More pressure on integrase strand-transfer inhibitors?

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Integrase strand-transfer inhibitors (INSTIs) have almost entirely replaced non-nucleoside reverse transcriptase and protease inhibitors for naive, second-line, and even subsequent-line treatment of HIV. As with any widely prescribed class of drug, potential adverse events undergo intense scrutiny. When an association between early pregnancy use of dolutegravir—currently the world's most prescribed INSTIs—and neural tube defects was reported in an observational cohort,[1] there were several years of uncertainty until the issue was resolved.

More recently there has been a focus on the association of the use of INSTIs with major adverse cardiovascular events and hypertension.[2] In *The Lancet HIV*, Dathan M Byonanebye and colleagues,[3] using data from the RESPOND consortium of cohorts, investigated whether changes in BMI differentially increase the risk of hypertension or dyslipidaemia in people living with HIV receiving INSTIs, tenofovir alafenamide, or in combination versus other contemporary regimens. Not surprisingly, dyslipidaemia was more common in participants using tenofovir alafenamide because most of the comparator regimens included tenofovir disoproxil fumarate, which is known to have lipid-lowering effects. Adjustment for BMI and confounders attenuated the risk of dyslipidaemia in those receiving tenofovir alafenamide alone, becoming non-significant. The baseline median 5-year cardiovascular disease risk score for this cohort was 1·7%, so any minor change in lipids would maintain this risk well below any threshold for initiating statins, even taking into account the REPRIEVE study data published in 2023.[4]

The prevalence of hypertension is high among people living with HIV, who have a risk of cardiovascular disease 2·2 times higher than the general population.[2] The risk of hypertension increases with increasing BMI, and the association of INSTIs and tenofovir alafenamide with more weight gain than seen with other regimens is well recognised. The probable explanation, based on clinical trial and pre-exposure prophylaxis and placebo data, is that INSTIs are mainly neutral regarding weight gain and efavirenz and tenofovir disoproxil fumarate suppress weight gain.[5]

The association of INSTIs with incident hypertension, which was not fully accounted for by increases in BMI in this study, raises important concerns especially given that this association has been raised elsewhere, albeit inconsistently.[6] Both BMI and blood pressure measures have issues. BMI is an imperfect measure of the metabolic and clinical health consequences of fat accumulation, whereas waist-to-hip ratio, waist circumference, and, in particular, weight variation per year might be better predictors of hypertension risk.[7] Blood pressure is rarely taken in a standardised way across sites, despite guidelines clearly stating the importance of consistent methods.[8]

There is little information on mechanisms by which ART can directly cause hypertension, and other factors associated with being HIV positive, such as inflammation or immune activation, increased sympathetic nervous system activity, adipokines, insulin, and immune restoration, might have a role. How drugs with such different pharmacology and metabolic pathways, and which have been shown to be so metabolically neutral, could directly affect a crude physiological measure such as blood pressure is difficult to understand.

Disproportionate weighting is often given to observational studies in the minds of clinicians due to the large number of included datapoints from routine clinical settings, but care should be given when inferring causality. As with all observational cohorts, RESPOND has the inherent limitation of missing data, selection bias, and measured (eg, blood pressure) and unmeasured confounding biases. The type of analysis used can also affect results, and any confounding by indication, immortal time, and selection biases could be reduced by a target trial framework.[9]

Arguably, with confounding factors being such important considerations, randomisation becomes crucial for removing biases, especially as blood pressure is a relatively routine measure at clinical visits. High-quality data from a large number of randomised studies allows for better understanding of the incidence of hypertension and the relationship to changes in weight. A pooled analysis of four randomised clinical trials of dolutegravir versus non-INSTI regimens in people living with HIV who are naive to ART and without evidence of baseline hypertension showed no significant change in mean blood pressure at week 96.[10] Changes in blood pressure on INSTIs-based regimens were seen

in ADVANCE and NAMSAL—both studies from Africa of participants naive to ART—but were thought to be related to weight gain.

There is potential that the data from Byonanebye and colleagues[3] might influence physicians to not prescribe INSTIs, especially in those at risk of or with established hypertension or dyslipidaemia. Small changes in lipids related to HIV therapy should not detract from interventions that need to be implemented, such as smoking cessation, hypertension treatment, diabetes screening, lipid treatment, and obesity management. Nevertheless, the RESPOND data draws attention to potential side-effects of regimens of INSTIs, tenofovir alafenamide, or in combination on hypertension and lipids, prompting future studies and new analyses of previous randomised controlled trials in this area. Globally only 42% of individuals with hypertension receive a diagnosis and appropriate treatments,[8] therefore careful monitoring and treatment of hypertension in people living with HIV, as suggested by the authors, is crucial.

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