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EDITORIAL COMMENTARY

Reassuring data for cardiovascular health after switching a boosted protease inhibitor to dolutegravir

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It has become near impossible to refute the mounting evidence that integrase strand transfer inhibitors (INSTIs), especially bictegravir (BIC) and dolutegravir (DTG), are associated with greater likelihood of weight gain than other types of antiretrovirals (ARVs). Does this higher propensity for weight gain translate to declines in cardiovascular health? Data on associations between INSTIs and specific cardiovascular outcomes are convoluted and this question remains unsolved. Principal findings come from longitudinal cohort studies, which have pros and cons. Such studies may be subject to unmeasured confounding and various biases, plus it is difficult to compare the various available analyses due to differing inclusion criteria and methodologies. Indeed, recent longitudinal cohort studies have yielded conflicting results [1,2]. Thus, the true impact of INSTIs on cardiovascular risk remains unclear. The morass of data begs an important, unanswered question: what change to cardiovascular health can one expect if switching an alternate anchor drug to an INSTI, such as DTG, especially if weight gain may occur?

In this issue of *Clinical Infectious Diseases*, Sempere and colleagues offer an analysis from a randomized clinical trial (RCT) that, while not a complete answer, helps to fill in some missing pieces of the puzzle, especially when juxtaposed with prior published findings. Like the longitudinal cohort studies, RCTs have pros and cons for assessing differences in cardiometabolic effects of various drugs. An advantage of the RCT design is the capacity to compare clinical parameters with or without a simple intervention: in this case, a single

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antiretroviral substitution. In NEAT-022, investigators enrolled individuals with sustained viral suppression on a boosted PI with two nucleoside reverse transcriptase inhibitors (NRTIs), then randomized participants to switch the boosted PI to DTG, either immediately or after 48 weeks. They previously reported that this ARV substitution led to comparable virologic efficacy, improvement in serum lipid parameters, and a trend toward reduction in estimated cardiovascular risk (using Framingham or D:A:D equations), despite a small amount of overall weight gain [3,4]. In both study groups, weight gain occurred primarily within 24 to 48 weeks after the switch and stabilized within that time frame, which is consistent with observations in other studies of weight change after switch to an INSTI, such a pooled analysis of RCT data [5].

Now, NEAT-022 investigators offer further data from the trial, focusing on blood pressure changes and incident hypertension after the boosted PI to DTG switch. The findings are clinically relevant. Namely, the risk of incident hypertension in the enrollees was relatively high and was associated with classic risk factors, but not with taking a boosted PI versus taking DTG. The take-away messages: 1) hypertension occurs frequently for individuals with HIV, particularly if over 50 years of age and/or with other risk factors for cardiovascular disease, 2) a focus on traditional, modifiable risk factors, like tobacco smoking and exercise, is more important to prevent and address hypertension than a focus on regimen choice, and, 3) there is no need to avoid switching a boosted PI to DTG due to concerns about cardiovascular effects of potential weight gain. Compiling data from NEAT-022, this particular ARV switch leads to some improvement in lipids, possible reduction in cardiovascular risk using estimating equations, and no substantial impact on blood pressure or incident hypertension, despite potential for mild weight gain over the first six to twelve months. Interestingly, changes in weight and body mass index (BMI) for participants in the trial did not correlate with changes in blood pressure or with incident hypertension, illustrating the difficulty predicting which patients will experience such clinical events and the importance of careful monitoring in clinic for cardiometabolic changes.

Despite advantages of the trial design, the analysis has limitations. The investigators intentionally enrolled individuals with risk for cardiovascular disease, so perhaps it is less notable that a fair proportion of enrollees had hypertension or were taking anti-hypertensive medications at baseline. In order to compare rates of incident stage 1 hypertension, they also excluded these individuals from the primary analysis, which reduced the sample size and power. Furthermore, the study population consisted primarily of persons who identified as male, so results cannot necessarily be extrapolated to all individuals. This is critical because studies have found that the metabolic impact of INSTIs may be most pronounced for individuals born female (reasons for this have not been fully elucidated) [6-7]. Additionally, the results only pertain to a boosted PI to INSTI switch. Thus, outstanding questions remain: would the findings and conclusions hold true for individuals who have low or average cardiovascular risk at baseline, or for individuals from other demographic groups? How would outcomes differ for individuals switching from an NNRTI, like efavirenz (EFV), to DTG, especially in light of data that EFV

suppresses weight gain and that this particular switch may lead to significant increases in BMI and may raise the likelihood of incident HTN [8,9]?

The above questions merit further investigation. Moreover, it is impossible to say that results of NEAT-022 definitively eliminate the possibility that a switch from a boosted PI to DTG raises risk of cardiovascular events. A limitation of RCT data is the relatively short follow-up period (96 weeks in this case) and low power to detect differences in clinically-important cardiovascular outcomes, like myocardial infarction, stroke, and others. Thus, returning to longitudinal cohort analyses, this illustrates their advantages and why they are necessary and beneficial: the ability to evaluate important clinical outcomes over relatively long periods of time. For now, key messages from NEAT-022 can be disseminated: switch of a boosted PI to DTG offers potential benefits to lipids and estimated cardiovascular risk and does not augment the likelihood of hypertension, despite potential for small, non-sustained increases in weight. Moreover, concentrated efforts to bolster cardiovascular disease prevention and address modifiable risk factors are important in HIV primary care. Clinical scenarios in which INSTIs may truly heighten risk of critical cardiovascular events over the long-term must be better defined. Replications of the longitudinal cohort analyses and further investigations into the mechanisms by which INSTIs affect cardiometabolic parameters will be necessary to fully solve this puzzle.

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