in the weight, gained due to dolutegravir, following switch to bictegravir

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Abstract

Background: HIV-infected individuals can live with the virus for decades, and the physicians have to review the long-term health implications of weight gain as they would for any other patient. Although the integrase strand transfer inhibitors (INSTIs) class of drugs are one of the most popular regimens used for rapid reduction and maintenance in HIV cases, the weight gain resulting from their use is concerning. The use of dolutegravir (DTG) an INSTI is observed to have a weight gain in people living with HIV. Since bictegravir is also an INSTI, it is expected to show a similar weight gain. **Objective:** This retrospective analyses the change in the weight in 22 patients, who showed a trend of increase in weight when on DTG and later when switched to bictegravir therapy showed reduction in the increased weight. **Methods:** This is a retrospective analysis from our clinic (Dr. Saple's Clinic) in Mumbai from the duration of March 2018 to March 2021. Excessive weight gain was observed when the patients were on DTG therapy. The therapy was then switched to an equally potent integrase strand inhibitor bictegravir to get the benefit of efficacy of antiretroviral therapy and avoid the weight gain effect seen with DTG. **Results:** In our case review, we found results contrary to this. After 22 patients were treated on DTG for 9 to 24 months (mean 20.68 months), the baseline weight of 74.04 kg increased significantly to 84.26 kg ($P < 0.05$). After switching over to bictegravir for a mean period of 8 – 12 months (mean 11.72 months), this weight reduced to mean of 77.08 kg, a drop was clinically observed but was not statistically significant. **Conclusion:** Our finding could be the first instance where weight loss has been reported post switching the patients from DTG therapy to Bictegravir. Considering smaller patient population this outcome may need further confirmed through large group study.

Key words: Bictegravir, body mass index, dolutegravir, weight

Introduction

Advancement in antiretroviral therapy (ART) has enabled people living with HIV (PLHIV) to have longer life expectancy and better quality of life. Newer drug options in ART have allowed us to use personalized approach for treatment, considering tolerability in individual patients. Integrase strand transfer inhibitors (INSTIs) are one of the most popular and accepted drug class in ART due to their high potency, high barrier to resistance, low toxicity, and good tolerability. This class of drug blocks the integration of the viral genome into the host genome hence inhibiting the transfer of strands.^[1] The Drug Controller General of India (DCGI) approved the first INSTI, raltegravir in January 2010, and later dolutegravir (DTG) in November 2016. The latest approval by DCGI among INSTIs is bictegravir in June 2018.^[2] In the real-world clinical use, INSTIs are generally well tolerated. Toxicity profiles earlier

observed with other antiretrovirals such as neurological and gastrointestinal were seen to be reduced with the use of INSTIs. On the contrary, other adverse events such as weight gain is been observed with INSTIs.^[1]

There is a high risk of cardiovascular disease in PLHIV as compared to people without HIV. Higher body mass index (BMI) is considered a risk factor for diabetes mellitus which is also a risk for myocardial infraction in the general population and PLHIV. To avoid these risk of metabolic disorders, it is important to control the two major issues in PLHIV of weight gain and increase in BMI. Reports have shown a possible of role of DTG in weight gain.^[3] DTG is a second-generation integrase inhibitor that was commonly used in high-income countries and is now rolled out in public market under NACO in India.

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Table 1: Baseline characteristics of patients switched from dolutegrovir to bictegrovir

Patient characteristics	All population (n=22)	Males (n=16)	Females (n=6)
Age of patients (years)			
Mean age (years)	49.68	49.43	49.35
Age (range in years)	23-59	42-59	23-55
Age (SD)	7.88	7.98	8.05
HIV disease duration (years)			
Mean disease duration (years)	10.86	10.43	9.95
Disease duration (range in years)	2-20	2-20	3-20
Disease duration (SD)	6.25	6.05	5.79
Duration of DTG therapy (months)			
Mean duration of DTG therapy (months)	20.68	20.52	20.35
Duration of DTG therapy (range in months)	9-24	9-24	18-24
Duration of DTG therapy (SD)	4.98	5.05	5.11
Duration of BIC therapy (months)			
Mean duration of BIC therapy (months)	11.68	11.86	11.65
Duration of BIC therapy (range in months)	8-12	10-12	8-12
Duration of BIC therapy (SD)	0.95	0.48	0.99

DTG=Dolutegrovir; BIC=Bictegrovir; SD=Standard deviation

Forty-eight-week results showed that DTG-based regimens were noninferior to efavirenz (EFV)-based therapy; however, the weight gain in patients taking DTG was striking.^[4] Bictegrovir (BIC) is the latest addition to INSTIs which is also considered being associated with weight gain but has limited data.

This case study analyses the change in the weight in 22 patients, who showed a trend of increase in weight when on DTG and later when switched to bictegrovir therapy showed reduction in the increased weight.

METHODS

This is a retrospective analysis from our clinic (Dr. Saple's Clinic) in Mumbai from the duration of March 2018 to March 2021. Excessive weight gain was observed when the patients were on DTG therapy. The therapy was then switched to an equally potent integrase strand inhibitor bictegrovir to get the benefit of efficacy of ART and avoid the weight gain effect seen with DTG. Total of 22 patients (16 males and 6 females) were switched from DTG-based therapy to bictegrovir-based regimen and were observed for various durations. The baseline characteristics of these patients are shown in Table 1.

Descriptive data and nonparametric statistics have been used for presentation.

In addition to the above, we had data of 39 patients who were switched from DTG to bictegrovir for reasons other than weight gain. The reasons were permutations of various factors such as cost, pill burden, menopause, prevention of resistance, increased serum creatinine, recently diagnosed diabetes, ART naïve, and single treatment regimen. In these cases, weight data were not available at the beginning of DTG. We only had data before and after bictegrovir. Hence, this data were separately analyzed to see if there is any effect on weight

Results

Table 2 shows the mean weight for the population in both DTG and bictegrovir therapy. After the patients were treated on DTG for 9 to 24 months (mean 20.68 months), the baseline weight of 74.04 kg increased significantly to 84.26 kg ($P < 0.05$). After switching over to bictegrovir for a mean period of 8 – 12 months (mean 11.72 months), this weight reduced to 77.08 kg, a drop was numerical but not statistically significant.

Table 2: Weights pre- and posttherapy of dolutegrovir and bictegrovir

Weight (kg)	All - mean (SE)	Males - mean (SE)	Females mean (SE)
n	22	16	6
Weight before DTG	71.05 (3.18)	73.0 (3.95)	66.83 (4.83)
Weight after DTG	81.23 (3.25)*	82.58 (3.95)	77.65 (5.87)
Weight after BCT	74.36 (2.84)**	75.93 (3.5)	70.02 (4.68)

* $P < 0.05$, weight loss after bictegrovir; **Not significant - Wilcoxon rank-sum test. Weight gain after dolutegrovir in all patient. SE=Standard error; DTG=dolutegrovir; BCT=Bictegrovir

The change in weights is shown in Table 3. Post-DTG, as compared to a mean weight gain of 9.55 kg in males, females had gained 11.82 kg (not significant by nonparametric tests). There is a numerical drop in weight post bictegrovir of 6.69 kg for males and 7.48 kg in females, but it is also not significant.

In the additional data, set of 39 cases who were switched to bictegrovir for reasons other than weight gain, the mean weights (standard error) pre- and postbictegrovir was 66.87 (1.89) kg and 66.28 (1.87) kg, respectively (no significant change).

Discussion

Although INSTIs are one of the most popular regimens used for rapid reduction and maintenance in HIV cases, the weight gain resulting from their use is concerning. Although it was initially thought that it could be as a consequence of the patient returning to health, this weight gain is unexplained and needs further study. Today, HIV is treated more as a chronic illness as opposed to the grim prognosis it had earlier. This means that patients can live with the virus for decades, and physicians have to review the long-term health implications of this weight gain as they would for any other patient.^[4]

This data were gathered after we noticed a drop in weight in some patients after switching to bictegrovir-based therapy from DTG.

A retrospective review of virologically suppressed 103 adult prisoners living with HIV on non-INSTI therapies who were switched to INSTIs, showed an average increase in weight of 4.3 kg. Patients received DTG, raltegravir, bictegrovir, and elvitegravir over a 12-month period.^[5]

Table 3: Change in weight pre- and posttherapy

Patient group	All population (n=22)	Males (n=16)	Females (n=6)
Weight gain in patients with DTG therapy			
Mean weight gain on DTG therapy (kg) (SE)	10.19 (0.80)	9.55 (0.62)	11.82 (2.49)*
Weight reduction in patients with BIC therapy			
Mean weight reduction on BIC therapy (kg) (SE)	6.87 (0.63)	6.69 (0.67)	7.48 (1.51)**

*And mean weight loss between males and females; **Was not significant Wilcoxon rank-sum test. Mean weight gain between males and females. SE=Standard error; DTG=Dolutegravir; BIC=Bictegravir

The ADVANCE trial compared the efficacy of DTG-based regimens versus an EFV-based regimen. While the efficacy in all groups was comparable, in the tenofovir alafenamide (TAF), emtricitabine (FTC), and DTG group, the mean weight gain was 7.1 kg.^[4]

In our study, there was a statistically significant weight gain of 10.19 kg over a 2-year period when patients were administered DTG-based regimens, much in keeping with earlier studies. The weight gain in women was more than males but failed to achieve significance, possibly due to small and unequal numbers in both the groups. In terms of percentage, however, the overall weight gain was 14.32%, 13.12% in males and 16.19% in females which would be clinically relevant. This is also in lines with other studies showing higher weight gain in women.^[6] All the patients switched to DTG were virologically suppressed; hence healthy weight gain can be ruled out.^[4]

When our patients were switched to a bictegravir-based regimen, it was observed that, over a year, they lost a mean of 6.87 kg in weight, a clinically relevant trend although not significant. Again, the weight loss in females was numerically greater than males, 7.63% versus 6.65%. TAF is also reported as per the US-based cohort^[7] to be causing weight gain in HIV patients when switched from TDF. TAF, a component in bictegravir triple-drug regimen, can also be considered to nullify the weight loss trend seen with bictegravir in all patients switched from DTG. This may be one of the reasons for not achieving significant weight loss on bictegravir regimen.

We do not have any reports of weight loss on a bictegravir-based regimen, although there are indicators.

A retrospective analysis with the use of BIC/FTC/TAF was performed to analyze the factors associated with $\geq 10\%$ BMI increases versus $< 10\%$ increase. The data showed that there were no significant changes in BMI between pre- and postswitch to BIC/FTC/TAF time periods. This data show that there is chance of increase in weight of patient with the use of DTG while there may be no change in weight with the use of BIC.^[8]

This is confirmed by our analysis of the additional 39 cases who had to be switched from DTG to bictegravir for reasons other than weight gain. In this group, the pre- and postbictegravir weights were 66.87 kg and 66.28 kg indicating no weight loss. Could this mean that in those who have a propensity to gain weight on DTG, a switch

to bictegravir is beneficial, whereas in others, a switch has no effect on weight? This needs further study.

It is a well-known fact that patients on DTG are seen to gain weight. Since bictegravir is also an INSTI, it is expected to show a similar weight gain. However, Vo D *et al.* have shown that no weight gain is observed in patients on bictegravir therapy. In this study, there is a significant weight gain on DTG and a nonsignificant but numerical weight loss after switching to bictegravir therapy. Our finding could be the first instance where weight loss has been reported post switching the patients from DTG therapy to Bictegravir. Considering smaller patient population this outcome may need further confirmed through large group study.

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Conflicts of interest

There are no conflicts of interest.

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