Do Integrase Inhibitors Raise the Risk of Cardiovascular Disease?

Certain drugs in this class may increase the likelihood of diabetes and hypertension, but cardiovascular risk factors can be managed.

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Studies continue to yield conflicting findings about the link between integrase inhibitors—especially dolutegravir—and metabolic problems associated with cardiovascular disease, including weight gain, diabetes and hypertension (high blood pressure). Reassuringly, one recent study found no link between integrase inhibitors and cardiovascular events, such as heart attacks. While much remains to be learned, management of cardiovascular risk factors is feasible and should be part of the standard of care for people with HIV as they age.

In recent years, there has been growing concern about weight gain and other metabolic problems after starting or switching antiretrovirals, and several studies have implicated integrase inhibitors specifically. Excess weight—especially abdominal fat accumulation—raises the risk for cardiovascular disease, fatty liver disease and other health problems. But study findings have been inconsistent, and the phenomenon remains poorly understood.

Some of the largest weight increases have been seen among people taking dolutegravir, especially when used in combination with tenofovir alafenamide (TAF). In part, this may be due to the fact that the older tenofovir disoproxil fumarate (TDF), and possibly efavirenz, can lead to weight loss and reduced blood fat levels, so people who switch away from these drugs may lose this protective effect.

Diabetes Risk

As reported at the International AIDS Society Conference on HIV Science (IAS 2023), Dhanushi Rupasinghe, of the Kirby Institute at the University of New South Wales, and colleagues explored the relationship between antiretroviral therapy (ART), body mass index (BMI) and the risk for new-onset type 2 diabetes among participants in the RESPOND study (abstract OAB0402) The analysis included 20,865 people living with HIV in Europe and Australia. Most were white men, and the median age was 45 years. More than three quarters were on antiretroviral treatment with an undetectable viral load. They were followed from January 2012 through December 2019.

Rupasinghe reported that 785 people (4%) were newly diagnosed with diabetes during follow-up,

for a rate of 7.3 cases per 1,000 person-years. As expected, people with a higher BMI were more likely to develop diabetes regardless of which HIV drugs they used. Men and older people were also more likely to develop diabetes, people of color had an 80% higher risk than white people and those with a CD4 T-cell count of 200 or less had about twice the risk of those with a count of 350 or higher. Those with high blood pressure had a 43% higher risk.

In an unadjusted analysis, integrase inhibitor use was associated with a 48% increase in the risk for diabetes. The association was partially reduced after adjusting for BMI and other factors, but it remained statistically significant. The researchers estimated that there would be three additional diabetes cases per 1,000 integrase inhibitor users. Looking at specific drugs, the risk increase was significant for dolutegravir and raltegravir, but not for other integrase inhibitors (for example, bictegravir or cabotegravir). People using TAF and TDF had similar diabetes risk. The researchers noted that the increased risk for diabetes among integrase inhibitor users was not dependent on weight gain.

However, a large study in Italy, published in the journal AIDS, came to a different conclusion. Lucia Taramasso, MD, PhD, of IRCCS Policlinico San Martino Hospital in Genoa, and colleagues looked at diabetes risk factors among participants on antiretroviral therapy in the SCOLTA study. The analysis included 4,366 participants enrolled between January 2003 and November 2021. Again, most were white men, and the median age was 46 years.

Weight gain was modest, about 3 pounds after two years, though it was greater among people taking dolutegravir (about 5 pounds) or bictegravir (about 6 pounds). During follow-up, 120 new cases of diabetes were diagnosed, or 1.26 cases per 100 person-years. Higher baseline weight—but not weight gain during follow-up—was significantly associated with diabetes incidence. Older age and detectable viral load were also associated with increased diabetes risk, and untreated high blood pressure nearly tripled the risk. But neither integrase inhibitors as a class nor specific drugs were associated with increased risk.

Likewise, a recent systematic review and meta-analysis that included 13 studies with nearly 75,000 participants, about 40% of whom used integrase inhibitors, did not find a link between these drugs and diabetes risk, except in two studies in Africa. In fact, a majority of the studies found that integrase inhibitors were associated with slightly lower diabetes risk compared with non-nucleoside reverse transcriptase inhibitors or protease inhibitors, especially with longer follow-up time. The researchers noted that more targeted studies of African people living with HIV are needed to shed light on the discrepancy.

High Blood Pressure

Two other studies presented at IAS 2023 analyzed links between antiretroviral use and high blood pressure. In addition to cardiovascular disease, hypertension can contribute to kidney damage, vision problems, cognitive impairment, erectile dysfunction and pregnancy complications.

In another analysis from the RESPOND trial, Dathan Mirembe Byonanebye, of the Kirby Institute

asked whether changes in BMI were associated with the risk for hypertension or dyslipidemia (abnormal blood fat levels) in people with HIV receiving integrase inhibitors or TAF (abstract OALBB0505).

Of the 9,704 participants without high blood pressure at baseline, 31% developed hypertension. In an unadjusted analysis, hypertension was more common among those who used an integrase inhibitor with or without TAF, compared to those who used other regimens. Just over half (51%) developed dyslipidemia, and this was associated with concurrent use of an integrase inhibitor plus TAF or TAF alone. These associations were reduced after adjusting for BMI. Hypertension and dyslipidemia both increased with rising BMI, but the association did not differ between antiretroviral regimens.

In the second study, Francois Venter, MD, of the University of the Witwatersrand, and colleagues evaluated the link between ART and hypertension among people starting HIV treatment for the first time in two large trials: NAMSAL, conducted in Cameroon, and ADVANCE, conducted in South Africa (abstract OALB0504). Hypertension is common in sub-Saharan Africa and is a leading cause of death, the researchers noted as background.

In NAMSAL, 613 people were randomly assigned to first-line therapy using dolutegravir/TDF/lamivudine or efavirenz/TDF/lamivudine. Two thirds were women, and the median age was 37 years. In ADVANCE, 1,053 participants were randomized to receive dolutegravir/TAF/emtricitabine, dolutegravir/TDF/emtricitabine or efavirenz/TDF/emtricitabine. About 60% were women, and the median age was 32. In both studies, the mean CD4 count was around 300, and baseline BMI was toward the upper end of normal.

Blood pressure was measured at every study visit. People who developed hypertension in ADVANCE were routinely offered antihypertensive medications to control blood pressure, but in NAMSAL, less than 1% received antihypertensives due to lack of funding.

In NAMSAL, weight rose steadily in both groups after starting HIV treatment but more so among people taking dolutegravir (about 20 pounds for women and 15 pounds for men). About 10% in both groups had hypertension at baseline. But by year four, 31% had developed Grade 1 or worse hypertension (systolic blood pressure over 140 or diastolic blood pressure over 90) in the dolutegravir/TDF/lamivudine group, compared with 19% in the efavirenz/TDF/lamivudine group. Hypertension was also associated with older age and higher BMI. In fact, 37% of participants with obesity and 20% of those with overweight had hypertension versus 9% of those with normal weight.

In ADVANCE, too, weight rose steadily in all groups, with the largest gains seen among dolutegravir/TAF/emtricitabine recipients (about 22 pounds for women and 16 pounds for men). About 10% of participants in all groups already had hypertension at baseline. Treatment-emergent Grade 1 hypertension was diagnosed in 13% of dolutegravir/TAF/emtricitabine recipients, 11% of dolutegravir/TDF/emtricitabine recipients and 8% of efavirenz/TDF/emtricitabine recipients. While further analysis is ongoing, Venter suggested hypertension may be due to differences in weight

gain, rather than a direct effect of specific antiretrovirals on blood pressure.

At four years, 54% of people assigned to either of the dolutegravir regimens had elevated blood pressure (systolic blood pressure over 130 or diastolic blood pressure over 85), compared with 45% in the efavirenz group. However, more than 90% of those who developed high blood pressure were treated for it, which brought the proportion with Grade 1 hypertension down to 6.4% in both groups.

First-line use of dolutegravir "was associated with significantly higher risks of treatment-emergent hypertension, especially when combined with TAF," Venter and colleagues concluded. In NAMSAL, where hypertension was not consistently treated, the risk of hypertension remained higher for dolutegravir/TDF/lamivudine recipients through week 192, but in ADVANCE, most cases of hypertension were successfully treated, and there was no significant difference between treatment arms by week 192.

"Hypertension can be diagnosed and treated with low-cost generic drugs," the researchers stressed. Routine blood pressure monitoring for people with HIV should be standardized, they advised, and HIV treatment programs need to include support and funding for diagnosis and treatment of hypertension and other non-communicable diseases.

Cardiovascular Risk

It is well known that diabetes and hypertension are risk factors for cardiovascular disease, but it remains unclear whether use of integrase inhibitors is associated with cardiovascular events, such as hearts attacks and strokes, in people starting antiretroviral treatment. However, a new analysis from the Swiss HIV Study, published in Clinical Infectious Diseases, offers reassurance. This is good news because integrase inhibitors are highly effective, and they are recommended for first-line treatment in the United States and worldwide.

Very relieved at the results of this analysis, which show no association with integrase-inhibitor based regimens and cardiovascular events once adjusting for other risk factors.

<<phew>> https://t.co/bstlhm35u4 pic.twitter.com/c9PpRUsRHM

— Paul Sax (@PaulSaxMD) September 18, 2023

Bernard Surial, MD, of the University of Bern, and colleagues investigated the effect of starting integrase inhibitors on cardiovascular events using a target trial emulation, a method that reduces the potential for confounding and selection bias.

The analysis included 5,362 cohort participants who started treatment for the first time after May 2008, when integrase inhibitors became available in Switzerland. About 80% were men, 15% were of African origin and the median age was 38. About one third started on an integrase inhibitor regimen, while the rest started on other drug classes.

A total of 116 cardiovascular events—myocardial infarction, stroke or invasive cardiovascular procedures—occurred during the study period. After adjusting for other risk factors, starting an integrase inhibitor regimen was not associated with an increased risk for these events over eight years of follow-up.

“In this target trial emulation, we found no difference in short- or long-term risk for cardiovascular events between treatment-naive people with human immunodeficiency virus who started [integrase inhibitor]-based ART and those on other ART,” the study authors concluded.

Taken together, this research suggests that dolutegravir, and possibly TAF, may contribute to weight gain and metabolic abnormalities in people with HIV, but these conditions can be managed, and they do not necessarily raise the risk for cardiovascular events. The findings underscore the importance of tailored treatment that takes into account comorbidities, other individual risk factors and personal preferences regarding side effects.

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