

Are new antiretroviral treatments increasing the risks of clinical obesity?

Andrew Hill^{1*}, Laura Waters² and Anton Pozniak³

¹Department of Translational Medicine, University of Liverpool, UK

²Central and North West London NHS Trust, Mortimer Market Centre, London, UK

³Chelsea and Westminster Hospital, London, UK; London School of Hygiene and Tropical Medicine, UK

Abstract

There is growing evidence that the use of integrase inhibitors could lead to statistically significant increases in body weight and even clinical obesity, although it is unclear whether these changes are clinically significant. The effects of integrase inhibitors on body weight need to be analysed for women and by race, because current evidence suggests different effects. Potential additional effects of NRTIs on body weight need to be evaluated. Combined, standardised analyses of Phase 3 and independent clinical trials, with endpoints following the US Food and Drug Administration (FDA) guidelines where feasible, should be conducted to answer this question definitively. Analyses should also include a range of laboratory markers of cardiovascular risk, as proposed by the FDA.

Keywords: antiretroviral therapy, integrase inhibitors, obesity, raltegravir, dolutegravir, bictegravir

Introduction

There is growing evidence that the use of integrase inhibitors could lead to statistically significant increases in body weight and even clinical obesity. These effects seem to be most pronounced in black people and women; the use of tenofovir disoproxil fumarate (tenofovir DF) seems to lessen these effects, compared to the use of tenofovir alafenamide (tenofovir AF), abacavir or nucleoside analogue- (NRTI) sparing treatments.

Before the widespread introduction of integrase inhibitors, the US NA-ACCORD study, including over 14,000 individuals, described weight gains on first-line ART in a 2015 analysis. After 3 years on ART, 22% of individuals with a normal body mass index (BMI, 18.5–24.9 kg/m²) at baseline had become overweight (BMI 25–29.9 kg/m²) and 18% of those overweight at baseline had become obese (BMI >30). These increases in BMI were largest for women and, for some subgroups, greater than age-matched population controls [1]. Among people without HIV, life expectancy is 4 years shorter for those with a BMI >30, compared with people with a normal BMI [2]. However, an increase in weight after initiating ART is a well-described phenomenon, considered part of the ‘return to health’ effect [3]. Additionally, much of the world is dealing with rising rates of obesity in the general population [4]. Analysing weight change in randomised trials and among individuals switching ART may be more informative.

Results from observational studies

In 2017–2018, results from four observational cohort studies suggested that the use of integrase inhibitors was associated with greater increases in body weight, particularly among women. In a French study of 517 individuals (most already virologically suppressed on ART), there was a mean increase of 4 kg in women treated with dolutegravir, versus an increase of 2 kg among men. Increases in body weight and BMI were also greater for people given dolutegravir in combination with abacavir, compared to tenofovir. Four individuals discontinued dolutegravir-based treatment because of abnormal weight gain [5]. Similar results were

seen in a US observational study of 495 individuals, comparing those switched from tenofovir DF/emtricitabine/efavirenz to either an integrase-based regimen or a protease inhibitor- (PI) based regimen. Patients switched to integrase-based treatment showed a mean rise in body weight of 2.9 kg at 18 months, compared with a rise of 0.9 kg among those switched to PIs. Among those switched to integrase-based treatment, those switched to abacavir/lamivudine/dolutegravir showed the greatest increases in body weight, with a mean increase of 5.3 kg by month 18 of treatment [6]. A Brazilian study of 1794 individuals who started ART also showed similar trends: development of clinical obesity was seven times more likely for individuals starting integrase-based treatment, compared with non-nucleoside reverse-transcriptase inhibitor- (NNRTI) or PI-based treatment. In this study, females were more likely to develop clinical obesity [7]. Finally, a study of 4048 individuals treated in Texas, USA, showed the largest increases in BMI for non-white females, especially if treated with integrase inhibitors [8]. The increases in BMI were greater for people treated with PIs than for NNRTIs.

These observational studies were not randomised, and so the differences between treatment classes in body weight might be explained by other factors. There was a prospective trial of dolutegravir monotherapy conducted at the same time, including eight individuals stable on ART switched to dolutegravir monotherapy. Among these individuals, there was a mean increase in body weight of 4 kg over 24 weeks [9].

Results from randomised studies

Results from five randomised studies support the association between use of integrase inhibitors and increases in weight. Summary results are shown in Table 1. Two studies have evaluated raltegravir, with three evaluating dolutegravir. In the ACTG 5257 trial, including 1809 individuals, those randomised to first-line treatment with raltegravir were significantly more likely to become either overweight or obese than individuals given either atazanavir/r or darunavir/r (all combined with a tenofovir DF/emtricitabine backbone). In addition, black participants were 55% more likely to become either overweight or obese, compared to white participants [10]. The results suggested that these weight changes were associated with abdominal fat, as waist circumference also rose significantly more for participants treated with

*Corresponding author: Andrew Hill, Department of Translational Medicine, University of Liverpool, 70 Pembroke Place, Liverpool L69 3GF, UK
Email: microhaart@aol.com

Table 1. Effects of raltegravir, dolutegravir and bicitegravir on body weight in randomised trials

Study [ref]	Design	Results
Raltegravir		
NEAT 001 [12] (naïve, <i>n</i> =126)	DRV/r+RAL DRV/r + TDF/FTC	DEXA sub-study: trunk fat 7.3% higher DRV/r/RAL vs TDF/FTC/RAL at week 96 (<i>P</i> =0.021)
ACTG 5260s [10,11] (naïve, <i>n</i> =126)	TDF/FTC/RAL TDF/FTC/DRV/r TDF/FTC/ATV/r	Higher risk of severe weight gain for RAL vs ATV/r
Dolutegravir		
NEAT 022 [13] (switch, <i>n</i> =415)	NRTIs + DTG NRTIs + PI/r	+1 kg increase in body weight to week 48 (<i>P</i> =0.002)
SPRING-1 [13] (naïve, <i>n</i> =204)	TDF/FTC/EFV TDF/FTC/DTG	Increases in body weight higher in DTG arms
Gilead 1490 [15] (naïve, <i>n</i> =645)	TAF/FTC/DTG TAF/FTC/BIC	+3.9 kg increase in body weight to week 96 +3.5 kg increase in body weight to week 96
MONODO [9] (naïve, <i>n</i> =8)	DTG monotherapy	+4.1 kg increase in body weight to week 24
ATV/r: atazanavir/ritonavir; BIC: bicitegravir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; FTC: emtricitabine; NRTI: nucleoside reverse transcriptase inhibitors; PI/r: ritonavir-boosted protease inhibitor; RAL: raltegravir; TAF: tenofovir AF; TDF: tenofovir DF.		

raltegravir [11]. Newly published results from the NEAT 001 study show greater increases in visceral (trunk) fat for people treated first-line with raltegravir plus darunavir/r, versus tenofovir DF/emtricitabine/darunavir/r [12].

The original dose-ranging trial of dolutegravir, SPRING-1, showed greater increases in body weight for first-line treatment with two NRTIs plus dolutegravir, compared with two NRTIs plus efavirenz (60 individuals per arm). In the NEAT-022 trial, presented at HIV Glasgow 2018, 415 individuals stable on a two NRTI + PI-based ART were randomised to continue PI-based treatment, or to switch the PI component to dolutegravir. In this study, there were statistically significant increases in weight for individuals who switched to dolutegravir, but the difference between the arms was only 1 kg [13]. In a parallel presentation of the same study, switching to a dolutegravir-based regimen was associated with declines in both sCD14 and adiponectin, and adiponectin decline correlated with weight gain [14]. These markers have opposite effects on cardiovascular risk in HIV-infected subjects, so it is not clear what the overall effects on cardiovascular risk may be.

The randomised Gilead 1490 trial (*n*=631), evaluating first-line treatment with two different integrase inhibitors, was also presented at HIV Glasgow 2018. This study was conducted in a mainly white, male, asymptomatic population with high baseline CD4 cell counts. The mean increase in body weight to week 96 was similar in the two arms: +3.5 kg on tenofovir AF/emtricitabine/bicitegravir versus +3.9 kg on tenofovir AF/emtricitabine/dolutegravir [15]. This suggests that, if there is an effect of dolutegravir on weight gain, the effects are likely to be similar for bicitegravir.

Additional effects of NRTIs on weight gain

Results from three other studies suggest that there may be an additional effect of NRTIs on weight gain. In the AMBER trial, there was a greater increase in body weight for individuals treated first-line with tenofovir AF/emtricitabine/darunavir/c (+1.8 kg) versus with tenofovir DF/emtricitabine/darunavir/c (0.8 kg) [16]. Results from a German cohort study also show mean increases in body weight of 2.3 kg after switching from tenofovir DF to tenofovir AF [17]. In the STEAL study, evaluating a randomised switch to either abacavir or tenofovir, increases in body weight

to week 96 were 1 kg higher in the abacavir arm [18]. Treatment with tenofovir DF/emtricitabine is known to reduce levels of total cholesterol, which might contribute to changes in body weight. The three studies evaluated so far have shown smaller increases in body weight for tenofovir DF/emtricitabine compared to other NRTI backbones. It is not clear whether the other NRTIs are actually causing increases in body weight, or whether the only effect is from tenofovir DF/emtricitabine potentially leading to decreases in body weight.

Other analyses needed

According to the European Product Assessment Report [19], *in vitro*, dolutegravir inhibited the binding of radiolabelled α -melanocyte-stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) receptor by 64% at a concentration equal to the clinical *C*_{max}. MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in MC4R is associated with monogenic obesity. It is not clear whether these *in vitro* findings are associated with changes in body weight in individuals. Equivalent studies are needed for other integrase inhibitors.

There are several randomised studies of dolutegravir versus efavirenz ongoing in sub-Saharan Africa, which will be reporting results by April 2018 [20]. These include the NAMSAL trial (first-line tenofovir DF/lamivudine/efavirenz versus tenofovir DF/lamivudine/DTG for 610 treatment naïve individuals in Cameroon), the DOLPHIN-1 and 2 trials [efavirenz versus dolutegravir, both with 2NRTIs, for 300 treatment naïve pregnant women in Uganda and South Africa) and the ADVANCE trial (tenofovir AF/emtricitabine/dolutegravir, tenofovir DF/emtricitabine/dolutegravir or tenofovir DF/emtricitabine/efavirenz for 1053 treatment-naïve individuals in South Africa). The participants in these randomised trials are predominantly black, and the majority are women. From the studies of weight gain published so far, it seems that women and black people are most likely to show weight gains on integrase-based treatment, especially when compared with NNRTI-based treatment. By contrast, the majority of people in Phase 3 randomised trials of integrase inhibitors are white and male. For example, in the Gilead 1490 trial, 91% were male and 57% were white [11]. If the increases in body weight were 3.5–3.8 kg over 96 weeks in this predominantly white, male population (a mean

Table 2. FDA recommendations for analysis of clinical trials evaluating treatments for weight loss

Primary efficacy endpoint	Mean: the difference in mean percentage loss of baseline body weight in the active-product versus placebo-treated group Categorical: the proportion of subjects who lose at least 5% of baseline body weight in the active-product versus placebo-treated group
Secondary efficacy endpoints	Should include, but are not limited to, changes in the following metabolic parameters: <ul style="list-style-type: none"> • Blood pressure and pulse • Lipoprotein lipids • Fasting glucose and insulin • HbA1c (in type 2 diabetics) • Waist circumference

5% increase), larger increases in body weight may be expected in clinical trials recruiting mainly black women.

In the search for articles on body weight for integrase-based treatment, there was no information available from the original Phase 3 trials of dolutegravir, for example SINGLE, ARIA, FLAMINGO, SPRING-2 or GEMINI. Apparently body weight was not measured prospectively in these studies [14], so it is not possible to evaluate the risk of clinical obesity. The publications from the main Phase 3 clinical trials of elvitegravir, raltegravir and bictegravir also do not contain any information on body weight. Searches for data on the website www.clinicaltrials.gov did not reveal any results from these Phase 3 trials for either body weight, BMI or obesity. Clinical trial protocols have not included advice for clinicians on when treatment should be stopped for unexpected weight gain.

The need for standardised analyses

The observational studies and randomised trials in this review have been analysed using a range of methods: mean change in body weight, change in BMI and categorisation of BMI as normal, overweight and obese are the most common methods. In the ACTG 5257 trial, ‘severe weight gain’ was defined as either a 10% increase in body weight or treatment-emergent progression to a higher BMI category (e.g. from normal to overweight, or from overweight to obese). It should be feasible to analyse most clinical trials using categorised measures of BMI, provided that body weight is measured at the start and end of treatment. In addition, where DEXA scans have been performed, additional information may be available on changes in trunk and limb fat.

The US Food and Drug Administration (FDA) have guidelines for the evaluation of clinical trials evaluating treatments to reduce weight [21]. The FDA consider a 5% loss in weight to be clinically significant. This suggests that if another treatment increases mean weight by at least 5%, this would also be clinically significant. The FDA recommend that efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight [21]. These analyses are summarised in Table 2.

Conclusions

It is currently unclear whether integrase inhibitors cause clinically significant changes in body weight (at least 5%), or whether

these changes are statistically significant but small (less than 5%). The effects of integrase inhibitors on body weight need to be analysed for women and by race, because current evidence suggests different effects. Potential additional effects of NRTIs on body weight need to be evaluated. Combined, standardised analyses of Phase 3 and independent clinical trials should be conducted within the next 6 months to answer this question definitively. The endpoint used in these analyses should follow FDA guidelines, where feasible. Analyses should also include a range of laboratory markers of cardiovascular risk, as proposed by FDA.

References

1. Koethe J, Jenkins C, Lau B *et al.* Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. *AIDS Res Hum Retroviruses* 2016; **32**: 50–58.
2. Bhaskaran K, dos Santos-Silva I, Leon D *et al.* Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol* 2018; **6**: 944–995.
3. Yuh B, Tate J, Butt AA *et al.* Weight change after antiretroviral therapy and mortality. *Clin Infect Dis* 2015; **60**: 1852–1859.
4. World Health Organization. Overweight and obesity, key facts. Available at: www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed January 2019).
5. Menard A, Meddeb L, Tissot-Dupont H *et al.* Dolutegravir and weight gain: an unexpected bothering side-effect. *AIDS* 2017; **31**: 1499–1500.
6. Norwood J, Turner C, Bofill C *et al.* Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr* 2017; **15**: 527–531.
7. Bakal D, Coelho L, Luz P *et al.* Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. *J Antimicrob Chemother* 2018; **73**: 2177–2185.
8. Bedimo R, Adams-Huet B, Xilong L *et al.* Integrase inhibitors-based HAART is associated with greater BMI gains in Blacks and Hispanics. *ID Week*. November 2018. San Francisco, CA, USA. Abstract 538.
9. Sculier D, Docco-Lecompte T, Yerly S *et al.* Stable HIV-1 reservoirs on dolutegravir maintenance monotherapy: the MONODO study. *HIV Med* 2018; epub ahead of print.
10. Bhagwat P, Ofofokun I, McComsey G *et al.* Predictors of severe weight/body mass index gain following antiretroviral therapy initiation. *Conference on Retroviruses and Opportunistic Infections*. February 2017. Seattle, WA, USA. Abstract 695.
11. Bhagwat P, Ofofokun I, McComsey G *et al.* Raltegravir is associated with greater abdominal fat increases after antiretroviral therapy initiation compared protease inhibitors. *18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV*. September 2016. New York, NY, USA. Abstract 007.
12. Bernadino J, Mocroft A, Wallet C *et al.* Body composition and adipokines changes after initial treatment with darunavir-ritonavir plus either raltegravir or tenofovir disoproxil fumarate-emtricitabine: a sub-study of the NEAT 001/ANRS 143 randomised trial. *PLoS Med* 2019; in press.
13. Waters L, Assoumou L, Rusconi S *et al.* Switch to dolutegravir from a boosted protease inhibitor associated with a significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial. *HIV Glasgow*. October 2018. Glasgow, UK. Abstract P102.
14. Martinez E, Assoumou L, Moyle G *et al.* 48-week changes in biomarkers in subjects with high cardiovascular risk switching from ritonavir-boosted protease inhibitors ro dolutegravir in the NEAT -022 study. *HIV Glasgow*. October 2018. Glasgow, UK. Abstract O113.
15. Stellbrink H, Arribas J, Stephens J *et al.* Phase III randomised, controlled clinical trial of bictegravir coformulated with FTC/TAF in a fixed dose combination (B/F/TAF) versus dolutegravir (DTG) + FTC/TAF in treatment-naïve HIV-1 positive adults. *HIV Glasgow*. October 2018. Glasgow, UK. Abstract O211.
16. Orkin C, Eron J, Rockstroh J *et al.* Efficacy and safety of the once-daily, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen (STG) in ART-naïve, HIV-1 infected adults: AMBER 96 week results. *HIV Glasgow*. October 2018. Glasgow, UK. Abstract O212.
17. Martin A, Bloch M, Amin J *et al.* Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomised, 96-week trial. *Clin Infect Dis* 2009; **49**: 1591–1601.
18. Gomez M, Seybold U, Roeder J *et al.* A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015–2017. *Infection* 2018; epub ahead of print.
19. European Medicines Agency. Assessment report. Dolutegravir (Tivicay) Available at: www.ema.europa.eu/documents/assessment-report/tivicay-epar-public-assessment-report_en.pdf (accessed January 2019).
20. Vitoria, M, Hill A, Ford N *et al.* The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries: what are the issues? *AIDS* 2018; **32**: 1551–1561.
21. Food and Drug Administration (USA). Guidance for Industry. Development of products for weight management. February 2007. Available at: www.fda.gov/downloads/Drugs/Guidances/ucm071612.pdf (accessed January 2019).