HIV/AIDS and ART: Its Implications to Metabolic Abnormalities

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**Introduction**

Although HIV virus is known to mankind since the last four decades, there are many advances in understanding the virus, its manifestation, and its therapy. With the evolution in drug therapy for HIV, morbidity and mortality in people living with HIV/AIDS (PLHA) drastically reduced. Nowadays very few PLHA present with opportunistic infections and HIV/AIDS turned into chronic manageable disease from one of the dreaded diseases in the past.

As the longevity of PLHA increased drastically, they present with many complications like malignancy, non-opportunistic infections, cardiovascular diseases, and metabolic disorders.

Metabolic abnormalities include lipid abnormalities, insulin resistance, increased blood sugar, increased body mass index, lipodystrophy, hypertension, and increased waist circumference, and it is studied and published by many authors.

**Lipid Profile**

Lipid abnormalities can occur due to HIV infection itself or drugs used for treatment. Studies have shown that PLHA without antiretroviral therapy (ART) has low total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) but increased triglycerides. Increased level of interferon α, C-reactive protein, and interleukin 6 (IL-6) is responsible for chronic inflammation which may cause an increase in the rates of basal lipolysis and hepatic lipid production.2

Pallab Sinha, Nandini Chatterjee, Souvik Ghatak et al. in the present JAPI journal showed a lower level of TC in treatment-naive PLHA compared to PLHA on ART. They further clarified that TC is increased significantly in PLHA on protease inhibitor (PI)—based regime compared to non-PI-based regime.

Antiretroviral therapy, especially PIs, is responsible for low HDL-C, high LDL-C, and high TC. PIs inhibit adipocyte differentiation and lipogenesis and lower the hepatocyte chylomicrons clearance. It increases triglyceride synthesis in the liver.3

**Effect of ART Drugs on Lipid Profile**4–6

- All nucleoside reverse transcriptase inhibitors (NRTIs) except tenofovir increase LDL-C and triglycerides.
- Non-NRTIs, efavirenz increases TC and triglycerides, while nevirapine has little effect on lipid profile.
- Enfuvirtide did not have any effect on lipid levels.
- Entry inhibitors, maraviroc improves the lipid profile of patients with dyslipidemia.
- Integrase strand transfer inhibitors are safer for lipid profile compared with PI.

**Hyperglycemia and Insulin Resistance**

Many studies have shown that PLHA with or without ART developed hyperglycemia and insulin resistance over time. The prevalence of diabetes or milder glucose metabolism disorders in PLHA is 2–14%.7 The D:A:D: study (Data Collection of Adverse events on Anti-HIV Drugs), one of the largest studies on PLHA, showed an incidence of type 2 diabetes mellitus (T2DM) of 4.2 per 1000 person-years.

Multicenter AIDS Cohort Study (MACS) showed the incidence of T2DM was 14% in PLHA taking PI (ritonavir and indinavir) and NRTIs ( stavudine, zidovudine, and didanosine).8 In Veterans Aging Cohort Study (VACS), there is a correlation between diabetes and weight gain. For each 2.26 kg of weight gained, PLHA had a 14% increased risk of DM. Low CD4 cell count and high levels of CRP and TNF receptors 1 and 2 are responsible for T2DM in these populations.9 Presence of lipodystrophy, HIV infection, coinfection with hepatitis C virus, decreased growth hormone, low CD4 count, and hepatic steatosis are responsible for insulin resistance.5,10 PLHA with lipodystrophy achieves lower insulin-stimulated glucose disposal, impaired glucose uptake by skeletal muscles, and increased intramyocellular lipids.11

People living with HIV/AIDS on a PI-based regime developed insulin resistance and DM due to the inhibition of glucose transporter GLUT, and increased cytokines like adiponectin and leptins. Adiponectinemia is low in the PLHA population which is responsible for insulin resistance [36]. NRTIs inhibit DNA polymerase-γ in mitochondria. Fat is not oxidized in the muscle and liver hence lipotoxic insulin resistance develops.12–15

In the latest publication of the American Diabetes Association’s Standards of Medical Care in Diabetes (2016), advised blood glucose levels before and after 3 months of ART in PLHA.16

People living with HIV/AIDS with lipodystrophy have increased levels of insulin and free fatty acids in the blood and over time may develop fatty liver disease.17

**ART and Lipodystrophy**

Antiretroviral therapy can cause lipoatrophy or lipohypertrophy in the same patient. There is loss of peripheral fat (limbs and face) and deposited centrally (pot belly and buffalo hump). This is more marked in stavudine and zidovudine-containing regime. Fat deposition also occurs in the liver and muscles.2 PLHA with longer duration of treatment, old patients, and low CD4 count are more prone to these complications.

**Lipid Abnormalities and Heart Disease**

One of the risk factors for atherosclerosis and coronary artery disease (CAD) is lipid abnormality. HIV itself can cause macrophage activation and endothelial dysfunction which may cause CAD. PLHA will have a 1.5–2-fold increased risk of CAD compared to HIV-negative individuals. They have a 4–5 fold increased risk of CAD at the end of 1 year.17

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Hypertension and Metabolic Syndrome

Many studies show that hypertension is more common in ART-treated than in ART-naïve PLHA and HIV-negative subjects. Prevalence of hypertension may reach 96% in PLHA with metabolic syndrome. Aging, metabolic abnormalities, endothelial dysfunction, inflammation caused by HIV virus infection, and longer ART treatment may be responsible for hypertension in PLHA. PLHA on dolutegravir regime tends to get obesity and obesity increases the risk of hypertension and metabolic syndrome.18

Nef, transcription protein (Tat), and glycoprotein 120 may have a link between metabolic syndrome and hypertension in genetically susceptible individuals. Inflammatory markers such as hsCRP and IL-6 are increased in PLHA with metabolic syndrome compared to PLHA without metabolic syndrome. This suggests that inflammation of metabolic syndrome has a role in the pathogenesis of hypertension in PLHA.19

References