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Todd T. Brown, MD, PhD is Assistant Professor of Medicine in the Division of Endocrinology and Metabolism at Johns Hopkins University where he is also the primary endocrine consultant to the Johns Hopkins HIV (Moore) Clinic. He is a graduate of Brown University and received his medical degree from Columbia University College of Physicians and Surgeons. After internal medicine residency at Georgetown University, he completed his fellowship in Endocrinology and Metabolism at Johns Hopkins University. He earned his doctoral degree in clinical investigation from Johns Hopkins Bloomberg School of Public Health. His research focuses on metabolic and endocrine abnormalities observed in HIV-infected patients. As a co-investigator in the Multicenter AIDS Cohort Study and the AIDS Clinical Trial Group, he has been interested in clarifying the epidemiology and risk factors for insulin resistance, diabetes mellitus, anthropometric changes, cardiovascular disease and osteoporosis in HIV-infected patients and studying their relationship to antiretroviral therapy. He is also actively involved in multiple studies evaluating novel treatments for the metabolic and skeletal abnormalities in HIV-infected patients.

"All of the drugs studied in A5257 were very effective at controlling HIV. In general, the regimens were all well tolerated, with the most problems coming from hyperbilirubinemia with atazanavir/ritonavir (ATV/r), a known side effect. From a bone perspective, the two PI arms were associated with more bone loss than RAL at the two sites (spine and hip) that are most important clinically. The take home message for clinicians was that TDF/FTC + a boosted PI may not be the best regimen for someone with pre-existing osteoporosis. The cardiovascular

picture was more complicated and less amenable to a clear clinical message. Both PI arms were associated with similar, yet modest increases in LDL-c and non-HDL-c, whereas RAL was neutral. Based on these numbers, it might be hypothesized that RAL would be associated with the slowest progression of carotid intima media thickness (CIMT), a surrogate of cardiovascular disease. However, what was observed was that those randomized to ATV/r experienced slower progression of CIMT than those assigned DRV/r, while those randomized to RAL had an intermediate degree of progression. Further analysis is underway to understand this unexpected finding, particularly to determine whether the low grade hyperbilirubinemia, which may have some anti-oxidant properties, helped to slow IMT in those receiving ATV/r. Until we can better understand these findings, I think that in someone with a high risk of CVD, a PI may not be the best choice, not only because of the lipid effects, but more importantly because of the potential interaction with rosuvastatin and atorvastatin which makes increasing to the maximal dose of statin more problematic. Getting on the high dose of statin for those at high risk of CVD has become increasingly important since the new cholesterol guidelines came out."

Ninety-six weeks after randomization in ACTG 5257, first-line raltegravir proved superior to atazanavir/ritonavir or darunavir/ritonavir (all taken with tenofovir/emtricitabine) in an endpoint combining virologic efficacy and safety. Atazanavir was inferior to raltegravir and darunavir in a tolerability endpoint and darunavir was superior to atazanavir in the combined efficacy/safety endpoint. ACTG 5257 aimed to compare the efficacy and safety of three nonnucleoside-sparing regimens in US antiretroviral-naive adults with a viral load above 1000 copies. Researchers randomized nearly 2000 people to standard doses of the three antiretrovirals, each with tenofovir/emtricitabine. The investigators followed participants until the last person reached week 96. The trial had three endpoints: time to virologic failure, defined as time from entry to a confirmed viral load above 1000 copies from week 16 to before week 24 or above 200 copies at or after week 24; time to tolerability failure, defined as time from entry to discontinuation of one of the three major study drugs for toxicity; a combined virologic/tolerability endpoint. The trial had 90% power to demonstrate equivalence in any pairwise (arm-versus-arm) comparison. Equivalence meant a 97.5% confidence interval (CI) entirely within +/- 10% in the pairwise difference in 96-week cumulative incidence. This analysis involved 1809 eligible participants, 42% of them non-Hispanic black, 34% non-Hispanic white, 22% Hispanic, and 24% women. Median pretreatment viral load stood at 4.6 log10 copies/mL (about 40,000 copies), and 70% of participants had a pretreatment load below 100,000 copies. Median pretreatment CD4 count was 308, and 30% of enrollees had a pretreatment count below 200. None of these baseline variables differed much from one arm to another. More than 90% of participants in each arm completed 96 weeks of study. Atazanavir, raltegravir, and darunavir proved equivalent in time to virologic failure at week 96. Cumulative incidence of virologic failure at 96 weeks was 13% with atazanavir, 10% with raltegravir, and 15% with darunavir. Intention-to-treat analysis ignoring antiretroviral changes determined that 88% assigned to atazanavir, 94% assigned to raltegravir, and 89% assigned to darunavir had a week-96 viral load below 50 copies. A snapshot analysis, in which discontinuation meant failure registered 96-week sub-50-copy rates of 63% with atazanavir, 80% with raltegravir, and 73% with darunavir. Among people with virologic failure, 9 of 75 atazanavir isolates sampled (12%) had any detectable resistance mutation, as did 18 of 65 raltegravir isolates (28%), and 4 of 99 darunavir isolates (4%). Proportions of people assigned to each drug who had virologic failure with resistance were 2.8% for atazanavir, 3.3% for raltegravir and 2.0% for darunavir. Tolerability failure was more frequent with atazanavir (14%) than with raltegravir (1%) or darunavir (5%), mainly because of clinical jaundice and hyperbilirubinemia with atazanavir. Statistical analysis indicated raltegravir was superior to atazanavir in time to tolerability failure (difference 13%, 95% CI 9.4% to 16%). Darunavir was also superior to atazanavir in time to tolerability failure (difference 9.2%, 95% CI 5.5% to 13%). Discontinuations for toxicity occurred in 16% assigned to atazanavir, 5% assigned to darunavir and 1% assigned to raltegravir. 47 of the 95 atazanavir

toxicity discontinuations (49%) were attributed to jaundice or hyperbilirubinemia and 25 (26%) to gastrointestinal toxicity. GI problems accounted for 14 of 32 darunavir toxicity discontinuations (44%). Only 2 people assigned to raltegravir had GI trouble. For the combined virologic failure/tolerability endpoint, raltegravir was superior to atazanavir (difference 15%, 95% CI 10% to 20%) and to darunavir (difference 7.5%, 95% CI 3.2% to 12%), and darunavir was superior to atazanavir (difference 7.5%, 95% CI 2.3% to 13%). ACTG investigators noted that virologic differences and toxicity largely explained the superiority of raltegravir to darunavir in this analysis. The ACTG team concluded that raltegravir proved superior to both protease inhibitors for the combined virologic/tolerability endpoint and darunavir proved superior to atazanavir for this endpoint. The clinical import of these findings is not as easily summarized. Raltegravir clearly emerged as a potent drug with minimal side effects in previously untreated people. Atazanavir suffered in the comparison because of well-appreciated and easily reversed problems like jaundice and high bilirubin, which the investigators made a point of calling "cosmetic hyperbilirubinemia." Clinician/researcher Jose Arribas observed after the presentation that a narrower equivalence range might have been preferable in the statistical analysis. ACTG presenter Raphael Landovitz did not dismiss that point but observed that previous ACTG research suggested this statistical approach is most appropriate for trials like this.

Hip and spine bone mineral density (BMD) dropped significantly more during 96 weeks of first-line boosted atazanavir or darunavir than with raltegravir, according to results of a randomized ACTG trial. Total body BMD fell more with atazanavir than with darunavir or raltegravir.

BMD drops 2% to 6% in the first 48 to 96 weeks of antiretroviral therapy, ACTG researchers noted, depending on which antiretrovirals a person takes. Greater BMD declines have been linked to tenofovir and protease inhibitors (PIs) but the relative impact of PIs and integrase inhibitors remained unknown until this substudy of ACTG A5257. The authors compared the percentage change in BMD at the lumbar spine, total hip, and total body over 96 weeks in HIV-infected treatment-naive participants randomized equally to open labeled Tenofovir Disoproxil Fumarate-Emtricitabine (TDF/FTC) plus Atazanavir-Ritonavir (ATV/r), Darunavir- Ritonavir (DRV/r), or Raltegravir (RAL) in a substudy of AIDS Clinical Trials Group A5257 (N= 1809) with randomization stratified by substudy participation. BMD was measured using standardized dual-energy x-ray absorptiometry (DXA) and centrally read. Because the substudy also assessed cardiovascular endpoints, the researchers excluded people with cardiovascular disease, diabetes, or lipid-lowering treatment. They used multivariable linear regression to compare percentage change in BMD in the three treatment arms and in the combined PI arms. We used linear regression with reverse Helmert contrasts to compare the 96-week percentage change in BMD in the two PI arms (ATV/r vs DRV/r) and if no difference was found, the BMD changes in the combined PI arms were compared to those in the RAL arm. Primary analyses were intent-to-treat, adjusted for the stratification factors of baseline cardiometabolic risk and HIV-1 RNA. 328 participants were randomized and had baseline DXA scans. At baseline 90% were male and 44% were white, non-Hispanic; the median HIV-1 RNA load was 4.55 log10 copies/mL; age was 37 years; CD4 count was 349 cells/μL. At week 96, the mean percentage changes from baseline in spine and hip were statistically significant in all arms ($p>0.001$) and similar in the PI arms (Spine: ATV/r -4.0% v DRV/r -3.6%, $p=0.42$; Hip: ATV/r -3.9% v DRV/r -3.4%, $p=0.36$), but were greater in the combined PI arms than the RAL arm (Spine: -3.8% v -1.8%, $p<0.001$; Hip -3.7% v -2.4%, $p=0.005$). The percentage changes in total body BMD were small, but statistically significant in all of the arms ($p<0.001$ for all), but the magnitude of the change was greater with ATV/r than DRV/r (-2.9% v -1.6%, $p=0.001$) or RAL (v -1.7%, $p=0.004$), but not different between the DRV/r and RAL arms ($p=0.72$). As-treated analyses led to similar results. The bone analysis also found associations between baseline markers of inflammation and immune activation and more hip BMD loss, independently of CD4 count and viral load. In ART-naive, HIV-infected individuals initiating ART with TDF/FTC, 96 week BMD losses at the lumbar spine and total hip were similar with the PIs, ATV/r and DRV/r, whereas the integrase inhibitor, RAL, had significantly less BMD loss at these sites than the combined PIs arms. In contrast, total body BMD loss was slightly greater with ATV/r than DRV/r.