

14th Conference on Retroviruses and Opportunistic Infections



Los Angeles, California - February 25-28, 2007

INTERRUPTION OF ART AND RISK OF CARDIOVASCULAR DISEASE: FINDINGS FROM SMART

Conf Retrovir Opportunistic Infect 2007 Feb 25-28;14: (abstract no. 41)

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BACKGROUND: SMART compared strategies of continuous (viral suppression arm; VS) and CD4-guided (drug conservation arm; DC; off ART when >350 and (re-)start when <250) ART. Patients in DC arm deferred/interrupted ART at baseline; those in VS arm started/continued ART. We compared risk of cardiovascular disease (CVD) events and lipid changes in the 2 arms.

METHODS: We used Cox models to assess the association between treatment arm and CVD risk and to study this effect in various subgroups, in particular those relating to specific drugs/classes used at baseline. Mean changes in lipids were assessed between baseline and year 1.

RESULTS: We randomized 5472 patients, of whom 79 (1.4%) developed major CVD events. The hazard ratio (HR [DC/VS]) was 1.57 (95%CI 1.00 to 2.46, $p = 0.05$). For the subset (84%) on ART at baseline (43% non-nucleoside reverse transcriptase inhibitor [NNRTI] and not protease inhibitor [PI], 45% on PI) the HR (DC/VS) was 1.37 (0.85 to 2.21, $p = 0.20$), while for those off ART at baseline (16%, 5% naïve) it was 4.41 (0.94 to 20.8, $p = 0.06$) (interaction $p = 0.16$). There was no evidence that currently being off ART (time-updated covariate) was associated with increased CVD risk (HR for being on ART vs off 0.91, 0.57 to 1.47, $p = 0.70$), nor was higher current viral load associated with increased CVD risk. Among those on ART at baseline, the HR (DC/VS) was higher in those on nucleoside-only (1.78) or NNRTI (2.07) regimens compared with those on a PI (1.00) (interaction $p = 0.37$). The HR was most marked in those on nevirapine at baseline (HR 9.29, 1.19 to 72.6, interaction $p = 0.05$). The HR for CVD events per additional year of exposure to the PI was consistent with that found in the DAD study in the VS arm (HR 1.17, 1.03 to 1.33) but not in the DC arm (HR 1.02, interaction $p =$

0.07), suggesting possibly reduced relevance of cumulative drug use in those who have interrupted. Total, LDL, and HDL cholesterol were reduced in those DC patients who interrupted ART, leading to a net unfavorable change in total/HDL-cholesterol ratio, again particularly in those on nucleoside-only (mean change in ratio from baseline +0.43) and nevirapine regimens (+0.58).

CONCLUSIONS: A borderline significant excess risk of CVD was observed in DC compared to VS patients in SMART. There was no evidence that interruption immediately increases risk of CVD, but longer-term consequences cannot be excluded. On balance, lipid changes were unfavorable after interruption in DC patients, and the extent of this differed according to baseline ART regimen.

2007-02-25

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