Case Report

A 44 Years Old Male with HIV-AIDS and STEMI:
From Pathogenesis and Risk Factors to Cardiovascular Disease Management in HIV Positive Patients

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Introduction

There were 33.4 million people who are living with human immunodeficiency virus (HIV) worldwide in 2008, of which 2.7 million were newly infected. In the United States, over 1 million people are currently infected with HIV, and about 40,000 new cases are diagnosed each year. Acquired immune deficiency syndrome (AIDS) was responsible for the deaths of 16,000 in the US in 2004. In Indonesia the cumulative case of infected persons are up to 20.000 by the year 2009, where the numbers only shown the tip of the epidemiological iceberg of HIV/AIDS infection in Indonesia, with real amount of case predicted to be around 240.000 cases.[1, 2]

Highly active antiretroviral therapy (HAART) has greatly reduced the risk of potential fatal opportunistic infections and thus has expanded the life span of these patients. Therefore, other possible causes of morbidity and mortality in the HIV-positive population have come to the forefront. In recent years, more and more clinical studies have indicated that people with HIV infection are epidemiologically at a significantly greater risk for coronary heart disease and myocardial infarction than uninfected people of the same age. A retrospective analysis in France reported that the incidence of coronary heart disease was between 5 and 5.5 per 1,000 person years among HIV-infected people, which was at least a threefold increase over the incidence (1.52 per 1,000 person-years) in the general French male population.[3, 4]

In another retrospective study of 28,513 HIV-infected people, HIV-infected men up to age 34 years and women up to age 44 years had a significantly higher incidence of cardiovascular disease than age-matched people without HIV infection (2.16–6.76 versus 1.53–2.47, $P < 0.01$). Furthermore, Klein et al. found that HIV-positive members of the Northern California Kaiser Permanente Medical Care Program, a large health maintenance organization, had a significantly higher rate of hospitalization for coronary heart disease than HIV-negative members (6.5 versus 3.8, $P = 0.03$) and that the rate of myocardial infarction was also greater (4.3 versus 2.9, $P = 0.07$).[3-5]

Clearly, acute coronary syndromes, in particular, myocardial infarction, are among these potential causes of morbidity and mortality in the HIV-positive population. The effects of many cardiovascular risk factors such as age, smoking, and hyperlipidemia on the incidence of coronary heart disease in the general population have been established. However, the pathogenic mechanisms of the increased incidence of HIV-associated vascular diseases are largely unknown. Thus, this important clinical problem is under active investigation.

There are several possible explanations for an increase in coronary events in HIV patients. HIV disease is associated with accelerated T-cell proliferation, heightened T-cell activation, and high levels of inflammatory markers, immunologic perturbations that persist even after the introduction of effective antiretroviral therapy. T lymphocytes and inflammatory cytokines both play key roles in atherogenesis. Thus, immunodeficiency and immune

reconstitution may accelerate atherosclerosis. Furthermore endothelial dysfunction, hypercoagulability, hypertriglyceridemia, and abnormal coronary artery pathology were in fact associated with HIV infection prior to the availability of protease inhibitor therapy.[6-11]

Despite the provocative pathological and physiological associations of endothelial dysfunction, hypercoagulability, and HIV infection, clinically manifest coronary artery disease was not commonly documented in HIV-infected patients in the pre–protease inhibitor era. This may, in part, be because of the reduced life expectancy of HIV-infected patients before the availability of protease inhibitors. In the present treatment era, highly active antiretroviral therapy (HAART) may be unmasking coronary disease that was previously clinically silent by reducing the incidence of comorbid disease and premature death. Although this may explain part of the increase in documentation of HIV and coronary artery disease, there are characteristic metabolic derangements from protease inhibitors that may predispose to premature coronary disease. Protease inhibitors induce deleterious metabolic effects such as dyslipidemia and insulin resistance.

As was shown above, the pathogenesis of acute coronary syndromes (ACS) may differ in HIV patients and therefore their clinical features and response to treatment may differ as well. Hsue in 2004 reported that HIV patients with ACS are younger and more likely to be males and current smokers and to have low HDL cholesterol levels compared with other ACS patients. Recent guidelines for the management of coronary risk factors in HIV-AIDS patients also stated that the management of HIV is becoming increasingly complex because of several juxtaposed problems: the need to continue ART to maintain viral suppression despite the presence of metabolic disturbances; the unique and poorly understood mechanisms of ARV-induced dyslipidemia and the incomplete response to lipid lowering therapy; the complex drug interactions between lipid-lowering agents and ARVs; and the uncertainty of the long-term consequences of ARV associated metabolic derangements.[5, 12, 13]

The above review has clearly stated that the management of cardiovascular risk factors in HIV-AIDS patients has become a very important matter; it has shown to have a broad and complex pathophysiological and management implications. However, little has been shown in interests and understanding for the incorporation of these finding in clinical practice. Here we presented a case of 46 years old man with HIV-AIDS and Acute ST-elevation Myocardial Infarction, as a case example for the further evaluation and management of cardiovascular risk factors in HIV-AIDS patients, particularly for the one in the hospitalized ARV naive setting and also for those using the current standard ARV regiment in Indonesia.

Case illustration

A 44 years old man with a history of intravenous drug using came to the emergency department of Cipto Mangunkusumo hospital with a complaint of prolonged diarrhea for one month. Subsequent anamnesis revealed a history of fluid watery diarrhea, without any signs of blood and mucus production, the diarrhea observed a frequency of 4 – 6 times daily from which the patients had tried various over the counter medicine with only minimal symptoms improvement. The patients also complained a productive cough with yellowish sputum for the last two weeks, there was no bloody sputum observed. There was also a history of recurrent low grade fever for the last 4 months, especially in the nights which made the patient sweating quite profusely. The patient's bodyweight has dropped 8 kilograms since and there was also profound fatigue which hampers the patient's activity of daily living.

The patient's was an intravenous drug user for 5 years from the year of 1997 to 2002, he admitted to had shared the needle used among friends, many of whom had died since. There was no history of free sex, homosexual activity and transfusions of blood products. The patients admit a history of alcohol consumption, starting from his youth up to now he regularly consumes 2 bottles of beer or wine each week. There was also a history of smoking since 20 years ago with 1 pack a day of cigarettes.

From the past medical history there was no history of diabetes, hypertension, and hyperlipidemia (based on routine medical evaluation). The patient also denies any history of prior unilateral weakness, chest pain and shortness of breath on exertion. There were no allergies, asthma and history of jaundice. The family history also revealed no significant family illness, such as diabetes, hypertension, stroke, heart disease and hypertension.

Physical examination revealed a medium build man with signs of mild dehydration and malnutrition, there was no signs of restlessness and the patients' resting comfortably in his bed. The patient is alert and well oriented and looked moderately ill. The hemodynamic status was stable with a BP of 110/60 mmHg, a pulse of 100 times per minute, respiratory rate of 24 times per minute and temperature of 38.4°C. The patient's recent bodyweight was 48 kg and with a height of 165 cm that gives the patient a body mass index (BMI) of 17.63. The pupil was symmetrical, round shaped and both reactive to light, the sclera was not icteric and the conjunctiva was not pale. There was no jugular venous distention, no palpable enlarged thyroid and no bruit was heard over the carotid arteries.

Chest examination revealed a symmetrical chest in static and dynamic condition, there was sonor percussion and symmetrical fremitus on both lungs. Auscultation revealed a vesicular breath sounds, ronchi over both lungs especially on the paracardial areas and there was mild bilateral wheezing observed. Heart examination revealed palpable heart pulse on the left midclavicular line, with no cardiomegaly, normal heart sounds, and no summation gallop and murmurs could be heard.

Abdominal examination revealed flat and non tender abdomen, with slight loss of turgor, the liver and spleen was not palpable. Abdominal auscultation revealed normal gut motility. The extremities were warm to palpation with a slight loss of turgor, the capillary refill time was normal and there was no edema observed.

Laboratory examination revealed slight anemia (Hb 10.3 g/dL) with a normochromic normocytic appearance (MCV 91.7 and MCHC 31.6), normal leukocyte (7700 cells/mcl) with monocytosis (24.0%) and limphopenia (3.8%) and normal platelet count. The CD4(+) cell count revealed a level of 43 cells/µL. There was an elevated erythrocyte sedimentation rate (125 mm/hour) and CRP (20 mg/dL), elevation of liver transaminases enzyme (AST 100 U/L and ALT 59 U/L), while the renal function test was normal (ureum 39 g/dL and creatinine 0.9 g/dL). Random blood glucose was also checked and the result came back normal (127 mg/dL). The electrolyte levels also within normal range (Sodium 134 mEq/L; Potassium 4.17 mEq/L and Chloride 102.0).

Blood gas analysis revealed compensated respiratory acidosis (pH 7.40; pCO2 49.20 mmHg; PO2 87.9 mmHg; HCO3 30.4 and O2sat 96.6%) with room air breathing. Preliminary hemostasis screening revealed an activated Partial Thromboplastin Time (APTT) level of 29.5 seconds with control of 32.0 (0.921 times control) and Prothrombin Time (PT) of 13.0 second with control of 12.5 (1.04 times control). Lipid profile examination (from patient's personal data) revealed a total cholesterol of 187 mg/dL, LDL cholesterol of 117 mg/dL, HDL of 34 mg/dL and triglyceride of 223 mg/dL. Anti hepatitis C virus antibody test results also came back positive.

Chest x-ray examination revealed a normal sized heart (CTR <50%) with bilateral paracardial and bibasilar infiltrates. The electrocardiogram showed a sinus rhythm with normal axis and a rate of 98 times per minute; normal P waves with normal PR interval (0.16 s); QRS waves showed no abnormality (0.06 s); there were no ST segment changes, no T wave's inversions, no left and right ventricular hypertrophy and also no bundle branch blocks.

Based on the anamnesis, physical examination and the initial laboratory and auxiliary examination, we made the initial diagnoses of chronic diarrhea with moderate dehydration, community acquired pneumonia grade IIIA, nutritional intake difficulties, oral candidiasis, elevated liver transaminases, normochromic normocytic anemia, chronic hepatitis C virus infection and HIV-AIDS ARV naïve.

The patient is then placed on infusions of normal saline 500cc/8 hours and Triofusin E™ 1000 500cc: Aminovel™ 500cc/12 hours; high calories high protein content diet of 2100 kcal, bed rest, ceftriaxone 1 x 2 grams, azithromycin 1 x 500 mg, ambroxol 3 x 1 tablespoon, mycostatin 4 x 2 cc, cotrimoksazole 2 x 960 mg, fluconazole 1 x 150 mg, new diatabs prn, omeprazole 2 x 20 mg, ondansetron 3 x 4 mg and lesichol 3 x 1 tablet.

On the 7th day of admission the patient complained about chest pain, which radiates to the jaw and back, the pain felt like heavy pressure on the chest. On subsequent physical

examination a new systolic murmur was found, but no other heart physical examination changes found. Electrocardiogram showed a new ST segment elevation on lead V1-V4 and cardiac enzymes examination showed an elevated CK-MB (62 IU/mL) and positive cardiac troponin-T.

A diagnosis of acute ST segment myocardial infarction (STEMI) was then made and the patient was put on heparinization for the target level of APTT 1.5-2.5 times control. Loading doses of clopidogrel (300mg) and aspirin (160mg) was given and the drugs were continued on the next subsequent day with 75 mg and 80 mg respectively. After 24 hours of acute phase captopril 12.5 QID and simvastatin 10 mg OD was given.

On the 11th day of admission the patients suddenly became unresponsive; there was no heart pulse and no breathing response. Emergency cardiopulmonary resuscitation was then performed for 20 minutes, but the patient was still unresponsive. The patient was then announced dead in front of family members and nurses with the causes of death sudden cardiac death in a patient with acute STEMI.

Discussions

As was shown in the previous section of introduction, HIV infection has been established as a leading risk factor for the development of cardiovascular disease. This is true especially in the ones who had been developing AIDS as a consequence of deprived immune function and opportunistic infections. Cardiovascular disease in the HIV-AIDS patients, as had been shown by Hsue et al, showed certain characteristics such as younger age, male predominance, current active smoker and tends to have low HDL cholesterol. The study also showed that they were less likely than controls to have diabetes or hyperlipidemia, and their TIMI (Thrombolysis in Myocardial Infarction) risk scores on admission were significantly lower.

These results were consistent with our patient's characteristic, which has an age of 44 years old, where the study results described the mean age of Acute Coronary Syndrome (ACS) on the non HIV patients were 61 years compared with 50 years for the HIV positive patients. The current active smoker status of our patient also in line with the study results, which placed him in a high risk category, so does a low HDL cholesterol level (the study revealed a mean of 35 mg/dL for HIV positive patients) and the predominant male sex status.[2]

Common population risks factors for Acute Coronary Syndromes, which has been validated by various clinical trials, also similarly implied in the HIV-AIDS population. The risks factors such as smoking, hypertension, diabetes, dyslipidemia, metabolic syndrome and male gender, also have the same effect on peoples living with HIV-AIDS (PLWHA), however they do have certain characteristics like the Hsue et al study implies.

The first step in assessing cardiovascular risks factors in HIV-AIDS patients is by using common risks assessment tools such as the Framingham Risks Calculator, which predicts 10 years cardiovascular event rate according to established risks factors such as gender, age, smoking status, diabetes, total cholesterol, HDL, and blood pressure. Implementing the Framingham Risk Calculator to our patient will reveal a 10 year cardiac event risk of 8%, slightly higher than the average risk of 7% for the general population according to age. This result showed that our patient actually didn't have a very high risk toward a cardiovascular event, though he still eventually suffered a fatal heart attack and it called for a further explanation for the cause of myocardial infarction in him.[14-16]

Recent clinical studies has pointed several risk factors associated with increased incidence of cardiovascular events among PLWHA, such as low CD4 count, high viral load, the presence of opportunistic infections, protease inhibitors, non nucleotide reverse transcriptase inhibitors (NNRTI), nucleotide reverse transcriptase inhibitors (NRTI), chronic inflammatory states, concomitant intravenous drug usage and also thrombophillic states. The most studied of them all is the effect of Highly Active Antiretroviral Therapy (HAART), especially the protease inhibitors, however because of our patient was antiretroviral naïve, we will discuss about the effect of HAART later on this paper.[3, 5, 13, 17]

The HIV infection, dyslipidemia and metabolic syndrome

The HIV infection itself, to be the first discussed, has recently been touted as important risk factors for atherosclerosis and cardiovascular events in PLWHA. Clinical studies have suggested that HIV-infected patients experience unexpectedly high rates of atherosclerotic disease. Autopsy reports provided the first data suggesting an association between coronary artery disease and HIV infection. Atherosclerotic pathology occurred in the absence of traditional risk factors involving coronary, peripheral, and cerebral arteries in HIV-infected patients. [3] Individuals infected with HIV may be at risk for vascular disease secondary to direct viral effects which induce chronic immune activation leading to increased expression of proinflammatory mediators by activated T cells and macrophages within the vasculature.[6]

Several pro-inflammatory cytokines and chemokines associated with HIV infection are linked to atherosclerosis, and may participate in vascular dysfunction in infected individuals. Monocyte chemoattractant protein-1 (MCP-1/CCL2) plays a crucial role in the pathogenesis of atherosclerosis, attracting monocytes into the arterial intima where they differentiate into macrophages, accumulate lipoproteins and become lipid-laden foam cells. A study by Flooris Moore et al demonstrated that human arterial smooth muscle cells (SMC) express the chemokine receptors CXCR4 and CCR5, and that HIV-infected SMC are themselves a source of MCP-1/CCL2, and have shown that MCP-1/CCL2 induces tissue factor, a major contributor to thrombosis associated with plaque rupture, in vascular SMC. These findings suggest that HIV infection promotes an inflammatory response in the vessel wall and may thereby accelerate atherosclerosis.[18] Furthermore, in a research that was conducted by Francisci et al, it was proven that HIV infection itself plays the dominant role in endothelial dysfunction and not antiretroviral treatment.[19]

HIV infection may also cause endothelial damage predisposing to atherosclerotic disease through its effect on triglyceride levels. The HIV infection itself is associated with dyslipidemia. Early studies of patients with advanced untreated HIV infection typically demonstrated reduced TC and LDL-C levels and moderately elevated TG levels, mainly in the form of very low-density lipoprotein (VLDL). Similarly, a recently published comparison of pre-seroconversion and post-HIV infection lipid values in 50 patients showed a substantial decrease in TC, HDL-C, and LDL-C. Other physical changes in the cardiac endothelium due to inflammation from HIV infection and interaction with the immune system may also contribute to CHD risk. In a study of symptomatic and asymptomatic HIV-infected persons, the extent of HDL-C decrease and TG increase was greater in patients with more profound immunosuppression (lower CD4+ counts). [5, 6, 13, 20, 21]

The lipid profile of our patients revealed an increased triglyceride and decreased HDL-C, although the profile of LDL-C more or less equal to the normal levels found on healthy patients. This pattern of lipid profile were consistent with the one implicated in studies about lipid profile in HIV positive patients, but was not an atherogenic one. Thus, in this

patient we need further exploration of his lipid profile, by subtracting the total cholesterol (187 mg/dL) with LDL-C (117 mg/dL) and HDL-C (34 mg/dL) gave a non LDL-C level of 36 mg/dL, compounded with an HDL-C of 34 mg/dL this gave the patient an atherogenic lipid profile. Important to be noted, this pattern of lipid profile was found to be associated with atherogenic plaque in patients with HIV-AIDS.

Furthermore chronic infection and inflammation in HIV/AIDS were associated with marked changes in lipid and lipoprotein metabolism. Many of the changes in lipoproteins during infection/inflammation help protect the host from harmful effects of the stimuli. In cases of chronic infection, inflammatory diseases, diabetes, obesity, metabolic syndrome, and heart failure, however, these cytokine-induced changes in the structure and function of lipoproteins could be deleterious and may contribute to the development of atherosclerosis.[22, 23]

Infection and inflammation induce the acute phase response (APR), leading to multiple alterations in lipid and lipoprotein metabolism, such as:

- Plasma triglyceride levels increase from increased VLDL secretion as a result of adipose tissue lipolysis, increased de novo hepatic fatty acid synthesis, and suppression of fatty acid oxidation.
- With more severe infection, VLDL clearance decreases secondary to decreased lipoprotein lipase and apolipoprotein E in VLDL. In rodents, hypercholesterolemia occurs attributable to increased hepatic cholesterol synthesis and decreased LDL clearance, conversion of cholesterol to bile acids, and secretion of cholesterol into the bile.
- Marked alterations of proteins important in HDL metabolism lead to decreased reverse cholesterol transport and increased cholesterol delivery to immune cells. Oxidation of LDL and VLDL increases, whereas HDL becomes a pro-inflammatory molecule.
- Lipoproteins become enriched in ceramide, glucosylceramide, and sphingomyelin, enhancing uptake by macrophages. Thus, many of the changes in lipoproteins are pro-atherogenic.[22]

Two primary risk factors of cardiovascular disease are chronically elevated plasma LDL and/or decreased HDL, and inflammation-driven activation of monocytes and vascular endothelium with heightened migration of monocytes into the atherogenic lesion and maturation into macrophages and lipid-rich foam cells. Plaque regression is associated with emigration of macrophages from the plaque, whereas chronic foam cell accumulation, together with their production of proatherogenic factors and their ultimate apoptosis and necrosis in a hypercholesterolemic patient, cause's plaque expansion and plaque instability, ultimately resulting in cardiovascular event(s). HIV infection is likely to affect each stage of

this process (indicated in red in figure 1), thereby increasing risk of cardiovascular disease above the effects of traditional risk factors.

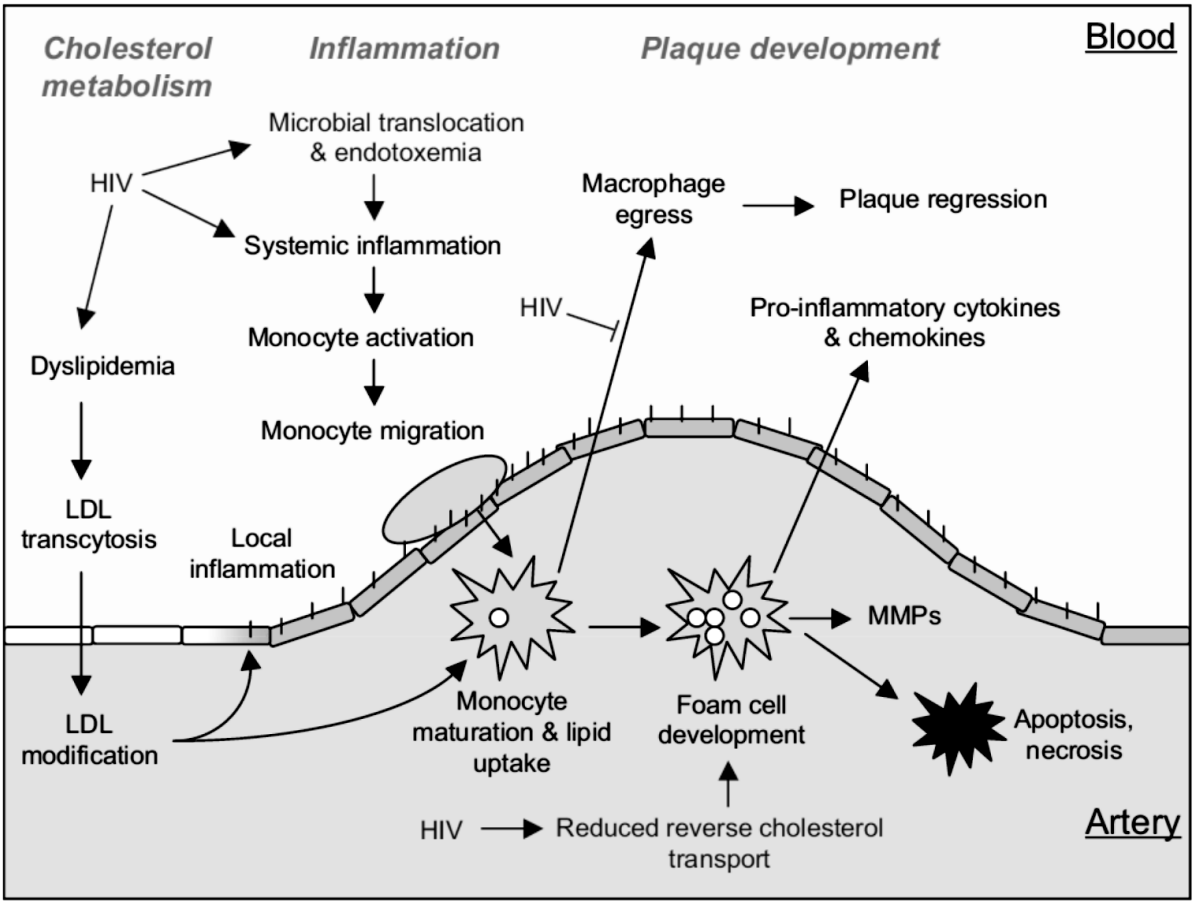


Figure 1. Stages in atherosclerosis which affected by HIV infection.

There are several possible mechanisms in which HIV-AIDS could increase the atherogenic potential and cause coronary artery disease, such as:

- ***Dyslipidemia***: Specific antiretroviral drugs (e.g., PIs) are associated with dyslipidemia (increased plasma LDL and triglycerides, decreased HDL). HIV infection itself may also promote dyslipidemia as a result of changes in cholesterol metabolism.
- ***Systemic inflammation***: Plasma levels of proinflammatory cytokines may be increased in viremic HIV-infected individuals and HIV-associated microbial translocation across gut epithelium results in chronic endotoxemia. Monocyte activation has been demonstrated in viremic HIV-infected individuals and is ameliorated only partially during virological suppression. Whether viremia-induced IFN-production and adaptive T cell responses have additional proatherogenic effects is not known.
- ***Macrophage egress***: Reverse transendothelial migration of monocyte-derived macrophages from the plaque requires basal to-apical migration across the vascular endothelium, which is defective in HIV-infected macrophages in vitro.

- ***Accumulation of foam cells***: Internalization of extracellular lipoprotein and development of lipid-laden foam cells are associated with reduced migratory capacity; defective cholesterol efflux by HIV-infected macrophages is likely to promote foam cell accumulation in plaques. Foam cells also produce proatherogenic factors such as chemokines, cytokines, and matrix metalloproteinases (MMPs), which promote plaque expansion and instability and can undergo apoptosis and/or necrosis in hypercholesterolemic settings.
- ***Impaired endothelial* function**: HIV-infected patients have significant impairment of endothelial function, and this impairment is worse among those with elevated levels of HIV replication, particularly injection drug users.[24]

Indeed, regarding to the above pathophysiological approach, it has been proven by a well documented study by Lo et al that HIV infection was correlated with subclinical atherosclerosis. Lo et al demonstrated that HIV-infected men showed higher prevalence of coronary atherosclerosis than non-HIV-infected men, higher coronary plaque volume, and greater number of coronary segments with plaque, despite similar Framingham 10-year risk for myocardial infarction, family history of CAD, and smoking status.

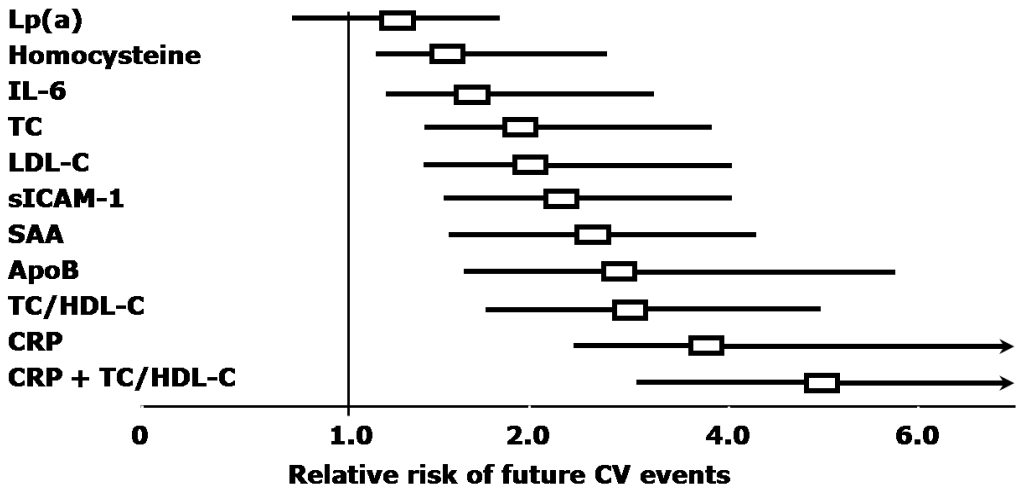
Duration of HIV infection was significantly associated with plaque volume and segments with plaque and these relationships remained significant after adjustment for age, traditional risk factors, or duration of antiretroviral therapy. A total of 6.5% (95% confidence interval 2-15%) of the study population demonstrated angiographic evidence of obstructive CAD (>70% luminal narrowing) as compared with 0% in controls.[25] According to a study by Grunfeld et al, the association of HIV infection with IMT was similar to that of traditional CVD risk factors, such as smoking. So that consideration should be made in regarding making HIV infection as one of the traditional risk factors for coronary arterial disease.[26]

Our patient was in a state of overwhelming infection, from chronic diarrhea, oral candidiasis, pneumonia and even the HIV infection itself, which promotes increased inflammatory mediator and mobilization of pro-atherogenic cells. Monocytosis in our patient, probably resulted from opportunistic infections such as tuberculosis or candidiasis, increased his pro-atherogenic state. So does the HIV itself will prevent the process called macrophage egress, the essential step of plaque regression. Impaired endothelial function, another important factor in the atherosclerosis process, was present particularly among intravenous drug user because of higher level of viral replication among this group. Our patient experienced his contamination with HIV virus through needle sharing, thus posing him to a higher risk of endothelial dysfunction.

Chronic systemic inflammation and atherosclerosis in PLWHA

Chronic systemic inflammation, as stated above, has been proven as a risk factor for coronary artery disease by various clinical studies (figure 2). In patients with HIV/AIDS the relationship between chronic inflammation, HIV infection and coronary artery disease was

further elaborated in a study conducted by Triant et al in 2009. In this study elevated CRP and HIV were each significantly associated with AMI [OR 2.51; 95% CI 2.27 to 2.78; P < 0.0001 for elevated CRP and OR 2.07; 95% CI 1.31 to 3.10; P = 0.001 for HIV]. Compared with patients with normal CRP and without HIV, the OR for AMI was increased more than 4-fold among patients with HIV and elevated CRP.[27]



Apo=apolipoprotein; CRP=C-reactive protein; CV=cardiovascular; HDL-C=high-density lipoprotein cholesterol; IL=interleukin; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein (a); SAA=serum amyloid A; sICAM-1=soluble intercellular adhesion molecule 1; TC=total cholesterol

Figure 2. Several risk factors for increased coronary events, note that several inflammatory markers such as IL-6, sICAM-1 and CRP was among the significant ones.

Chronic systemic inflammation was also present, as indicated by elevated ESR and CRP in this patient, further compromising his atherogenic status toward a deleterious one. Elevated CRP level, recently has also been touted as an important marker for increased risk for myocardial infarction and stroke. The JUPITER trial, a recent and breakthrough study, has also implicated that statin therapy for patients with elevated CRP provide a benefit of cardiovascular events reduction. Though, it's implication for PLWHA still has to be proven, especially because of the numerous drug interactions present in HAART population.

The level of CD4+ lymphocytes has also been established as one of the important risk factors for cardiac events in PLWHA, the reduced level of these cells will resulted in an increased cardiac events. Among HIV-infected individuals, a low CD4+ T cell count was independently associated with an increased prevalence of carotid lesions. Compared to the reference group of HIV-uninfected individuals, the adjusted PR for lesions among HIV-infected individuals with CD4+ T-cell count <200 cells/mm3 was 2.00 (95% confidence interval 1.22, 3.28) in women and 1.74 (95% confidence interval 1.04, 2.93) in men.[28]

A study by Coll et al on 2007 in 141 patients with HIV infection for 2 years had shown that lower CD4+ cell count were associated with a higher progressivity of carotid and femoral artery intima media thickness (IMT) as a surrogate marker for atherosclerosis. The study divided the progressivity of intima media thickness to four different categories, which were

the regressors, minimal progressors, slow progressors and rapid progressors, the patients with slow and rapid progression were showed to have a significantly lower CD4+ levels (figure 3).[7]

Decreased CD4(+) level also present in our patients, with a level of 43 cells/µL and as a consequence putting this patients further to an atherogenic state. As we can see from the previous discussion, compiled clinical and laboratory features in this patient presented numerous novel clinical risk of atherosclerosis. This kind of profile present not only in our patients, but also in most of PLWHA so we need to be able to further analyzed the atherosclerosis risk in PLWHA as an holistic approach. This approach could be evaluated as in part of the metabolic syndrome, comprising of obesity, hypertension, dyslipidemia and diabetes mellitus.

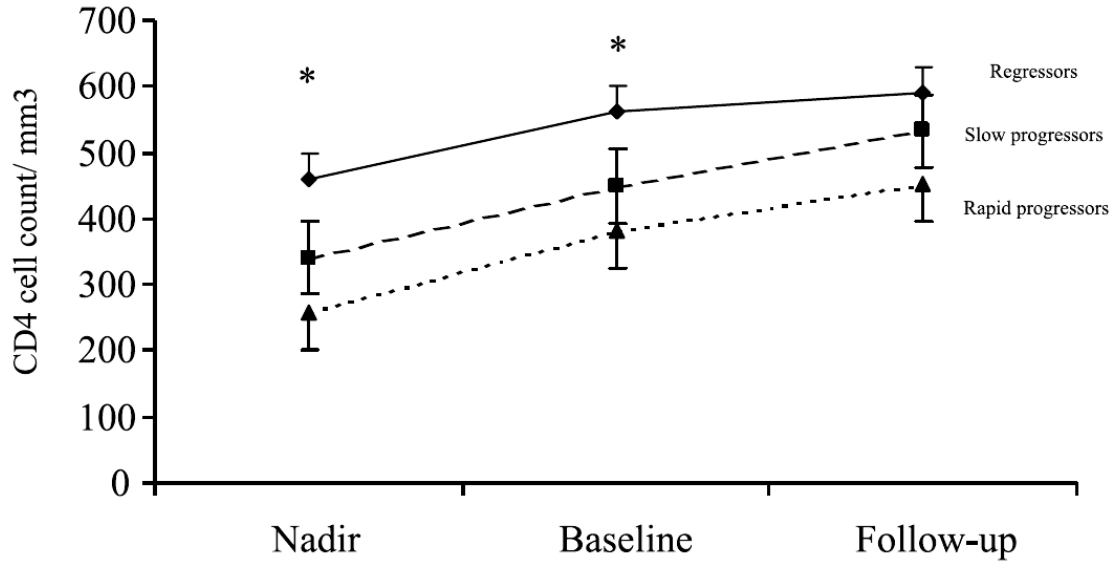


Figure 3. Rate of IMT progression segregated with respect to selected genotypes. *P<0.05 and ‡P<0.04 comparing the different rates of IMT progression segregated with respect to SDF-1 and CX3CR-1, respectively (analysis of variance).

New-onset diabetes mellitus, clinically similar to type 2 Diabetes, affects a small proportion (1% to 6%) of HIV-infected patients treated with PI-based antiretroviral regimens. Many more patients receiving PI therapy have evidence of insulin resistance without frank diabetes. However; insulin resistance may also be associated with HIV infection itself in patients not receiving PI therapy, perhaps resulting from the direct effects of the HIV virus on pancreatic cell function and insulin secretion. Regardless of causality, the high prevalence of insulin resistance in patients infected with HIV, which frequently coexists with dyslipidemia and abdominal obesity, raises concern about the eventual development of increased cardiovascular morbidity in this population. [29, 30]

The prevalence of systemic hypertension among HIV-infected patients is much higher than that in the general population: It has been estimated as 20%–25% before the introduction of HAART and as approximately 74% among patients who undergo HAART with protease

inhibitors and who subsequently develop lipodystrophy and metabolic syndrome. Systemic hypertension in HIV-positive patients seems to have a significant effect on their risk of premature cardiovascular disease: Compared with normotensive HIV-positive patients, hypertensive patients have a higher frequency of coronary heart disease (16.1% vs. 1.3%) and a higher incidence of myocardial infarction (8.1% vs 0.7%).[31, 32]

The above risk factors for cardiovascular disease had been studied to be included in the metabolic syndrome (MetS) criterion of three between five categories (elevated fasting glucose, elevated triglycerides, decreased HDL-C, high waist circumference and high blood pressure). The SHIVA study which analyzed the prevalence of metabolic syndrome in patients with HIV-AIDS concluded that the prevalence of metabolic syndrome (10.9%) was much lower than previously reported in patients with HIV but remained higher than among the general population (4.8%). MetS is a powerful independent risk factor for CVD. It is highly associated with IMT and with plaque formation in HIV cohort as well as in the general population. MetS in these patients results from the independent association of various side effects of ART (high triglycerides, lower HDL-C and hypertension) and direct effects of HIV disease. Furthermore, MetS status is strongly linked to CVD markers and can be used to decide about primary CVD prevention.[33]

Thromboembolism as an important cause of cardiovascular events in hospitalized PLWHA

Another factor that should be acknowledged as an important cause of acute myocardial infarction in PLWHA, especially for the hospitalized patient, is thromboembolism. Multiple acquired and persistent thrombophillic abnormalities are more frequently observed in HIV-infected patients than in the healthy population. Epidemiological studies with populations numbering from 60 to 42,935 showed that the occurrence of venous thromboembolic complications among HIV-infected people is twofold to tenfold higher than in healthy populations of comparable age. Recent literature describes an incidence ranging from 0.26% to 7.6%; higher incidence is seen in patients with active opportunistic infections or malignancy, and in patients with the acquired immunodeficiency syndrome. Furthermore, the development of venous thrombosis is found to be associated with the severity of HIV infection, with an incidence twice as high in AIDS patients as in simple HIV infection patients. Hospitalized HIV patients were especially prone to the risk of thromboembolism, as the study conducted by Ahonkai et al concluded; it is the single strongest risk factors for thromboembolism (OR = 13, 95% CI: 6.4 to 27).[34-36]

Another study by Crum-Cianflone in 2008 also stated that, PLWHA tends to have a high risk for thrombosis and it is associated with a lower CD4+ levels. The Crum-Cianflone study showed that PLWHA with thrombosis compared to those without had significantly lower current CD4 (153 vs. 520 cells/mm3, $p<0.001$) and nadir (76 vs. 276 cells/mm3, $p<0.001$)

CD4 counts, higher viral loads (3.6 vs. 1.7 log10 copies/ml, p=0.003), and more likely to have a diagnosis of AIDS (76% vs. 32%, p<0.001).[9]

A considerable number of studies in HIV-infected patients described various haemostatic changes that are associated with the risk of developing venous thrombosis. Procoagulant factors, such as endothelial Tissue Factor (TF) expression and thrombogenic properties of microparticles, were upregulated, whereas anticoagulant factors, including Antithrombin (AT), Heparin Cofactor (HC) II and the protein C pathway, were downregulated. In addition, fibrinolytic proteins were present in elevated concentrations and endothelial soluble Thrombomodulin (sTM) production was increased. Taken together, these changes represented a general hypercoagulable state in HIV-infected patients and this state could be responsible for the increased risk of venous thrombosis (figure 4).[37]

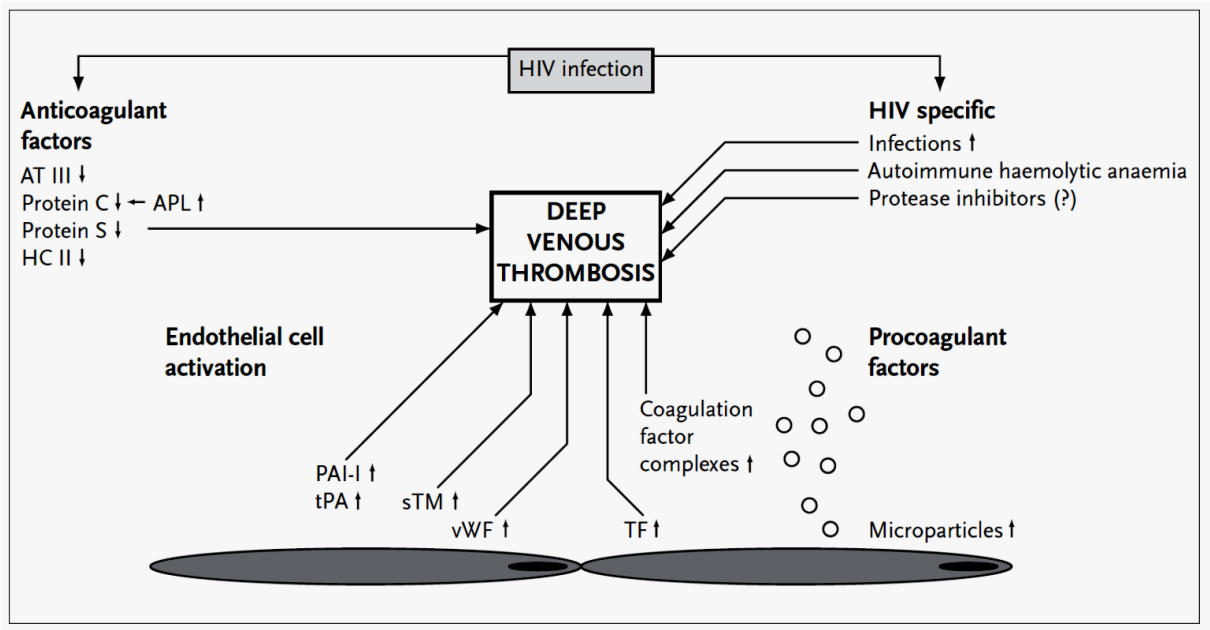


Figure 3. A Diagram summarizing the hypercoagulable state in HIV-infected patients

In a recent study of 109 HIV positive patients by Lijfering, it is shown that after HIV infection was diagnosed, 16% of the patients experienced symptomatic thrombosis (venous, 10%; arterial, 6%). Repeated measurements established protein C deficiency in 9% of the patients, increased factor VIII concentrations in 41%, high fibrinogen concentrations in 22%, and free protein S deficiency in 60%. Median factor VIII concentrations were higher in patients with AIDS (CD4 cell counts <2 x 108/L) than in patients with a non–AIDS-defining illness (2260 IU/L vs 1 490 IU/L; P<0.001), whereas median free protein S concentrations were lower (450 IU/L vs 580 IU/L; P< 0.001). Developing AIDS was associated with increasing factor VIII concentrations and decreasing free protein S concentrations. Increasing factor VIII concentrations were correlated with increasing fibrinogen concentrations and decreasing free protein S concentrations.[35]

As noted above, hospitalization was the single most important risk factors for thromboembolism in PLWHA with an odd ratio as high as 13. Several factors collaborated to

increased thromboembolic tendencies in our patient, from chronic inflammation, infection, and immobilization and also suspicion of procoagulant state (with decreased APTT). The procoagulant state in this patient was also found in most of hospitalized PLHWA, so that a comprehensive plan for thromboprophylaxis and its impact must be instituted and evaluated promptly.

Highly active antiretroviral therapy (HAART) was also highly associated with the development of cardiovascular disease in PLWHA, especially in this case acute coronary syndromes, there are several mechanisms in which HAART could cause an increased risk of CVD among PLWHA, such as:

- **HAART-associated lipodystrophy and metabolic syndrome** HAART regimens, especially those including protease inhibitors (PI) have shown to cause, in a high proportion of HIV-infected patients, somatic (lipodystrophy /lipoatrophy) and metabolic (dyslipidemia,insulinresistance) changes that in the general population are associated with an increased risk of cardiovascular disease. HIV-associated lipodystrophy or lipoatrophy, unreported prior to introduction of HAART, was first described in 1998. It is characterized by the presence of a dorsocervical fat pad (also known as *buffalo hump)*, increased abdominal girth and breast size, lipoatrophy of subcutaneous fat of the face, buttocks and limbs, and prominence of veins on the limbs. The severity of these metabolic abnormalities increases with growing severity of lipodystrophy, and are associated with a raised risk of cardiovascular events: approximately 1.4 cardiac events per 1000 years of therapy according to the Framingham score [3, 5, 13, 36, 38].
- **HAART-associated endothelial dysfunction.** *In vitro* data reported by Fiala et al. suggest that some HAART regimens, such as those including zidovudine, some non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz) and PI disrupt endothelial cell junctions and cytoskeleton action of the endothelial cells leading to endothelial dysfunction.[6, 10, 21]
- **HAART-associated coagulation disorders.** HIV-infected patients receiving HAART, especially those with fat redistribution and insulin resistance, might develop coagulation abnormalities, including increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, or deficiency of protein S.[4, 9, 39]
- **HAART-associated systemic arterial hypertension.** Prevalence of arterial hypertension in HIV disease has been approximated to be around 74% among patients who undergo HAART. HIV-associated endothelial dysfunction and injury, autoimmune reaction to viral infection (vasculitis), and renal disease have been hypothesized to play a role in the pathogenesis of HIV-associated hypertension.[23, 31-33]
- **HAART-associated coronary artery disease.** HIV-infected patients receiving HAART with preexisting additional risk factors (e.g. hypertension, diabetes or

increased plasma homocysteine levels) might be at raised risk of developing coronary artery disease because of accelerated atherosclerosis. Longer exposure to HAART and/or PI seems to increase the risk of myocardial infarction. Results of the Data Collection on Adverse Events of Anti-HIV Drugs study showed that HAART therapy is associated with a 26% relative risk increase in the rate of myocardial infarction per year of HAART exposure.[40]

Cardiovascular risk reduction in PLWHA

As we can see from the previous discussion about increased atherogenic states in PLWHA, it is prudent for us to be able to conceive a systematic plan to reduce the burden of it. The first step in managing the cardiovascular risk of PLWHA, with or without HAART, is to determine the cardiovascular risk and examining the lipid profile. The patient's level of cardiovascular risk determines the target lipid levels and the aggressiveness of lipid-lowering therapy (table 1). High-risk patients include those with established CHD or those considered a coronary risk ''equivalent''; the latter category includes patients with cerebrovascular disease, peripheral vascular disease, diabetes mellitus, or multiple risk factors that predict a 10-year risk of cardiac death or MI of 20%.[5, 13, 17]

Table 1. Lipid Goals and Cutoffs for Therapy in IDSA/AACTG Guidelines[13, 41]

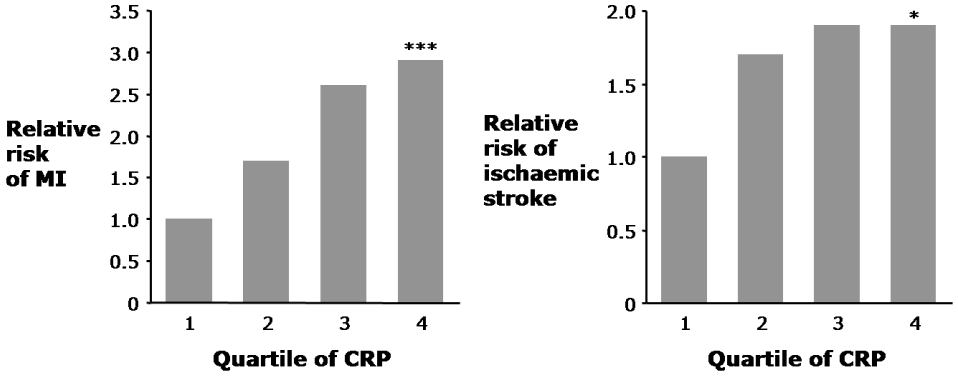
Risk Category	LDL-C Goal	LDL-C to Initiate Therapeutic Lifestyle Change	LDL-C to Consider Drug Therapy	Non–HDL-C Goal
CHD or risk equivalent	<100	≥100	≥130*	<130
≥2 risk factors and	<130	≥130		<160
10-year risk 10%–20%			≥130	
10-year risk <10%			≥160	
0–1 risk factor	<160	≥160	≥190†	<190

*LDL-C of 100 to 129 mg/dL, drug therapy optional, consider treating HDL-C and triglycerides disorders. This recommendation is likely to change based on new data.
†LDL-C of 160 to 189 mg/dL, drug therapy optional.

Important to be noted for physicians treating dyslipidemia and intending to prevent atherosclerosis in PLWHA, this population is under various novel risk factors that have profound impact but yet to be validated. People living with HIV-AIDS, as has been noted above, are living under chronic inflammatory states with elevated levels of pro-inflammatory cytokines that disrupts the equilibrium within endothels and increase the risks for MI. This inflammatory state, as represented by elevated levels of C-Reactive Proteins (CRP, figure 5), heightens the atherosclerosis process and has been recently proven by the JUPITER study that statin therapy in this group of patients improve survival and prevent acute coronary syndromes. Thus, one should always consider this point, when evaluating and treating dyslipidemia in PLWHA. We should, probably instituted a statin therapy for patients with elevated CRP, with or without atherogenic dyslipidemia in PLWHA, but this

approach still yet to be validated and subject to complicated administration in the HAART group with frequent and numerous drug interactions. [5, 13, 14, 20, 42]

After identifying high-risk patients, the remaining patients are categorized by counting the presence of risk factors that modify lipid-lowering therapy. These risk factors include smoking cigarettes, hypertension (blood pressure ≥140/90 mm Hg or treatment with an anti-hypertensive medication), low HDL-C (<40 mg/dL), a family history of premature CHD (in a male first-degree relative <55 years old or a female first-degree relative <65 years old), and increased age (man ≥45 years old or woman ≥55 years old). Evaluation of dyslipidemia begins with obtaining a lipid panel after a minimum of 8 hours, and preferably 12 hours, of fasting. The screening lipid panel should include measurement of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides levels, from which low-density lipoprotein cholesterol (LDL-C) and non–HDL-C levels should be calculated.[12, 13, 17, 20, 41]



CRP=C-reactive protein; MI=myocardial infarction
*p=0.02 versus quartile 1; ***p<0.001 versus quartile 1

Figure 5. Elevated levels of CRP was associated with increased risks of MI.[14]

After 10-year coronary risk has been estimated, lipid targets should be determined (Table 1). Except for patients with triglycerides >500 mg/dL, in whom the primary goal of therapy is to reduce triglycerides levels and prevent pancreatitis, the primary target is reduction of LDL-C (see Fig. 6). When patients have triglycerides >200 mg/dL, the cholesterol content of triglyceride-rich lipoproteins is increased and the estimated LDL-C underestimates the number of atherogenic particles. Non–HDL-C (calculated as total cholesterol minus HDL-C) becomes a secondary target of therapy. Non–HDL-C contains all the cholesterol that is carried by the lipoproteins that are currently considered to be atherogenic, independently predicts CHD risk, and makes management of triglycerides and mixed lipid disorders less confusing. It also has the advantage of being measurable under non-fasting conditions. The non–HDL-C goal is simply the LDL-C goal plus 30 mg/dL, representing the usual cholesterol concentration carried in VLDLs. [12, 13, 17, 20, 41]

Although there are limited data in the HIV-infected population, the therapeutic lifestyle changes recommended in the NCEP guidelines should be initiated for patients at risk of CHD.

Based upon data generated in the HIV seronegative population, lifestyle changes have been recommended for HIV-infected persons at high risk of CHD. These include regular monitoring of cholesterol and other lipid factors, cessation of smoking, appropriate management of hypertension and diabetes, and diet and exercise to improve lipid levels. In one small randomized trial of HIV-infected patients involving dietary counseling, diet alone resulted in a reduction in TC by 0.34 mmol/L after 24 weeks with no change in LDL-C, TG, or HDL-C. [12, 13, 17, 20, 41]

When pharmacologic therapy is needed, initial choices are based on the predominant lipid abnormality. For patients with hypertriglyceridemia (≥500 mg/dL), a fibrate such as gemfibrozil or fenofibrate is preferred, with prescription niacin or fish oil capsules as an alternative. For patients with triglycerides <500 mg/dL, LDL-C is the primary target. If LDL-C is greater than the target level (or non–HDL-C when triglycerides are between 200 and 500 mg/dL), a statin is the first choice, with fibrates or prescription niacin as alternatives in patients with mixed disorders. The preferred statins in the IDSA/AACTG guidelines are pravastatin, atorvastatin, and fluvastatin because they have been prospectively studied in this population of patients without reports of significant toxicity. Unfortunately, the lipid-lowering effects of statins in patients receiving PIs have not frequently led to achievement of target goals. [12, 13, 17, 20, 41]

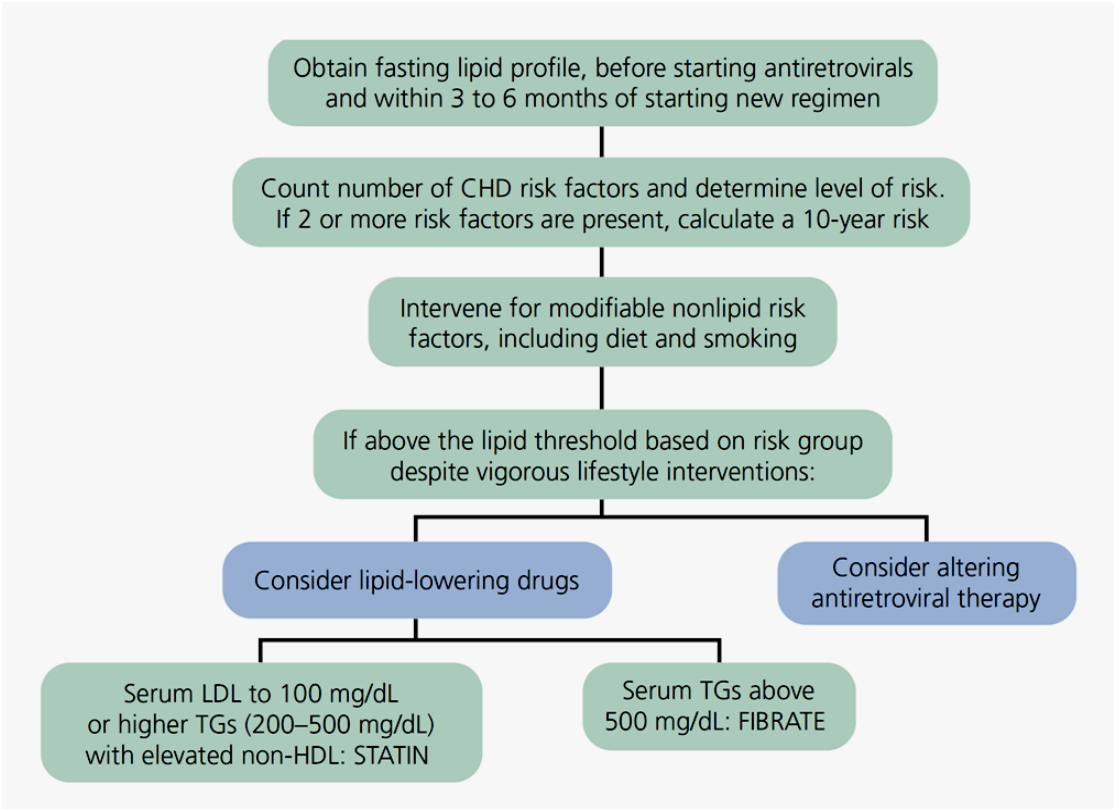


Figure 6. Summary of Infectious Disease Society of America and Adult AIDS Clinical Trials Group guidelines for evaluation and management of dyslipidemia. BP indicates blood pressure; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.[20, 41, 43, 44]

Pravastatin and fluvastatin have the least potential for drug interaction but are relatively less potent lipid-lowering agents. Pravastatin levels have been shown to decrease in combination with saquinavir/ritonavir, but more potent statins such as atorvastatin and simvastatin have been associated with significantly increased serum levels. Simvastatin and lovastatin should not be used in patients taking PIs; however, atorvastatin and the combination of pravastatin and fenofibrate can be used cautiously in patients on PIs. Studies investigating the safety and efficacy of rosuvastatin are expected within the next few years. [12, 13, 17, 20, 41]

It is important to note that many PIs interact with the cytochrome P450 system and may affect the potential toxicities of other medications. Statins and fibrates may cause changes in hepatic transaminase levels. Routine laboratory monitoring, including baseline hepatic transaminase levels and repeat assessment after 4 to 6 weeks, followed by per-product labeling, should be instituted for all patients receiving lipid-lowering therapy so that lipid levels and toxicity can be monitored. Routine testing of muscle enzymes is not recommended. [12, 13, 17, 20, 41]

Second-line agents include ezetimibe for patients with increased LDL-C levels; however, studies in patients with HIV infection have not been reported. Similarly, fish oils are useful in patients with hypertriglyceridemia but have not yet been studied in detail in HIV-infected patients. Prescription niacin is useful as a second-line therapy for all dyslipidemias and is currently under study by the AACTG. Niacin and ezetimibe also require monitoring of hepatic transaminases. Niacin may cause hyperglycemia and hyperuremia. Combination therapy with a statin is needed in many patients. When fibrates and statins are used together, hepatotoxicity and muscle toxicity may be observed. When statins are combined with a fibrate, fenofibrate is preferred because it has been studied in patients with PI-associated dyslipidemia and it interferes less with statin metabolism. [12, 13, 17, 20, 41]

Dyslipidemia in HIV-infected persons is a complex problem that often requires multiple interventions. Viral suppression is the first goal of treatment, and this suppression, along with regeneration of CD4+ cells, must be maintained. Quality of life is an important consideration that influences the choice of ART; factors that should be considered include pill burden, convenience of the regimen, and adverse effects of treatment. Last, complications of ART, like metabolic disturbances, motivate initial and subsequent choices of ARVs. [12, 13, 17, 20, 41]

Individuals with adequate viral suppression and dyslipidemia or other metabolic disturbances often consider switching to a regimen that is less likely to induce these effects. The strategic approach to switching ARVs relies upon the tolerability and potency of a new regimen, absence of underlying archived resistance to the new ARVs, and the likelihood of improvement in the metabolic derangements. Switching to a triple NRTI or NNRTI-based regimen has been shown to improve lipid profiles in patients who have developed dyslipidemia while on PI-based regimens. The likelihood of virologic failure has ranged from

10%–15% in most published trials of switch studies. This annual rate of failure is probably too high to consider this approach completely successful, because the morbidity and mortality from inadequately treated AIDS is substantial. [12, 13, 17, 20, 41]

The greatest improvements in lipids have been observed when patients switch from a PI-based regimen to abacavir (an NRTI), some improvements have been observed in patients switching to nevirapine (an NNRTI), and few changes in lipid levels have been observed in patients switching to efavirenz (an NNRTI). In persons at higher risk for CHD, particularly those with ART-associated dyslipidemia and/or insulin resistance, one of the first considerations should be a switch to a less atherogenic ART regimen. Clinicians must consider the history of ARV use, the resistance profile of HIV, and other quality-of-life issues in determining the benefits of switching therapy. [12, 13, 17, 20, 41]

Table 2. Influence of antiretroviral drugs on the cardiovascular system[45]

	Atherosclerosis	Hyperlipidemia	Glucose intolerance/ diabetes mellitus	Arterial hypertension
PI	PI > than NNRTI or NRTI	↑↑ Triglycerides ↑ LDL ↓ HDL	↓ Glucose metabolism ↑ Insulin levels ↑ Insulin resistance ↓ Glucose metabolism	↑Blood pressure
NNRT		↑ Triglycerides ↑ LDL may increase HDL level (nevirapine)		
NRTI		↑ Triglycerides (stavudine)		

Although no study has compared the strategy of switching therapy for dyslipidemia versus treatment with lipid-lowering agents, it seems generally preferable to switch therapy if possible to avoid adding to the burden of pills ingested daily, the added costs of additional therapy, and the potential for adverse drug–drug interactions. If patients can use NNRTI-based regimens, this is certainly indicated. Patients who require a PI-based regimen may want to use atazanavir preferentially because of its lesser effects on lipid or glucose metabolism. Studies comparing a switch to an NNRTI regimen versus atazanavir would be helpful. Switching from a PI-based regimen to a triple NRTI regimen or one containing abacavir is limited by higher rates of virologic failure. [12, 13, 17, 20, 41]

Insulin resistance in PLWHA also occurs and contributes to the metabolic syndrome affecting the PLWHA population. This resistance if neglected will develop to over type 2 diabetes mellitus, thus we need to asses and treat this condition promptly. The main culprit of glucose intolerance in PLWHA was PIs, but recent study also suggested that HIV itself plays a great deal of damage to the beta cell of pancreas. The diabetes and insulin resistance that occur during antiretroviral therapy appear to have a clinical appearance similar to the common form of type 2 diabetes in the general population. Thus, treatments that are appropriate for established type 2 diabetes and persons at risk for type 2 diabetes are also reasonable for patients infected with HIV with these disorders.[7]

Prudent to the hospitalized HIV-AIDS patients is the assessment of thromboembolic complications, as has been discussed earlier it was the main mortality and morbidity cause in this group of patients. Patients with HIV-AIDS, especially the critically ill ones, were exposed to numerous causative factors of thromboembolism whether venous or arterial, however little has been reviewed about this complication.

The assessment of thromboembolism should be an integrated part of every hospitalized PLWHA assessment, though some issues persist, such as there is no specialized assessment for this population, no proven assessment on arterial thrombosis risk factors, and also the multitude and complex interaction within the pathogenesis of thromboembolism in HIV-AIDS. There are several risk factors for VTE involved in patients with HIV-AIDS, known as the Virchow's triad (circulatory stasis, endothelial injury and hypercoagulable state), such as immobility, malignancy, infection, respiratory failure, smoking and inherited/acquired thrombophilia, many of which occurred simultaneously in the hospitalized PLWHA (table 3).[46, 47]

Table 3. Risks factors for VTE

Surgery	Infection
Trauma	Heart failure
Immobility, paresis	Respiratory failure
Malignancy	Inflammatory bowel disease
Cancer therapy (hormonal chemotherapy or radiotherapy)	Nephrotic syndrome
Previous VTE	Myeloproliferative disorders
Increased age (especially > 75 yr)	Obesity
Pregnancy and postpartum status	Smoking
Estrogen-containing oral contraception, or HRT or SERM therapy	Varicose veins
	Central venous catheterization
	Inherited/acquired thrombophilia
	Travel

VTE = venous thromboembolism; HRT = hormone replacement therapy; SERM = selective estrogen receptor modulator

Two general approaches are used to stratify the risk of thromboembolism in hospitalized patients (and thereby to help select a prophylaxis option). The first approach uses one of a number of scoring systems that consider the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Thromboprophylaxis is then individually prescribed based on the composite risk estimate. Formal risk assessment models (RAMs) for DVT have been proposed to assist with this process. Although we can support the concept of individualized patient risk assessment, this approach has not been adequately validated, is cumbersome to use, and there is little formal understanding of how the various risk factors interact in a quantitative manner to decide where a particular patient lies along the continuous spectrum of thromboembolic risk. Finally, individual RAMs may not be worth the effort because there are only a small number of thromboprophylaxis options to choose from and one of the principles of effective prevention strategies is to reduce complexity in decision making.[9, 35, 47]

The second approach involves routine implementation of standardized thromboprophylaxis to all patients in a large group, for example, major orthopedic surgery or major general surgery, unless a particular patient has a contraindication to the standard option. We support this approach for most patients for several reasons. Although a number of patient-specific factors contribute to the variability in VTE rates, the principal factor is the patient's primary reason for hospitalization, whether because of a surgical procedure or an acute medical illness.

Furthermore, we are not able to confidently identify the relatively small proportion of patients within each target group that may not require thromboprophylaxis. Individualized risk assessment has not been subjected to rigorous clinical evaluation, while group risk assignment is the basis for most thromboprophylaxis intervention trials and clinical practice guidelines. Finally, the complexity of individualized risk assessment may reduce compliance unless an intensive and sustained, systematic implementation strategy is in place (table 4).[46, 47]

As we can see from the previous discussions about the pathophysiology, epidemiology and risks of thromboembolism in PLWHA, it is essential that every hospitalized patients to be given thromboprophylaxis. However, the evidence supporting this claim was still not available yet; further study about this issue is warranted. For the mean time there are several pharmacologic options for the prevention of thromboembolism that could be used; such as:

- **Unfractionated heparin (UFH)** inhibits factor Xa and factor IIa equally. Because it is a large heterogeneous molecule, UFH is not well absorbed in subcutaneous tissue. Its anticoagulant response is variable because of its short half-life. It must be dosed two or three times daily subcutaneously for thromboembolism prophylaxis, and must be given intravenously for treatment of thromboembolism.

- **Low-molecular-weight heparins (LMWHs)** preferentially inhibit factor Xa compared to factor IIa. The LMWHs (ie, enoxaparin [Lovenox], dalteparin [Frag-min]) are derived from UFH through a chemical depolymerization and defractionation process that results in a much smaller molecule. LMWHs are well absorbed from subcutaneous tissue and have a predictable dose response attributable to their longer half-life (relative to UFH), which allows for once-daily or twice-daily subcutaneous dosing.
- **Fondaparinux** (Arixtra) is a synthetic pentasaccharide that acts as a pure inhibitor of factor Xa. It binds antithrombin III, causing a conformational change by which it inhibits factor Xa and thereby inhibits coagulation further downstream. Fondaparinux has a long half-life (18 to 19 hours), which enables once-daily subcutaneous dosing but which also may require administration of the costly activated factor VII (NovoSeven) to reverse its effects in cases of bleeding.

Tabel 4. Risk stratification and thromboprophylaxis options in the hospitalized patients.

Patient groups	Recommended thromboprophylaxis options*	Optimal duration of prophylaxis
Low VTE Risk: ▪ Medical – fully mobile, brief admission, no additional risk factors ▪ Surgical – procedure < 30 minutes, patient mobile, no additional risk factors	▪ No prophylaxis ▪ Early and frequent ambulation	Not applicable.
Moderate VTE Risk: ▪ Acute medical illness ▪ Major general surgery ▪ Major gynecologic surgery ▪ Major urologic surgery ▪ Thoracic surgery ▪ Bariatric surgery	▪ Low-molecular-weight heparin ▪ Low-dose heparin ▪ Fondaparinux ▪ Combinations of a mechanical method and an anticoagulant	Continue until discharge for the majority of patients. Selected patients may benefit from post-discharge prophylaxis.
High VTE Risk: ▪ Hip or knee arthroplasty ▪ Hip fracture surgery	▪ Low-molecular-weight heparin ▪ Fondaparinux ▪ Rivaroxaban or dabigatran ▪ Warfarin (target INR 2-3)	Minimum of 10 days and up to 35 days.
High VTE Risk: ▪ Major trauma, (including spinal cord injury)	▪ Low-molecular-weight heparin ▪ Combinations of a mechanical method and an anticoagulant	Continue until discharge for the majority of patients. Prophylaxis should be continued for the inpatient rehabilitation period.
High bleeding risk	▪ Mechanical method of prophylaxis (GCS, PCD, VFP) ▪ Consider anticoagulant prophylaxis when bleeding risk decreases	Duration appropriate for the specific patient risk group.

*The recommended options may differ somewhat for specific patient groups based on available evidence. See the 8th ACCP Guidelines on the Prevention of VTE.[1]
GCS indicates graduated compression stocking; PCD, pneumatic compression device, VFP, venous foot pump.

Conclusion

The incidence of cardiovascular disease increased profoundly in PLWHA, mainly because of improved life expectancy and quality by the institution of HAART. However, this still remain an underdiagnosed issue and challenge still at large at providing an adequate and comprehensive risk factors management. Pathophysiological, clinical and therapeutic factors interacts one another and cause increased cardiovascular disease risk in this population.

Chronic inflammation especially poses a challenging yet promisingly manageable risk for cardiovascular event, such presented by the JUPITER trial. Treatment of chronic inflammation by means of statins provides an opportunity to treat chronic inflammation and reduces cardiovascular risks. Dyslipidemia, another important causative factor for cardiovascular event must be managed accordingly in line with the recommendation from NCEP-ATP III and adjusted with specific recommendation from IDSA.

Pertinent to the hospitalized PLWHA, thrombosis was an important cause of cardiovascular event. Its management was critical in terms of reducing morbidity and mortality for the hospitalized PLWHA. Risk assessment and prophylactic management of thrombosis using anticoagulant are important efforts to be implemented comprehensively. Further researches are needed to confirm this recommendation.

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