No link between weight gain on integrase inhibitors and diabetes

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A large Italian study demonstrates that integrase inhibitor-based antiretroviral regimens are not associated with the risk of developing type 2 diabetes. It also reveals that it is not the weight that people gain while on these drugs, but their weight when they start taking them (at baseline) which is the main factor

associated with the onset of diabetes. Another study pooling previously published research on this issue concludes that the risk of diabetes is not increased with these drugs compared with other antiretrovirals, except in two studies conducted in African countries.

Multiple reports of weight gain on integrase inhibitors have raised concerns among people living with HIV, who are already at higher risk of developing diabetes than the general population. The potential association of weight gain with an additional risk of diabetes in people with HIV is a recurrent question, about which research has produced interesting, but so far inconclusive results.

Dr Antonio di Bagio from Genoa University and colleagues analysed data on incidence of diabetes during antiretroviral treatment from SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) collected between 2003 and 2021.

Glossary

diabetes

integrase inhibitors (INI, INSTI)

nucleoside

glucose

reverse transcriptase

SCOLTA is an observational study involving 25 Italian infectious disease centres. It follows people with HIV who start an antiretroviral regimen that includes a newly approved medication to identify drug toxicities in a real-life setting, rather than in clinical trials. Both people who were never before treated for HIV and people changing therapy can be included in SCOLTA.

For this analysis, the investigators defined diabetes as a confirmed minimum fasting glucose above 125 mg/dl or above (normal is below 100 mg/dL, 100 to 125 mg/dL indicates prediabetes, above 125 mg/dL indicates diabetes) or a single glucose value of 200 mg/dl or more (when measured after a meal, the norm is below 180 mg/dl). Starting an antidiabetic drug during follow-up also indicated diabetes.

Among 4,597 people with HIV enrolled in SCOLTA during the study period, 231 (5%) were excluded because they already had diabetes. Of the remaining 4,366 participants, 3,170 (73%) were male, with a mean age of 46 years and a median CD4 cell count of 460. At baseline, 356 participants (8%) were on statin

treatment and 587 (13%) had hypertension (treated in 512, untreated in 75). Mean weight was 71kg and mean body mass index (BMI) was 24, which is within the normal range of 18.5-24.9. In terms of antiretrovirals, 2,627 participants started an integrase inhibitor-based regimen, 1,288 a protease inhibitor-based regimen and 451 a non-nucleoside reverse transcriptase inhibitor-based regimen.

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The mean weight increase in the study was moderate – 0.7kg (95% CI 0.5-0.8) at one year and 1.3kg (95% CI 1.1-1.5) at two years of follow-up. Of note, it was more significant in male participants on dolutegravir (2.3kg at two years) and bictegravir (2.7kg), when compared with those showing the next highest increases: 1.2kg each with elvitegravir, raltegravir and darunavir at two years.

There were 120 incident (new) cases of diabetes, with an estimated incidence of 1.26 cases (95% CI 1.05-1.50) per 100 person years of follow-up. Baseline weight, but not the amount of weight gain, turned out to be significantly correlated to diabetes incidence (adjusted hazard ratio 1.03 for each additional kilo, 95% CI 1.01-1.04). This was also the case for older age (aHR by one year 1.03, 95% CI 1.01-1.06), having untreated hypertension (aHR 2.90, 95% 1.30-6.45) or a fasting glucose > 100 mg/dl (aHR 5.47, 95% CI 3.82-7.85) at baseline: these are all risk factors associated with diabetes in the general population.

Participants who had taken antiretroviral therapy and were not completely virally suppressed at study entry were more than two times at risk of diabetes than those with an undetectable viral load (aHR 2.27, 95% CI 1.48-3.49). No significant association between antiretrovirals and the risk of diabetes was found, whether the analysis focused on individual medications or drug classes. Only raltegravir appeared to distance itself from the others: compared to dolutegravir, it increased the risk by 70%. However, this was of borderline statistical significance.

More news from Italy

After highlighting that neither integrase inhibitor-based regimens, nor weight gain, are associated with the onset of diabetes, Di Bagio and colleagues underline that the incidence of 1.26 cases per 100 person years they have found is in line with previous studies of people with HIV. However, they also say that a possible explanation for the lack of association between weight gain and

an increased risk of diabetes may lie in the moderate weight gains seen in the SCOLTA cohort.

The other study was a systematic review and meta-analysis conducted by Dr Frank Mulindwa from Makerere University in Kampala, Uganda and colleagues. It pooled the results of previous studies in order to establish whether integrase inhibitors are associated with a higher risk of new cases of type 2 diabetes than other antiretrovirals. To be eligible for this analysis, these previous studies had to have reported incident diabetes from cohorts of people with HIV taking integrase inhibitors for at least twelve weeks, in comparison with either non-nucleoside reverse transcriptase inhibitors or protease inhibitors.

Thirteen such studies were identified between 2000-2022 and their results – representing over 72,000 participants – were pooled.

Integrase inhibitor-based therapy was associated with a 20% lower risk of incident diabetes (Risk Ratio 0.80, 95% CI 0.67 to 0.96), of which eight randomised controlled trials demonstrated a 12% reduced risk (RR 0.88, 95% CI 0.81 to 0.96). Overall, integrase inhibitors had a lower risk than non-nucleoside reverse transcriptase inhibitors (RR 0.75, 95% CI 0.63 to 0.89), but the reduction in risk was of borderline significance compared to protease inhibitors (RR 0.78, 95% CI 0.61 to 1.01). The investigators also found that the risk was lower in studies with longer follow-up (RR 0.70, 95% CI 0.53 to 0.94) and in patients who had never taken antiretrovirals (RR 0.78, 95% CI 0.65 to 0.94).

However, integrase inhibitors were associated with a three-times greater risk in African populations (RR 2.99, 95% CI 2.53 to 3.54). This finding was based on two studies; the majority of participants in the other studies were in high-income countries.
Mulindwa and colleagues therefore conclude that integrase inhibitor-based regimens do not pose higher risk of diabetes than other antiretroviral regimens. Nevertheless, they say that more targeted research is needed in African people living with HIV and that clinicians should monitor diabetes “in certain high-risk groups”.

References

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