Mechanisms driving increased atherosclerosis risk in people living with HIV on cART.

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Background:
HIV+ individuals have a >2 fold increased risk of cardiovascular disease (CVD), despite effective cART. This includes increased risk of CVD events such as myocardial infarction and stroke, as well as a thickening of the artery walls (atherosclerosis), which underlies the development of most CVD. The mechanisms driving increased atherosclerosis in HIV are not clear, but monocytes and macrophages are known to play a critical role in early atherosclerotic events. Here, we investigated the atherosclerosis-promoting activities of monocytes from people with HIV to uncover potential mechanisms driving increased CVD risk in this population.

Methods:
The atherogenic activity of purified monocytes was investigated using our established *in vitro* model, which measures monocyte differentiation into atherosclerosis-promoting foam cells following migration across activated primary human endothelial cell monolayers into a collagen matrix. The potential of high density lipoprotein (HDL) isolated from HIV+ individuals, shown to have abnormal cholesterol acceptor function, to potentiate formation of foam cells by monocytes was also investigated using this model. Carotid intima-media thickness (cIMT) was measured as a surrogate measure of atherosclerosis.

Results:
Samples were analysed from HIV- (n=25, median age [IQR] 52 [37-70] years) and HIV+ (n=40, age 52 [39-67] years, all virologically suppressed on cART) males. Whilst atherosclerosis as indicated by cIMT was low and not significantly different between HIV- and HIV+ individuals (0.6mm for both), monocytes from HIV+ individuals showed increased ability to form atherosclerosis-promoting foam cells (median 27.6% [18.4–33.3] vs 36.9% [25.6-42.1] for HIV- vs HIV+ respectively, p=0.002). HDL purified from plasma of HIV+ individuals (and shown previously to have lower cholesterol acceptor activity) increased foam cell formation by monocytes as compared to HDL purified from HIV- individuals (p=0.015).

Conclusions:

In this cohort of virologically suppressed HIV+ individuals on cART with no clinical evidence of atherosclerosis, persistent changes to monocyte function were detected which may potentiate early atherosclerotic events. Furthermore, a novel form of modified, dysfunctional HDL which is elevated in HIV+ individuals has the potential to catalyse additional foam cell formation. These data may provide important insights into the mechanism driving increased atherosclerosis in HIV.