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TAKING KALETRA CAPSULES UP-REGULATES MONOCYTE/MACROPHAGE CD36 AND CELLULAR CHOLESTEROL: A 5 VOLUNTEER STUDY

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Our previous studies using cell culture and animal models demonstrated that certain HIV protease inhibitors (including Ritonavir, Indinavir, and Amprenavir) upregulate monocyte CD36 (a scavenger receptor) and accumulation of cholesteryl ester in human monocytes. We showed that this effect was dependent on up-regulation of macrophage/monocyte CD36. Murine *in vivo* studies demonstrated that these PIs, given at doses that did not alter plasma cholesterol and triglycerides levels, promoted atherosclerosis. We postulated that the induction of CD36 in monocytes is due in part to the activation of transcription factor PPAR γ (peroxisome proliferator activated receptor γ) along with other nuclear hormones that heterodimerize with RXR (retinoid X receptor). Induction of PPAR γ by HIV PIs appears to involve protein kinase C (PKC).

We have now extended our studies to a human trial with Kaletra to evaluate if taking Kaletra up-regulated CD36 and cholesterol levels in monocytes. Five healthy uninfected males, ages 20 to 27 years, consented to take Kaletra capsules, 3 twice a day, for 28 days. All had normal lipid profiles, EKG, routine hematology and blood chemistries, negative drug screens, and normal physical examinations. Blood samples were collected prior to taking Kaletra and at weeks 2, 4 and 6 after starting Kaletra. Volunteers reported soft stools and nausea while taking Kaletra. After 28 days of Kaletra, the mean serum cholesterol increased from 155 ± 6 to 192 ± 16 mg/ml ($P < 0.05$, 2-tailed) and the serum triglycerides increased from 116 ± 25 to 227 ± 51 mg/ml ($P = 0.09$, 2-tailed). After 28 days on Kaletra, blood macrophage CD36 levels (arbitrary units based on Western blot with controls) increased 3-fold, macrophage cellular cholesterol content 1.5-fold, PPAR γ 4.8-fold, and PKC activity 3-fold. There was no effect on monocyte levels of scavenger receptors SRA and SR-BI or blood insulin levels. Two weeks after stopping Kaletra, all

increased levels were lower but not back to baseline. These results suggest that some HIV-1 PIs induce alterations in CD36 receptor-dependent uptake and efflux of cholesterol in macrophages/monocytes and thereby induce the subsequent accumulation of sterol in macrophages/monocytes. This accumulation of macrophage sterol may not be dependent on elevations in blood lipids.

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8

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