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EDITORIAL COMMENTARY

Life-long Antiretroviral Therapy: Playing the Long Game

Brian Conway

Medical Director and President, Vancouver Infectious Diseases Centre, Vancouver, British Columbia, Canada

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An enduring image of the first decade of the AIDS epidemic is that of a wasted individual with advanced immune disease. Provision of antiretroviral therapy (ART, as imperfect as it was at the time) led to a temporary but significant improvement in the general state of health. This was invariably accompanied by weight gain, which was viewed as a sign of success. In the current era, when all infected adults are offered potent combination therapy from the time of diagnosis, there is a concern that we select a regimen that is as simple as possible to ensure long-term adherence, as effective as possible to ensure rapid and sustained virologic suppression, and as safe as possible to ensure long-term health. From a societal perspective, the epidemic of human immunodeficiency virus (HIV) infection is intersecting with the epidemic of obesity. As reported by the Centers for Disease Control and Prevention, between 1999–2000 and 2017–2108, the prevalence of obesity in the United States increased from 30.5% to 42.4%, and severe obesity from 4.7% to 9.2% [1].

It is understandable that if any ART were to be associated with increased weight gain (due, perhaps to off target effects that lead to increased drug toxicity), this could be greatly problematic. This may parallel the effects of certain nucleoside analog combinations associated with mitochondrial toxicity and disfiguring lipodystrophy. In vitro data suggest dolutegravir may block the binding of melanocyte stimulating hormone (MSH) to its receptor by 64% at therapeutic concentrations [2]. This could, in theory, affect energy homeostasis and increase appetite, leading to unintended weight gain. A review of clinical trials of integrase strand transfer inhibitors (INSTIs) appears to show a consistent pattern of weight gain following their initiation as a possible "class effect" [3]. This seems to be most marked with the newer agents dolutegravir and bictegravir, with a weight gain of 4.0 kg over 24–96 weeks being reported with either drug in carefully conducted studies. There is a call for additional analyses to be conducted with stratification by sex and race, with additional evaluations to measure the health consequences of weight gain should it occur.

In the current issue of *Clinical Infectious Diseases* [4], Griesel and colleagues provide us with insightful information to address these pertinent issues. The ADVANCE study, conducted in South Africa, was an open-label 3-arm randomized study to compare dolutegravir (with emtricitabine [FTC] and either tenofovir dipivoxil [TDF] or tenofovir alafenamide [TAF]) and efavirenz (with FTC and TDF) -based therapy among individuals who had not received ART for ≥6 months. The hypothesis to be tested is that certain CYP2B6 metabolizer genotypes would be associated with higher efavirenz concentrations that would impair the expected beneficial weight gain associated with ART initiation. This could relate to mitochondrial toxicity, impaired adipocyte differentiation, and increased release of catabolic pro-inflammatory cytokines stimulated by efavirenz. All of these are credible mechanisms with some prior validation. Of the individuals on efavirenz, 171/351 agreed to the genetic testing. It is important to note that these individuals were a representative subset of all those enrolled in this arm of the study. The greatest weight gain (3.5% body weight) was observed among CYP2B6 extensive metabolizers, with a graded effect recorded among intermediate (0.3%) and slow (−1.7%) metabolizers. Weight gain in patients receiving dolutegravir was no different than that observed in rapid metabolizers receiving efavirenz. Weight gain was greater among patients with lower baseline CD4 cell counts and higher baseline plasma viral load measures, representing those with more advanced HIV-related disease.

Weight gain associated with the initiation of ART is not a new phenomenon and not only limited to the early phases of the AIDS epidemic. A comprehensive review of 17 North American cohorts including over 14 000 patients is particularly instructive [5]. In comparing those initiating any form of ART between 1998 and 2010 (all dates well into the era of highly active triple combination ART), it was reported that the median baseline body mass index (BMI) increased from

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Correspondence: B. Conway, Vancouver Infectious Diseases Centre, 201–1200 Burrard St, Vancouver, British Columbia, V6Z2C7, Cs (brian.conway@vidc.ca).

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23.8 to 24.8 kg/m^2, with the proportion of those with a BMI above 30 kg/m^2 doubling from 9 to 18%. This reflects the increase in obesity among North Americans over this same period and the fact that HIV-infected patients were receiving therapy at earlier disease stages. After 3 years on ART (at a time when non-INSTI-based combinations were the standard of care), 22% of nonobese subjects had become overweight, whereas 18% of those who were overweight had become obese.

Even in the current era, there is increasing evidence that weight gain is associated with both INSTI and non-INSTI-based combinations [6]. In a cohort of over 1100 patients evaluating patients on 1 of 3 INSTIs (dolutegravir, raltegravir, elvitegravir), darunavir or rilpivirine, weight gain was associated with all regimens over 12 months. It is interesting to note that the least significant increase in weight was recorded in the participants receiving the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine. A recent review puts forward another NNRTI, doravirine, as a solution to avoid weight gain associated with INSTIs, as well as other "negative" metabolic consequences [7].

So how do the data presented by Griesel and colleagues better inform what we should tell our patients to expect when initiating ART? If they are adherent, they should expect full and lasting virologic suppression and a healthy life expectancy that approaches that of an HIV uninfected population. Depending on the chosen regimen, they can expect some short-term side effects that are usually transient or easily addressed by a therapeutic modification. Once a well-tolerated and effective regimen is in place, the conversation inevitably turns to the long game. What can I expect 10–20 years from now? It could be that, as was the case when we were prescribing zidovudine monotherapy a generation ago, weight gain will be part of the "new normal." Regimens that do not lead to such effects may well be the ones having off target effects that prevent a healthy, manageable increase in weight from taking place and not the other way around. This is not to say that our goal should be to allow an individual's BMI to increase in an uncontrolled way as an unavoidable consequence of modern INSTI-based ART, particularly within a societal context when obesity is on the rise for reasons quite apart from HIV infection and its treatment. As we work with our patients to ensure that they receive optimal ART, we should also offer a multidisciplinary program of intervention to address their general health. This should include a program to encourage a healthy diet, a robust plan of physical activity along with, screening for hypertension, glucose intolerance, and other conditions on the rise in many parts of the world. This is all the more important in that the ART that is preventing them from succumbing to the effects of their HIV infection may, as part of its natural beneficial effects, be adding to the burden of weight gain that may, if unchecked, affect their health in a deleterious way. Partnering with our patients in this holistic way is the long game we are called to play.

Note

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