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EDITORIAL COMMENTARY

Darunavir and Cardiovascular Risk: Evaluating the Data to Inform Clinical Care

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(See the Major Article by Costagliola et al, on pages 516–22.)

People with human immunodeficiency virus (PWH) confront an increased risk of aging-associated chronic diseases including cardiovascular disease (CVD) [1]. Studies have delineated a complex, multifactorial mechanism contributing to increased CVD risk in PWH [1]. Understanding the factors that contribute to this risk—particularly those unique to human immunodeficiency virus (HIV)—is important to enable HIV caregivers to better estimate risk, prevent and manage disease, and improve health for PWH.

Antiretroviral therapy (ART) has been implicated as contributing to CVD risk in PWH. Historically, protease inhibitors (PIs) used in earlier treatment eras have been associated with an increased risk of myocardial infarction (MI) that increases with cumulative use of the drugs and is explained only in part by dyslipidemia [2]. The nucleoside reverse-transcriptase inhibitor abacavir has also been associated with MI risk in some studies; risk is increased with recent use, and it appears to abate after discontinuation, in contrast to cumulative use with the PI class [3]. In addition, contemporary PIs have now been assessed, with a Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study demonstrating increased MI risk with exposure to darunavir but not to atazanavir [4].

Cardiovascular risk associated with PIs remains highly relevant in the contemporary treatment era. Although European and US HIV treatment guidelines favor integrase-strand transfer inhibitor (INSTI)-based regimens for initial ART in ART-naive PWH, the European AIDS Clinical Society guidelines include darunavir in recommended regimens; older PIs, including atazanavir, are in wide use in lower-resource settings as standard, second-line therapy as per World Health Organization guidelines. Moreover, recent data showing weight gain after INSTI initiation suggest that some medications in this increasingly used class may have adverse metabolic effects that will need to be considered when selecting ART regimens [5].

In this issue of the *Journal of Infectious Diseases*, Costagliola et al investigated the risk of MI associated with darunavir and atazanavir in the large, well established, multicenter French Hospital Database on HIV (FHDH-ANRS CO4). The study was a nested case-control study of PWH who had an MI event between 2006 and 2012, with the study period selected to reflect PI availability in France. Of 81 294 eligible patients, 408 had an MI; 1250 controls without MI and followed contemporaneously were matched to the cases by age and sex. Myocardial infarction was identified initially by *International Classification of Diseases* (ICD)-10 code I21, with each event adjudicated by a cardiologist. Antiretroviral (ARV) drug exposure was defined as cumulative exposure. Models were built adjusting for ARVs with or without confounding covariates and replicated limiting each model to include only the ARVs used in the D:A:D models (abacavir, lopinavir-ritonavir, and indinavir). They found no significant association between either darunavir or atazanavir and odds of MI in any of the models (darunavir adjusted odds ratio [aOR] = 0.51, 95% confidence interval [CI] = .11–2.32, atazanavir aOR = 1.54, 95% CI = .87–2.73 in fully adjusted models accounting for all other ARVs and confounders not on the causal pathway).

The absence of a significant association of darunavir with MI in the FHDH study represents an apparent discordance with the results of the recent, large D:A:D study, which demonstrated a significant, approximately 50% increased risk of MI per 5 years of darunavir exposure. Although the results of the present study do not support the findings of the D:A:D study, they also do not contradict the results. As noted in the discussion of the FHDH study, the CI was wide and, notably, encompassed the entirety of the D:A:D study CI (FHDH CI = .11–2.32, D:A:D CI = 1.13–2.02), suggesting that even though the estimates were qualitatively different, the margin of error encompassed both negative and positive associations with the outcome. Despite a large cohort with ample follow-up time, the median duration of darunavir

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exposure in the FHDH study was only 1 year for MI cases and 1.2 years for controls without MI, and the number of patients exposed to darunavir was relatively low (10% of cases and 9% of controls). Studies examining the association of PIs on MI risk have consistently shown increased risk to be associated with increased duration of exposure, including in prior FHDH studies [6], prior D:A:D studies [2], and the recent D:A:D study [4], which compared duration of less than 1 year to more than 6 years. It is possible that with longer duration of darunavir exposure in the current study, and a larger sample size of individuals exposed to it, a qualitatively different or statistically significant effect would be observed.

The DAD and FHDH studies were similar in many aspects, including baseline characteristics, HIV-related parameters, and CVD risk profiles of the cohorts. Events in both studies were centrally validated or adjudicated. The D:A:D study used a broader outcome definition (MI, stroke, sudden cardiac death, or invasive cardiovascular procedures), but in sensitivity analyses with the definition limited to MI, results were similar to the original analyses, with a statistically significant increased MI risk with darunavir. Although modeling strategies differed, including with regards to how to handle covariates on the causal pathway from ARV exposure to MI (included at baseline in D:A:D but only in sensitivity analyses in FHDH), the FHDH study included models that replicated the ARVs included in the D:A:D study. The FHDH study did not report CVD risk profiles by regimen, but confounding by indication could have influenced results in either cohort. Nonetheless, the results of the D:A:D study were published after the observation period of the FHDH study, and the D:A:D study tested several interactions that did not suggest confounding by indication.

There were some important differences that could further explain the contrasting results. Factors that differed between the studies included geographic distribution, study period (2006–2012 for FHDH vs 2009–2016 for D:A:D), method of MI outcome ascertainment (ICD code for FHDH vs clinical variables from standardized data collection forms for D:A:D), median duration of darunavir exposure (1 year for FHDH vs 2.56 years for D:A:D), and inclusion of bilirubin as a covariate (included in the D:A:D study). Moreover, the FHDH study imputed values for parameters missing for fewer than 50% of individuals, which has the potential to misestimate confounding factors. Importantly, given the matching approach of incidence density sampling used, the odds ratio from the FHDH study can be compared with the incidence rate ratio in the D:A:D study.

Additional reports are conflicting with regard to the potential cardiovascular effects of darunavir. Darunavir has been associated with worsening of CVD risk factors and surrogate markers of atherosclerosis in some other investigations [7–9]. Lipid alterations are known to occur in the setting of darunavir use [10]; yet, in the D:A:D study, the effect of darunavir on MI was not modified by dyslipidemia. Several published studies have failed to show a significant association of darunavir with MI [11, 12]. A study of Janssen-sponsored clinical trials, postmarketing pharmacovigilance data, and administrative claims data showed that rates of a composite CVD outcome did not increase with increasing yearly intervals of exposure to darunavir, but the study was limited by median trial duration of 2 years and missing data in some trials [11]. In contrast to darunavir, prior studies have consistently failed to show increased CVD risk with atazanavir use or have shown decreased risk compared with other regimens [13, 14]. Atazanavir appears to be the outlier with regards to CVD risk in the PI class, and its apparent protective association has been hypothesized to result from antioxidant and anti-inflammatory effects of unconjugated bilirubin [15–18].

Reviewing the findings of the FHDH and D:A:D studies underscores several factors important to consider in interpretation of longitudinal observational cohorts. In contrast to randomized controlled trails, which lend strong support to causal relationships, questions addressed by cohort studies lend less support for a causal association due both unmeasured and residual confounding. For these study designs, findings are bolstered through reproducibility, when multiple studies address the same question. In cases such as the D:A:D study and FHDH, when results are discordant—or at least not concordant—and a clear methodological explanation does not explain the differing results, it is reasonable to maintain a conservative approach while awaiting further data.

In summary, this important study by Costalgiola et al underscores the complexity of mitigating CVD risk in HIV and of interpreting observational cohort studies. Given the wide CIs reported on the relationship between darunavir use and MI, and contrasting results with other similar studies, additional studies with longer follow-up time and more events in darunavir-exposed individuals may offer further clarification. Until that time, it is plausible that CVD risk increases with darunavir exposure, and this should be considered as a factor during selection of ARVs. Specifically, prolonged darunavir use could be considered as an HIV-Related CVD Risk-Enhancing factor per the American Heart Association statement on HIV and CVD [1], and clinicians might consider selecting an alternate ARV in PWH at high underlying CVD risk. While we await further data to help clarify this issue, supported practices to reduce CVD risk, such as achieving and maintaining virologic suppression, careful attention to risk factor management, and high suspicion for CVD risk among PWH, should continue to drive treatment decisions for this high-risk population.

Notes

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