Protecting the heart after HAART; understanding the pathogenesis of cardiovascular disease in people living with HIV

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Advances in the management of HIV and antiretroviral therapy (ART) have led to substantial improvements in disease-free survival for patients with HIV. Life-expectancy is approaching that of the general population. Yet these gains have been tempered by increasing rates of non-AIDS-related co-morbidities. In fact the major burden of illness, health care utilisation and premature death in HIV positive patients is now due to diseases of ageing. Cardiovascular disease (CVD) occurs at two times the rate in the general population and is a cause of significant morbidity and mortality. Lifestyle factors such as cigarette smoking and underlying genetics are clearly important. Yet in HIV patients CVD is also promoted by complex interactions between HIV and ART driven coagulation, dyslipidaemia, inflammation and immune dysfunction. Understanding the pathogenesis of CVD in HIV will be of increasing importance as the HIV population ages. This will enable targeted prevention strategies and personalised antiretroviral regimens to be utilised. Some of the recent advances in the field are discussed in this review.

It is important to highlight that the contribution of HIV specific factors (such as immune deregulation and ART) on cardiovascular risk is relatively small when compared with those of traditional risk factors such as age, family history and cigarette smoking (Figure 1). In fact smoking is responsible for over half of the total CVD risk in HIV. This is partly because HIV positive patients are 2–3 times more likely to smoke than age matched controls; in some cohorts up to 59% of patients smoke[1]. There may also be a synergistic effect between HIV and smoking related endothelial inflammation which could contribute to atherosclerosis. While eliciting behaviour change is difficult, there is growing evidence that improved education and a sustained focus on smoking cessation can lower smoking rates and improve patient outcomes[2].

As mentioned above, inflammation is a key component in the pathogenesis of atherosclerosis and acute cardiovascular events. Metabolic derangements and inflammation have complex and likely bidirectional relationships. It is known that lipids are more likely to infiltrate the arterial wall in the setting of inflammatory stimuli. There they activate endothelial cells to increase expression of adhesion molecules and recruit further inflammatory cells, in particular T-cells. Ultimately this cycle results in unstable, chronically inflamed atherosclerotic plaques[3]. HIV positive patients in general have higher baseline levels of inflammatory biomarkers (such as high sensitivity C-reactive protein and interleukin-6) which have been associated with increased rates of cardiovascular events and all-cause mortality[4]. Immune dysregulation also plays an important role in the progression of HIV related CVD. There is evidence that increased levels of T cell activation predict subclinical carotid artery disease[5]. Research performed in Melbourne has demonstrated that a change in expression of monocyte surface markers CX3CR1 (a chemokine receptor important in cell signalling) and CD11b (an integrin involved in adhesion to the endothelial wall) are associated with subclinical atherosclerosis[6]. And while cardiovascular risk does decrease with successful ART it does not return to the levels seen in the general population. This may be partly explained by the finding that chronic inflammation and immune activation
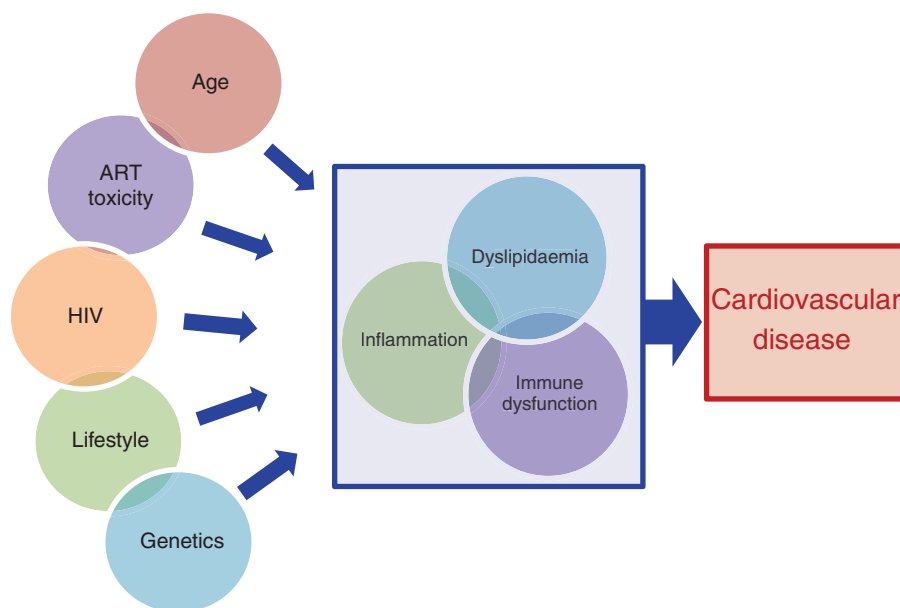
Figure 1. Inter-related factors that promote atherosclerosis in HIV. In HIV positive patients complex interactions between HIV, antiretroviral therapy and traditional risk factors lead to immune activation, inflammation and dyslipidaemia; which in turn interact to drive atherosclerosis. For instance, high inflammatory states lead to oxidation of plasma low-density lipoprotein cholesterol causing the release of phospholipids, which further activate endothelial cells and promote entry of foam cell forming macrophages into the developing plaque.

associated with HIV infection persists even in the setting of viral suppression[7]. The pro-atherogenic, and possibly pro-thrombotic, side effects of some antiretroviral agents are clearly also contributing.

The Data collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study provided the first evidence of an increased risk of CVD associated with ART; demonstrating a 26% increased rate of acute myocardial infarction per year of ART use[8]. The cohort has since gone on to describe that the degree of risk differs according to type of antiretroviral, in particular increased exposure to some protease inhibitors (e.g. indinavir and ritonavir-boosted lopinavir) and current abacavir use have been implicated[9]. While the relationship between abacavir and CVD has been hotly debated in the literature, a case-control study performed at our institution also identified an association between current abacavir use and symptomatic coronary artery disease[10]. Our group and others are currently attempting to delineate a pathogenic link between the two, and there is early evidence that increasing platelet activation may be involved[11].

A significant portion of the elevated cardiovascular risk in HIV patients can be explained by viral and antiretroviral-associated dyslipidaemia. Australian research has demonstrated that HIV impairs reverse cholesterol transport from macrophages by modifying high density lipoprotein (HDL) cholesterol metabolism and redirecting cholesterol to apoB-containing lipoproteins[12]. In the presence of HIV macrophages can thus accumulate substantial amounts of lipid and come to resemble foam cells, a classic component of atherosclerotic plaques. Untreated HIV is commonly associated with low total-, HDL and low-density lipoprotein- (LDL) cholesterol along with elevated serum triglycerides. Initiation of ART can lead to an increase in total and LDL cholesterol (at times to well above the normal range) without a corresponding rise in HDL[13]. The degree of dyslipidaemia is determined in part by the antiretroviral regimen chosen. Lipid profiles consisting of high LDL and low HDL have been shown to be on the causal pathway towards cardiovascular events in the general population.

The optimal management of ART and HIV associated dyslipidaemia is not yet clear with a number of strategies currently being investigated including switching within or between antiretroviral classes to avoid agents most associated with dyslipidaemia, versus adding a lipid modifying agent such as HMG-CoA reductase inhibitors (statins), niacins or fish oils. Statins in particular provide an attractive option in HIV given their dual lipid lowering and anti-inflammatory properties but further work is needed to guide their optimal use.

Conclusion

CVD is a significant cause of morbidity and mortality in HIV positive patients in the modern era. Ongoing work to understand the pathogenesis of CVD must remain a key priority so that recent gains in the health and life-expectancy of patients living with HIV can be maintained.

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Biographies

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Therapeutic vaccination in HIV infection

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The concept of using a vaccine to induce or enhance HIV-specific immune responses in those with established HIV infection has been through alternating waves of enthusiasm and skepticism over the past three decades of the HIV epidemic. The earliest therapeutic vaccination trials were conducted in subjects with uncontrolled viremia or suboptimal therapy and the highly activated and dysfunctional immune environment of such individuals would significantly impede the efficacy of any immunostimulatory approaches. Contemporary antiretroviral treatment assures potent and sustained inhibition of HIV replication, reduces immune activation and restores a variety of specific immune functions. This provides the context for a renewed level of scientific interest in the possibility of inducing HIV-specific immunity that could clear virally infected cells, retain long lived memory, and help reduce latent reservoirs of HIV that cannot be eliminated by current drugs or intensification strategies.

To date the most studied approaches for vaccination have been based on viral vectors, plasmid DNA and more recently, autologous dendritic cells (DCs). Among the vectored vaccines, the recombinant canarypox vaccine ALVAC is the most extensively studied across more than 15 preventative vaccine trials, including as the prime to subtype B/E gp120 protein boost in the RV144 'Thai' trial that reduced HIV acquisition by 31%[1]. Notably, there was no effect on levels of viremia and/or CD4 T cell count in vaccinated subjects who ultimately acquired HIV and in the therapeutic vaccination setting, results with ALVAC based vaccines have been contradictory. While an open label single arm study found that up to 11% of patients who stopped their antiretroviral treatment after vaccination could remain off treatment for 44 weeks[2], the largest randomised, placebo controlled studies have shown either no effect on the level of