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Commentary

A Commentary on Lipid Disorder and HDL-Cholesterol in HIV Patients: Changing Trends

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With the advent of highly active antiretroviral therapy (HAART) there have been remarkable improvements in the survival of HIV patients. However, complications in the form of dyslipidaemia, insulin resistance, bone problems and liver and kidney disorders have been found to be more noticeable compared to AIDS defining illnesses. The continuous exposures of antivirals of different class with different side effects profile have led to a new trend of problems.

There is a significant body of evidence suggesting that exposure to Antiretroviral Therapy (ART) may be associated with a measureable increase in cardiovascular events [1]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group reported outcomes demonstrating an increased incidence of myocardial infarction (MI) that was proportional to the cumulative duration of HAART [2]. After adjusting for conventional risk factors, low HDL-cholesterol, total cholesterol and duration of exposure of HAART particularly the use of abacavir and lopinavir were associated with increased risk of Cardiovascular Diseases (CVD). On the other hand, some studies did not provide evidence of an association between ART and increased CVD events or mortality. However there are common findings suggesting that the risk of CVD is significantly associated with the traditional risk factors that include raised total cholesterol and low HDL-C level.

The lipid disorders seen in individuals with HIV infection include elevated triglycerides (TG), total cholesterol (TC), a decrease in HDL-C, and variable effects on low-density lipoprotein (LDL) cholesterol. The exact mechanism is still not clear and the cause could be multifactorial. The individual contributions of HIV infection, specific antiretroviral agents, host genetics and changes in body composition, all should be considered [3]. Cholesterol, triglycerides and Apo lipoproteins assembled in the liver are secreted into the blood as lipoproteins. Depending upon their size, shape and density they are called very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low-density lipoproteins (LDL) and small LDL. Each of these contains apolipoprotein-B (apo-B) along with other apolipoproteins. As the lipoproteins circulate through the body, they become smaller and denser and richer in cholesterol content. The small LDL is more likely to be taken up by mononuclear cells and can potentially lead to atherosclerosis. High Density Lipoprotein (HDL) constitutes a heterogeneous group of particles varying in shape, size and density and apolipoprotein content. Apolipoprotein A1-A4 are major apolipoproteins with A1 being the most common ingredient. Apolipoprotein A secreted from liver and intestine transports cholesterol from peripheral tissue as HDL cholesterol (HDL-C) back to the liver and kidneys for elimination(figure 1). Research has demonstrated that patients with HIV infection have either increased synthesis of apo-B containing lipoproteins and or delay in the clearance of apo-B containing lipoproteins thereby increasing the apo-B pool and increasing the risk of atherosclerosis [4]. Apo-A containing lipoproteins as HDL-C tend to prevent atherosclerosis by lowering cholesterol burden in the tissues and preventing oxidative changes in LDL-C and mostly small LDL-C. While there has been more understanding about apo-B kinetics there is very limited knowledge about apo-A kinetics in HIV patients.

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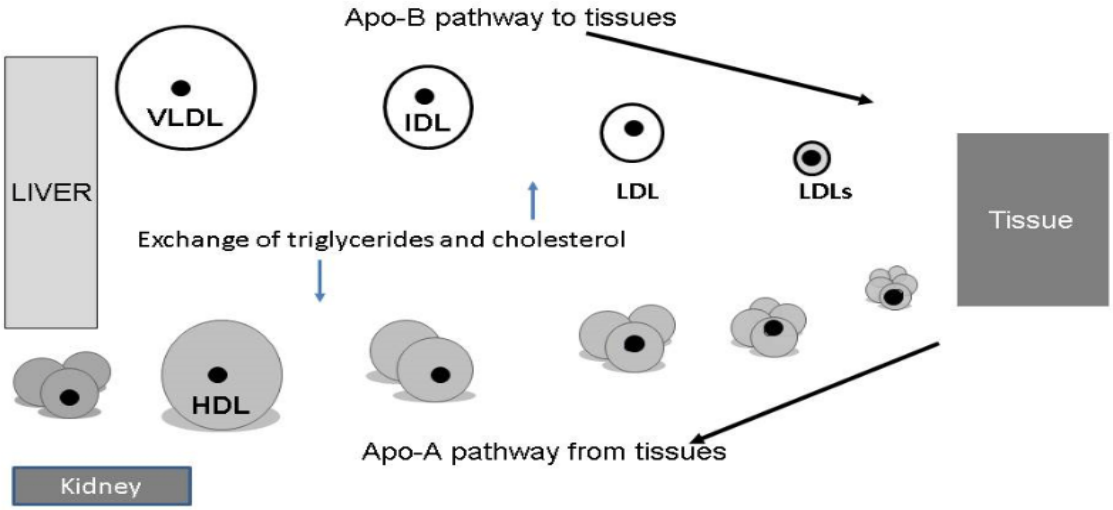

Figure 1: Lipoprotein Transport

There have been changes in the pattern of dyslipidaemia in HIV patients. This is because most of the newer antiretrovirals that include integrase inhibitors like raltegravir, dolutegravir, bictegravir and chemokine receptor 5 (CCR-5) inhibitor as maraviroc have better lipid profile, either they are lipid neutral or cause mild dyslipidaemia. Raised lipids have been observed less often and low HDL-C has also been observed less frequently. The Multicentre AIDS Cohort Study (MACS) showed that immediately after HIV infection TC and HDL-C dropped and when treatment is started TC goes back and HDL-C comes back to normal or near normal [5]. We wonder whether HDL-C can go above normal or even abnormally high in some patients when they are on treatment for a long time. Raised HDL-C has been observed with nevirapine use, but is not known to be associated with an abnormally high level. Abnormally high HDL-C has been noted in HIV patients but the actual prevalence of abnormally high HDL-C is not reported.

HDL Cholesterol (HDL-C) is known to be cardio-protective. Several large epidemiological studies demonstrated that low HDL-C can be an independent predictor of increased risk of cardiovascular disease. Increasing HDL-C levels in animals have shown markedly reduced susceptibility to the development of arteriosclerosis in animal models. It is estimated that for each increment of 0.25 mmol/L in HDL-C the risk of CVD can reduce up to 2% in men and 3% in women. However, the interventional studies increasing the level of HDL-C in humans yet to demonstrate any beneficial effect on the outcome of cardiovascular disease. There is hardly any evidence to suggest that HDL-C above 1.8 mmol/L has any beneficial effect in reducing the risk of CVD. More over results from two large population-based research showed that all-cause mortality including CVD related deaths is high in men and women with very high levels of HDL-C [6]. Similar findings were observed in a Canadian observational cohort study involving over 650000 participants [7].This study demonstrated that the risk of all-cause mortality in both men and women were higher when their HDL-C level were either in the lower range or at the very highest levels, compared to the levels which were in the intermediate range.

Obviously, these studies raised questions about the protective effect of HDL-C at extreme levels either very low or very high. It appears that the HDL-C level instead of having a linear relationship with the risk of cardiovascular disease, it appears to have a 'U' shape relationship, where the two arms of 'U' represents either lower HDL-C or the higher HDL-C level (figure 2).

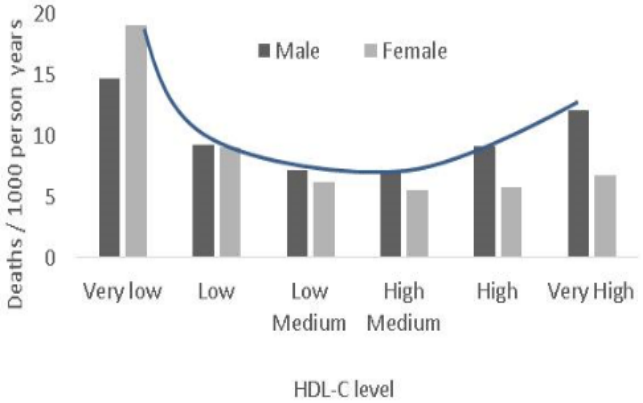

Figure 2: Relationship between crude all-cause mortality rate and HDL-C level [6]. Very low HDL-C <0.7 mmol/L, Very high HDL-C > 2.3 mmol/L.

The function of HDL-C is complex, however some of them are well-known and they are related to efflux of cholesterol from the macrophages, reverse cholesterol transport, antioxidant and anti-inflammatory effect on blood vessels. Impaired cholesterol efflux in reverse cholesterol transport has been found to be an important reason for low HDL cholesterol in HIV patients particularly when they are not on antiretroviral treatment. HIV within the macrophages can inhibit ATP binding cassette (ABC) transporter, a key enzyme for cholesterol efflux from macrophages and keep the cholesterol within the macrophages. With antiretroviral treatment the macrophages tend to clear from HIV and cholesterol efflux starts resulting in normalization of plasma HDL-C level.

The plasma level of HDL-C may not reflect the actual function of HDL-C. There are several different types of HDL-C and depends upon their cholesterol content and the size of the HDL cholesterol. There has been debate on the ability of HDL-C to have its function when the cholesterol content within the particle is high or low. Probably it is more important to see the number of HDL particles rather than the actual concentration of HDL-C.

Considering the fact that patients with HIV infection have a higher risk of CVD the national guidelines recommend that these patients should have CVD risk assessment on an annual basis [8]. The algorithms which assess the risk of cardiovascular disease, like Framingham Risk Calculation or Q-Risk Calculation, all use total cholesterol and HDL ratio (TC/HDL) and patients with raised TC along with raised HDL-C may give a total TC/HDL ratio within the normal range. This may under-estimate the risk of cardiovascular disease. In this context it becomes more important to see whether abnormally raised HDL-C has got the functional ability to prevent arteriosclerosis. However, assessment of function of HDL-C in clinical practice is far from reality at present.

It is important that we make the effort to understand the extent of the problem HIV patients may have with abnormally high HDL-C level and underlying any risk factor associated with that. In the absence of any clear guidance about the interventions we need to take to deal with abnormally raised HDL-C we need to continue to manage individual known modifiable cardiovascular risk factors. At present our aim has been to reduce TC level and increasing HDL-C level and we consider different statins which can reduce cholesterol at the same time can increase HDL-C levels. Research in the HIV population gave priority to use drugs which can lower total cholesterol levels and increase HDL-C level. Of note there is hardly any antiretroviral agent which has shown reduction to the TC/HDL ratio. So far, we never had to consider whether we need to lower abnormally high HDL-C level. In fact, we are not sure which should be our priority when individuals present with abnormally raised HDL-C with raised total cholesterol level. This appears to be a different scenario and we do not have any clarity about what interventions to use.

Hence in the absence of any definite guidance about how to deal with abnormally raised HDL-C we should aim to focus on assessment and modification of other known risk factors like smoking, hypertension and insulin resistance and raised total cholesterol level. Choice of ARV regimens should be individualised for the patient to achieve maximal and durable viral suppression as well as avoiding long-term toxicities. It would be reasonable to target raised total cholesterol levels with lipid lowering agents, which is the case at present in the general population, for HIV patients

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