More Studies Link Dolutegravir to Weight Gain

The effect is greater for women, and it could have a detrimental effect on pregnancy outcomes at the population level.

August 20, 2020 By Liz Highleyman

A growing body of evidence continues to show that people who use the integrase inhibitor dolutegravir are more likely to gain weight after starting treatment, according to reports presented last month at the International AIDS Conference (AIDS 2020:Virtual).

Weight gain after starting antiretroviral treatment has become a concern in recent years. People with advanced immune suppression and opportunistic illnesses often gain weight as they return to health after starting treatment, and some people with HIV develop lipohypertrophy, a specific type of weight gain that often involves accumulation of internal abdominal fat. But the weight gain that occurs among people who start treatment with modern antiretrovirals before they sustain serious immune system damage appears to be a different phenomenon.

Although weight gain can occur after starting any class of antiretroviral drug, it has most frequently been reported among those taking potent integrase inhibitors, including dolutegravir (Tivicay, also in the Triumeq, Juluca and Dovato coformulations), and tenofovir alafenamide (TAF), the newer version of the drug in Descovy and several other combination pills.

Weight Gain and Hyperglycemia

At AIDS 2020, Julie Ake, MD, MSc, of the U.S. Military HIV Research Program, presented findings from a study of weight gain and hyperglycemia (high blood glucose) during the transition to dolutegravir in Africa.

Dolutegravir is one of the most effective antiretrovirals, and U.S. and World Health Organization guidelines recommend it for first-line treatment. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) has adopted dolutegravir, tenofovir disoproxil fumarate (TDF, the older version of the drug) and lamivudine as the preferred regimen for its funded global programs.

The African Cohort Study (AFRICOS) enrolled nearly 2,000 HIV-positive participants between January 2013 and November 2019 at 12 PEPFAR-supported clinics in Kenya, Nigeria, Tanzania and Uganda.

Of these, 742 started treatment with dolutegravir/TDF/lamivudine, while 1,212 either started another regimen or had not yet started treatment. Although women and men were about equally represented in the study, use of dolutegravir was less common among women due to concerns about neural tube birth defects in children born to mothers taking the drug around the time of conception; these fears were allayed after further research.

Body mass index (BMI) was assessed every six months, and blood glucose levels were measured once a year. Overweight was defined as a BMI of 25 to 29, while obesity was defined as a BMI of 30 or above. Those with overweight, obesity or hyperglycemia at enrollment were excluded from the analysis.

People who used dolutegravir/TDF/lamivudine were 85% more likely to develop overweight or obesity than those taking other antiretroviral regimens after adjusting for sex, age, study site and the presence of depression. In contrast, those who had not yet started treatment were 55% less likely to develop overweight or obesity than those on non-dolutegravir regimens.

Compared with people on non-dolutegravir regimens, those taking dolutegravir/TDF/lamivudine were 27% more likely to develop hyperglycemia, while those not yet on treatment were 78% less likely. However, the difference between those taking dolutegravir/TDF/lamivudine and non-dolutegravir regimens did not reach statistical significance after adjusting for sex, age, study site and BMI.

The researchers concluded that antiretroviral therapy in general was associated with both weight gain and hyperglycemia. While dolutegravir was clearly associated with an increased risk for a high BMI, they noted that if there is an additional effect of dolutegravir on hyperglycemia, it is likely to be small.

Other Studies

Other studies presented at the conference also saw a link between dolutegravir and weight gain.

Simiso Sokhela, MBChB, of the University of the Witwatersrand in Johannesburg, reported the latest findings from the ADVANCE study, a large randomized trial that compared first-line treatment using dolutegravir/TAF/emtricitabine, dolutegravir/TDF/lamivudine or efavirenz/TDF/emtricitabine (the drugs in Atripla). The study enrolled more than 1,000 participants in South Africa. Almost all were Black, about 60% were women and the average age was 32.

As previously reported, treatment with the dolutegravir-based and efavirenz-based regimens was similarly effective at 48 weeks, and TDF and TAF were equally well tolerated, although people on TAF saw smaller changes in bone density and kidney function. But people starting dolutegravir experienced greater weight gain, and this was especially pronounced when it was combined with TAF.

These results held up at 96 weeks, Sokhela reported. At that point, the average weight gain among men in the study was 5.2 kilograms (about 12 pounds) in the

dolutegravir/TAF/emtricitabine group, 3.6 kg (about 8 pounds) in the dolutegravir/TDF/lamivudine group and just 1.4 kg (about 3 pounds) in the efavirenz/TDF/emtricitabine group. Among women, the average gain was 8.2 kg (about 18 pounds), 4.6 kg (about 10 pounds) and 3.2 kg (about 7 pounds), respectively.

Weight continued to rise in a smaller subset of people followed through 144 weeks. At that point, the average gain among men reached 7.2 kg (about 16 pounds) in the dolutegravir/TAF/emtricitabine group, 5.5 kg (about 12 pounds) in the dolutegravir/TDF/lamivudine group and 2.6 kg (about 6 pounds) in the efavirenz/TDF/emtricitabine group. Among women, the average 144-week gain was 12.3 kg (about 27 pounds), 7.4 kg (about 16 pounds) and 5.5 kg (about 12 pounds), respectively.

Looking at body composition, the researchers found that the weight gain consisted largely of fat rather than lean muscle mass and was primarily distributed in the torso and limbs. Fat gain was significantly greater among women compared with men. What's more, people taking the dolutegravir-based regimens were more likely to develop metabolic syndrome, a cluster of cardiovascular risk factors that include abdominal fat, high blood pressure, and abnormal blood glucose and blood fat levels.

Another research group performed a systematic review of adverse pregnancy outcomes related to obesity in an effort to estimate the impact of antiretroviral treatment. Based on the ADVANCE results, they calculated that for every 1,000 pregnant women, 140 of those treated with dolutegravir/TAF/emtricitabine and 80 of those treated with dolutegravir/TDF/emtricitabine for 96 weeks would develop obesity.

Using these figures, they estimated that there could be an additional 77 adverse birth outcomes linked to dolutegravir/TAF/emtricitabine and 41 such outcomes linked to dolutegravir/TDF/emtricitabine. In the dolutegravir/TAF/emtricitabine group, these included an additional 19 Cesarean deliveries, 11 more cases of gestational hypertension, seven cases of gestational diabetes, 20 infants large for their gestational age (an effect of maternal diabetes), 10 more cases of preeclampsia and three additional preterm births.

Finally, another study analyzed more than 600 African adolescents (ages 10 to 19) who switched to a dolutegravir-based regimen, mostly taken with TDF and lamivudine. This study also saw an increasing likelihood of weight gain over time, with the odds of overweight or obesity rising by about 1% for every additional day on dolutegravir.

Taken together, these studies confirm prior research linking dolutegravir and weight gain, especially among women. Treatment-associated weight gain is still poorly understood—experts do not yet know what causes it or how best to manage it—but this is an active area of research, as overweight and obesity raise the risk of cardiovascular disease, diabetes and other health problems.

Click here to see all POZ coverage of AIDS 2020:Virtual.
Click here to learn more about weight gain among people with HIV.