HIV-ASSOCIATED METABOLIC ABNORMALITIES:
Prevalence, Pathogenesis, Cardiovascular Risk and Management

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Biosketch

Dr. Bedimo is Chief, Infectious Disease Section at the VA North Texas Health Care System, Dallas, Texas and Director of the ID Fellowship Training Program at UT Southwestern Medical Center.
His research interests include:

1. Analysis of the trends of Non-AIDS-defining malignancies among HIV-infected patients comparing incidences pre- and post-Highly Active Antiretroviral Therapy (HAART), and analysis of factors associated with increased risk
2. Clinical studies of the prevention and management of dyslipidemia, lipodystrophy and bone mineral loss among HIV-infected patients.
3. Laboratory-based studies of the mechanisms of dyslipidemia among HIV and HIV/HCV co-infected patients.
4. Novel therapies for patients with drug resistant HIV

I. The Changing Face of HIV Disease

a. Increased survival of HIV-infected Patients

What is the prognosis of HIV disease in 2006?

Two developments in the past two decades have lead to a dramatic improvement in the survival of HIV-infected patients. The first of these is the widespread use of prophylactic and curative therapy for opportunistic infections [1], resulting in an up to 6-fold decline in the incidence of the three major opportunistic infections (*Pneumocystis jeroveci* pneumonia, *Mycobacterium avium* complex disease, and *Cytomegalovirus* retinitis) from 1994 to 1997 [2]. What has however arguably made the greatest impact on the survival of HIV-infected patients is the discovery and widespread use of protease inhibitors (PI) in the context of combination antiretroviral therapy – labeled Highly Active Antiretroviral Therapy (HAART) [2]. HAART essentially transformed HIV disease from an almost inevitably fatal disease to a chronic condition that is manageable for many people in the developed world. During the second half of the 1990's decade, mortality of HIV-infected patients in the U.S. and Europe dropped to less than 1/3 of the rate of the previous half-decade [2, 3]. A recent analysis of two HIV cohorts in France revealed that HIV-infected patients who experience a good virologic and immunologic response to HAART, maintaining a CD4 count of 500 or above had mortality rates identical to those of uninfected age-matched controls [4]

b. Trends in causes of death among persons with HIV/AIDS in the era of highly active antiretroviral therapy

What are the prevalent causes of morbidity and mortality among HIV infected patients today?

The increase in overall survival of HIV-infected patients has been associated with a shift in underlying cause of death among these patients, with lesser representation of "AIDS-related causes" and greater representation of "non-AIDS-related" deaths. Between 1999 and 2004, the proportion of deaths due to non–AIDS-related causes increased by 33% in New York [5]. Similar trends have been observed across North America and Europe [6-8]. Among the "non-AIDS-related" causes, those most commonly reported are chronic liver disease – resulting from hepatitis C co-infection, alcohol and drug dependence – metabolic complications including cardiovascular disease, and non–AIDS-defining malignancies cancer [5-8].

II. HIV-Associated Lipodystrophy Syndrome

What is the HIV-Associated "Lipodystrophy Syndrome"?

Appearance in HIV patients of features reminiscent of rare congenital and acquired lipodystrophy syndromes – including wasting of subcutaneous fat in the face and limbs – in patients on HAART led to the coining of the term HIV-associated 'lipodystrophy syndrome' in two reports, published in the late 1990's. Among these patients, body fat redistribution was associated with dyslipidemias and insulin resistance in variable proportions [9-11]. Since then, several other metabolic complications have been observed to be associated with HIV disease. These include mitochondrial toxicity (presenting as anemia, myopathy, pancreatitis, neuropathy, hepatic steatosis and lactic acidosis), and bone density abnormalities (osteoporosis and osteonecrosis) [12]

Estimates on the prevalence of the lipodystrophy syndrome vary widely due to poorly standardized definition and assessment tools [12]. The prevalence of individual components of the syndrome are estimated to be about 50% for the body fat redistribution, 70% for dyslipidemia and 8 to 10% for diabetes [11]. In this review we'll focus on the triad of dyslipidemias, insulin resistance and body fat redistribution, their risk factors, pathogenesis and potential impact on the cardiovascular morbidity of HIV infected patients [13-16].

III. Body Fat Redistribution Syndrome

What are the morphologic phenotypes of the lipodystrophy syndrome?

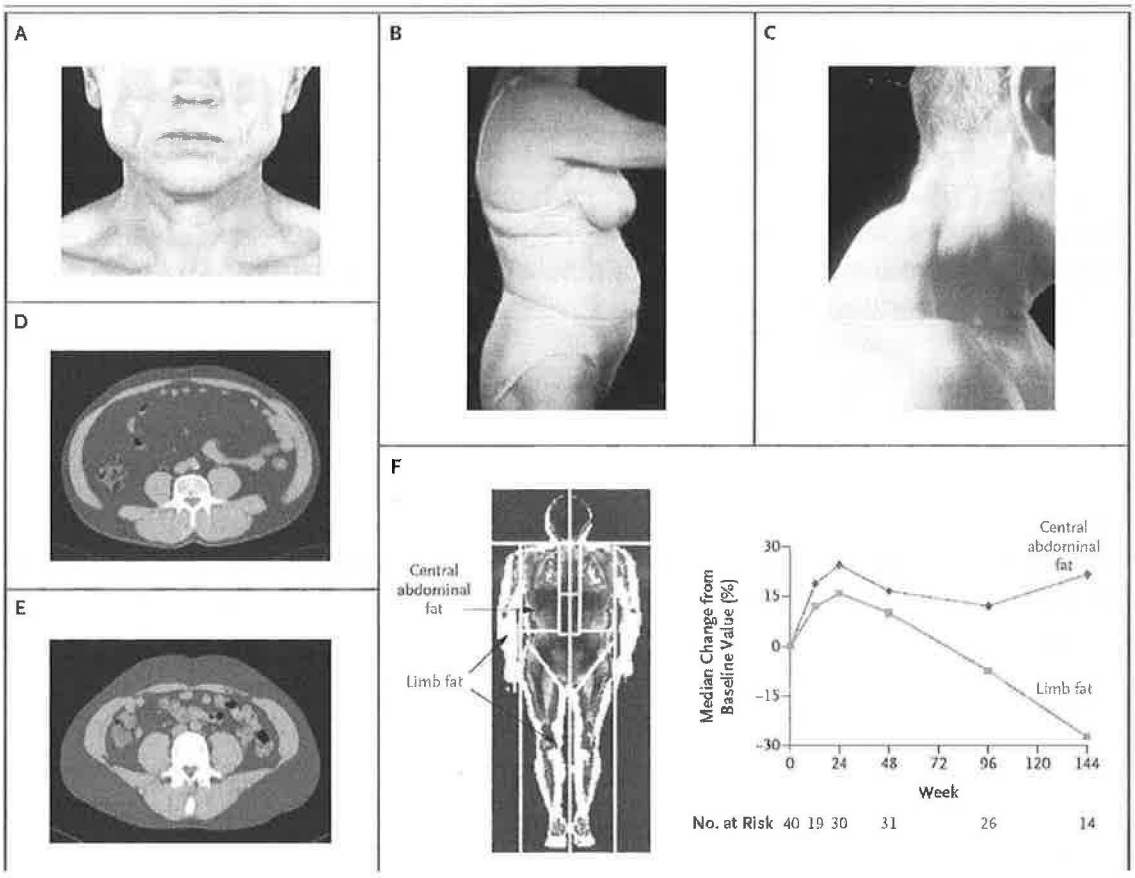
Morphologic changes have been described by several other groups in HIV-infected patients, predominantly (but not exclusively) associated with the use of PIs and nucleoside reverse transcriptase inhibitors (NRTI) [17]. Although initially attributed solely to antiretroviral toxicity, other factors (including viral, immunologic and host genetic factors) were later found to be associated with fat redistribution.

Fat redistribution was also later divided into two syndromes that did not necessarily co-exist in the same patient, and with probably different pathogenic mechanisms [18-21]. Lipoatrophy involves the loss of subcutaneous fat in the face, arms, legs, abdomen, and/or buttocks. In contrast to the traditional wasting syndrome of advancing HIV disease, lipoatrophy is distinguished by the preferential loss of fat tissue without substantial loss of lean tissue mass, and by the fact that it most frequently occurs among patients who are responding to HIV therapy [19, 22].

Accumulating data demonstrate that exposure to NRTIs – mainly thymidine NRTIs – is the major factor associated with lipoatrophy [22-24] although concomitant use of PIs seems to play a role as well. It's pathophysiology is thought to be mitochondrial toxicity due to NRTI-induced inhibition of mitochondrial DNA polymerase γ [25, 26], but recent studies by Mallon et al showed that NRTIs might also lead to lipoatrophy by decreased transcription of mitochondrial RNA without significant depletion of mitochondrial DNA [27].

Increased age and decreased CD4 cell count at initiation of HIV therapy have been associated with self-reported lipoatrophy [23, 24]. More objective measurement of lipoatrophy, using dual energy X-ray absorptiometry (DEXA) scanning however casts doubt over these associations [20, 21]

Lipohypertrophy is defined as the accumulation of adipose tissue within the abdomen, dorsocervical fat pad ("buffalo hump"), anterior neck, and breasts. It has also been reported since the advent of HAART. Unlike lipoatrophy, fat accumulation has been shown to have a strong association with use of PIs [28, 29] Cohort studies have also shown an association with increased age, higher baseline fat content, greater body mass index, white race, and low CD4 cell count at initiation of antiretroviral therapy [28, 29]



From Grinspoon and Carr, N Engl J Med. 2005 Jan 6;352(1):48-62

IV. Lipid abnormalities, Insulin Resistance and Cardiovascular Risk in HIV

a. Metabolic Phenotype of HIV-Infected Patients

What alterations of the lipid profiles and glycemia are observed in HIV-infected patients with or without HAART?

i. Hypercholesterolemia and Hypertriglyceridemia

Advanced HIV disease in the absence of combination antiretroviral therapy has been associated with hypertriglyceridemia, low levels of total cholesterol (TC), low levels of low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) [13, 30]. However, the most profound lipid changes observed in HIV patients are associated with the use of PIs, which induce profound alterations in the lipid metabolism. Dyslipidemia associated with PI-containing HAART therapy is characterized by increased levels of LDL, TG and triglyceride-rich lipoproteins [31, 32]. These alterations appear to be less marked with the use of newer PIs. However, most of them, with the possible exception of atazanavir, are associated with an elevation in levels of TC, triglycerides, and LDL-C [28]. Nonnucleoside reverse-transcriptase inhibitors (NNRTIs) also produce dyslipidemias mostly characterized by high levels of TC, LDL-C and TG.

Apart from LDL-C, other lipid parameters have been found to be associated with increased risk of cardiovascular events. These include decreased plasma HDL-cholesterol, increased plasma triglyceride, non-HDL-cholesterol, Apo-B lipoprotein concentration ([33, 34]

ii. Decreased HDL Levels

HIV-infected patients tend to have lower levels of HDL – the pathophysiologic mechanism of these changes is still incompletely elucidated [35]. Negative correlations were found among HDL-C level, peak and current viral load, and duration of the disease and the treatment [32]. There are discordant data in the literature regarding the direction and magnitude of change on HDL induced by protease inhibitor therapy [32, 35, 36]. NNRTI therapy leads to significant increases in HDL-C, greater for nevirapine than with efavirenz. They also lead to a relatively smaller increase in LDL-C, [37].

iii. Atherogenic Lipoprotein Particle Size Distribution

A recent study showed that the HDL subpopulation profile changed unfavorably after PI-based HAART, with increased concentrations of the small, lipid-poor pre-beta-1 HDL, and decreased concentration of the large, cholesterol-rich alpha-1 HDL [35]. With higher TG and LDL, lower HDL concentrations and smaller denser particle sizes, HAART-treated HIV patients therefore tend to adopt the so-called Pattern B lipoprotein phenotype known to be associated with the metabolic syndrome and to predispose to cardiovascular morbidity [38]. Furthermore, higher levels of ApoC-III – a major constituent of triglyceride-rich lipoproteins (chylomicrons and very low density lipoproteins (VLDLs) – have been found to be associated with increased risk hypertriglyceridemia and cardiovascular events [39]. Levels of apo C-III have been found to be significantly elevated in HIV-

infected patients treated with PIs, suggesting that they might be a marker of cardiovascular risk in this population as well [40, 41].

iv. Insulin Resistance

Insulin resistance (IR) appears to be common in untreated HIV patients and associated with similar factors as in the general population [42]. PI and NNRTI were associated with worse insulin resistance in men but not women, but NRTI might also play a role [43]. PI used have been shown to be associated with an up to 3-fold higher risk of diabetes mellitus [44]. Studies in healthy subjects show that insulin resistance can be rapidly induced by PI therapy and is not necessarily secondary to changes in fat distribution (i.e. subcutaneous fat wasting or visceral fat accumulation) nor does it depend on HIV infection [45]. This is likely very relevant since a defective biological activity of insulin has been found to be predict cardiovascular disease independently of LDL-cholesterol and other major cardiovascular risk factors [46]

In summary, the metabolic phenotype of HIV-infected patients is well known to be atherogenic and to predispose to cardiovascular morbidity. These intracellular pathogenic mechanisms, together with the inter-individual variability in the prevalence and severity of ART-associated dyslipidemia, suggest an important role for genetic factors in the pathogenesis of this dyslipidemia. Determining the effect of SNPs or groups of SNPs (halotypes) on an individual's response to either drugs or disease may help to limit these adverse drug reactions [41].

b. Pathogenesis of dyslipidemia and insulin resistance in HIV

What are the pathogenic mechanisms of dyslipidemia and insulin resistance in HIV?

Lipodystrophy, dysregulation of fatty acid metabolism and insulin resistance are interrelated in HIV-infected patients. A number of studies have shown that insulin resistance often precedes lipodystrophy, suggesting that insulin resistance may be a primary feature of the metabolic syndrome in this population. Whereas numerous studies have investigated the role of anti-HIV drugs in lipodystrophy and dyslipidemia, the effects of HIV infection on lipid concentrations and lipid metabolism have been poorly studied because of lack of suitable patient cohort studied before and after HIV infection and prior to therapy **[30].**

i. Increased Lipolysis

Lipid kinetic studies have shown increased rates of lipolysis and increased total free fatty acid (FFA) levels in HIV-infected subjects, especially among those with fat redistribution [47-50]. This increases FFA transfer to the liver for

incorporation into lipoprotein triglycerides that are secreted, and to skeletal muscle where they impair normal insulin signaling [48]. Increased lipolysis may therefore also contribute to insulin resistance in HIV patients and the ability of insulin to suppress both endogenous glucose production and lipolysis is markedly suppressed among them [49].

Insulin plays a critical role in coordinating the post-prandial metabolic response, in which carbohydrates are utilized as the primary source of fuel for oxidative reactions while fatty acids are directed into adipose stores and converted to triglyceride. Insulin resistance decreases delipidation of chylomicrons (derived from dietary fat) and VLDL-C (from hepatic processing of fatty acids) at the level of lipoprotein lipase, which is produced and secreted by adipocyte in response to insulin. Indeed a markedly decreased clearance of triglyceride-enriched VLDL and chylomicrons in lipodystrophic HIV patients has also been observed [48].

The interrelations of insulin resistance and dyslipidemia are well-summarized by Nolan et al [15]. Increased lipolysis from adipocytes and increased chylomicron remnants increase hepatic processing to produce VLDL-C.

ii. Altered Lipoprotein Metabolism and Particle Size Distribution

VLDL metabolism normally produces LDL that is then readily cleared by LDL receptors. However, "altered", triglyceride-enriched VLDL is diverted towards the production of IDL from HDL, as well as small, dense LDL that is less effectively cleared via the LDL receptor and is more susceptible to oxidative modification.

Altered lipoporotein metabolism – partly induced by insulin resistance – often results in transfer of cholesterol esters from LDL and HDL particles to VLDL, in exchange for triglycerides. This process leads to a lipoprotein size distribution - smaller and denser LDL [51] and HDL particles and larger VLDL particles [52] – known to be more atherogenic (pattern B) [53, 54]. In these patients, profound derangements of lipoprotein metabolism can exist despite normal mild changes in plasma lipid concentrations [38, 55].

In a cohort of HIV-infected patients at the VA North Texas Health Care System, we recently observed a trend towards reduction in LDL particle sizes in a small group of patients switched from a protease-inhibitor-containing regimen to Atazanavir – a newer protease inhibitor previously shown to result in much less profound rates of dyslipidemia. (Busti et al, 8th ADRL meeting, San Francisco, September 2006)

iii. Defective Activation and Nuclear Translocation of the Transcription Factor Sterol Regulatory Element-Binding Protein 1

PIs impair the intranuclear localization of the sterol regulatory element-binding protein-1 (SREBP-1) and peroxisome proliferator-activated receptor-gamma (PPAR-gamma), and induces insulin resistance [56]. Also, PI treatment inhibits proteasomal degradation of nascent apolipoprotein B, the principal protein component of triglyceride and cholesterol-rich plasma lipoproteins [57].

iv. Direct, Reversible Inhibition of Insulin-Sensitive Glucose Transporter-4

The rate-limiting step in the uptake of glucose is glucose transport, and the predominant glucose transporter (GLUT) in muscle and fat is GLUT-4. Specific protease inhibitors (PIs) have been associated with decreased GLUT-4-mediated glucose transport and insulin resistance both in vitro and in vivo, whereas newer protease inhibitors may have fewer effects on insulin sensitivity [11]. Under euglycemic hyperinsulinemic clamp conditions in lean mice, a dose-dependent reduction in the peripheral glucose disposal rate was observed with all the PIs except atazanavir [58]. These mechanisms probably account for the very rapid induction of insulin resistance by PI therapy [45]. Also, Furthermore PI treatment withdrawal among lipodystrophic HIV-positive patients leads to partial reversal of the increased lipolysis and partial restoration of the glucose metabolism, but these changes occur without significant change in body fat redistribution [49].

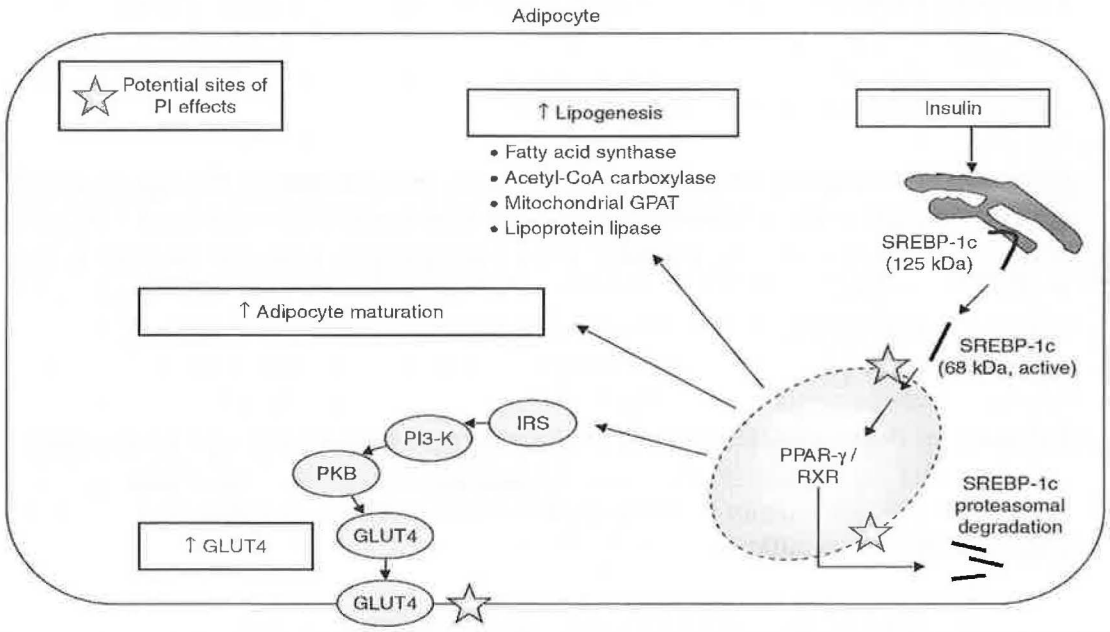


Fig. 4. SREBP-1, PPAR-γ and insulin signalling pathways. SREBP is activated by insulin and acts to promote lipogenesis and adipocyte differentiation via multiple pathways, acting both directly and via intranuclear activation of PPAR-γ/RXR nuclear transcription factors. Potential sites of protease inhibitor (PI) effects on metabolism are indicated. **Acetyl-CoA** = acetyl-coenzyme A; **GLUT4** = insulin-sensitive glucose transporter 4; **GPAT** = glycerol phosphate acyltransferase; **IRS** = insulin receptor substrate; **PI3-K** = phosphatidylinositol 3-kinase; **PKB** = protein kinase B; **PPAR-γ** = peroxisome proliferator activated receptor-γ; **RXR** = retinoid-X receptor; **SREBP** = sterol regulatory element-binding protein.

From Nolan, D. Drugs. 2003;63(23):2555-74

V. The Metabolic Syndrome in HIV

a. Metabolic Syndrome, Lipodystrophy Syndrome and Cardiovascular Risk in HIV

Does the HIV Lipodystrophy Syndrome differ from the Metabolic Syndrome?
Are either of the syndrome Useful in evaluation and prediction of Cardiovascular Morbidity in HIV?

All three criteria for the lipodystrophy syndrome are part of the metabolic syndrome criteria. It's therefore important to assess the prevalence of this syndrome (if it is indeed a separate syndrome) against the extensive background of the metabolic syndrome.
Among participants of the National Health and Nutrition Examination Survey (NHANES), the unadjusted and age-adjusted prevalence of the metabolic syndrome as defined by the ATP-III criteria were 21.8% and 23.7%, respectively [59]. However, since the prevalence of the metabolic syndrome markedly increases with age, more useful estimates would be age-adjusted rates. The prevalence of the metabolic syndrome is <10% in individuals aged 20–29 years, 20% in individuals aged 40–49 years, and 45% in individuals aged 60–69 years. Thus it might be more useful to suggest that the estimated prevalence of the metabolic syndrome is an individual's age minus 20 [59, 60]. As the survival of HIV-infected patients increases – and with it the duration of their exposure to HAART – it's reasonable to expect an increase in metabolic syndrome in this patients population in the next few years.

Although controversy still exist over the very prevalence of the lipodystrophy syndrome [12] and it's potential impact on the cardiovascular morbidity of HIV-infected patients [14, 61], several factors have been well-established about the metabolic syndrome: 1) Statistical "confirmatory factor analysis" have confirmed that the components of the metabolic syndrome are manifestations of a single common factor [62]. 2) The metabolic syndrome has been conclusively shown to predict cardiovascular morbidity and mortality [63]. More and more studies have focused on the evaluation of the metabolic syndrome among HIV-infected patients and its impact on their cardiovascular morbidity and mortality [64, 65]. That said, it's not certain that the metabolic syndrome is more prevalent in HIV than non-HIV populations.

b. Prevalence of the Metabolic Syndrome in HIV

Is the Metabolic Syndrome More Prevalent in HIV than non-HIV Populations?

Recent evidence fails to show a significant increase of the metabolic syndrome among HIV-infected patients compared to that previously reported in uninfected

individuals [65, 66]. A recent evaluation of the prevalence of metabolic syndrome among HIV-infected adults in the Nutrition for Healthy Living (NFHL) study (2000-2003) actually showed that it was significantly lower in both HAART and non-HAART users compared with NHANES participants unadjusted for body mass index [67]. Among HAART users, only Lopinavir/Ritonavir and Stavudine were significantly associated with the onset of metabolic syndrome.

Samaras et al.,[68] evaluated the prevalence of the metabolic syndrome, using both the International Diabetes Federation (IDF) and ATP III criteria in HIV patients with or without the "lipodystrophy syndrome" and found the prevalence of metabolic syndrome – 14% and 18% by the IDF and the ATP III criteria, respectively – to be similar to those seen in the age-matched general population.

Only one study so far suggests an increase in the prevalence of metabolic syndrome in HIV patients after three years of HAART [69]. In that patient group, the metabolic syndrome was present at baseline in 11% and 9% of patients with the IDF and ATP III criteria respectively. During follow-up, progression to metabolic syndrome among participants who didn't have it at baseline was 32% (ATP-III) and 22% (IDF). The presence of MS at baseline was associated with an increased risk of CVD (ATP-III: RR=2.58; P=0.051 and IDF: RR=2.97; P=0.026). Incident MS during follow-up (ATP-III and IDF) was not significantly associated with an increased risk of CVD-related events.

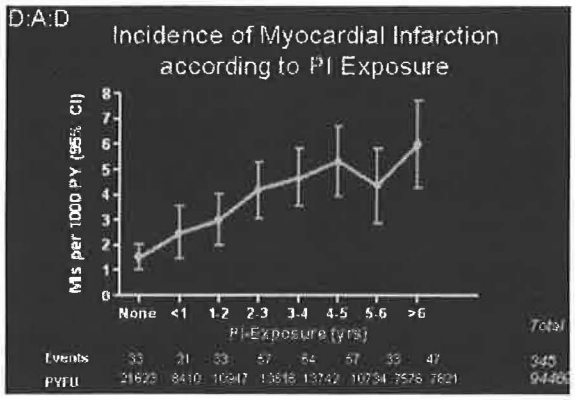
The only conclusion one can draw from the available body of literature is that the presence of MS at HAART initiation identifies individuals in whom preventive strategies should be considered.

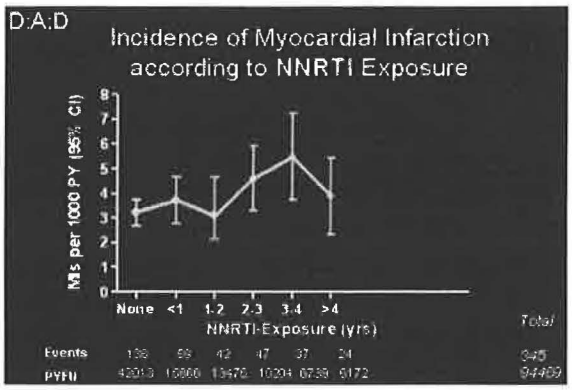
VI. Cardiovascular Disease in HIV

a. Epidemiology of Cardiovascular Disease in HIV

How prevalent is cardiovascular disease in HIV?

The high prevalence of metabolic complications in HIV has logically led to an evaluation of the potential cardiovascular morbidity and mortality among HIV-infected patients. The early epidemiological studies revealed rather conflicting data [14, 61]. Several other studies have been published since then, indicating a small but significant increase in cardiovascular morbidity proportional to the duration of antiretroviral therapy [70-72]. In the most recent analysis of the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) Study, a prospective observational study on a cohort of 23 468 patients with HIV infection, the incidence of myocardial infarction (MI) increased by 26% per year of exposure to HAART. This is probably the most convincing study, because it has the highest reported patient-years of follow-up on HAART. A sensitivity analysis of this data showed that almost all of the risk was associated with PI use and virtually none from NNRTI use [73].





From Friis-Moller et al., D:A:D Study Group; 13th CROI

b. Prediction of Cardiovascular Disease in HIV

Can We Predict Cardiovasular Disease in HIV? Use of the Framingham Risk Score.

The Framingham risk score is beginning to be used to predict cardiovascular morbidity in HIV [36]. However, since it remains unclear whether the observed increase in the rate of MI in this population can be attributed to changes in conventional cardiovascular risk factors, its validation in this population is not well established. In a recent analysis [72], the Framingham equation was applied to a large international cohort of patients on HAART. Although the observed and expected rates of MI increased in parallel fashion with increased HAART duration, the equation tended to consistently underestimate the observed numbers of MIs during follow-up, suggesting that the observed increase in risk of MI was only partly explained by HAART-induced changes.

When compared with age-, sex-, and body mass index-matched controls, HIV-infected patients (with or without fat redistribution) receiving HAART were shown in another study to have comparable 10-year coronary heart disease (CHD) risk estimates [65]. However, the CHD risk estimate was greatest in HIV-infected patients who had primary lipoatrophy, compared with those who had either lipohypertrophy or mixed fat redistribution. Therefore, the pattern of fat distribution is a potential important component in determining the risk in this population.

Also, in multivariable analysis of the D:A:D cohort, the effect of PIs on the increased risk of MI was only partly explained by the dyslipidemia known to be induced by this drug class. Indeed, PI use was associated with a RR of MI of 1.16/year of use. Controlling for PI-induced dyslipidemia, PI use was still associated with an increased risk of MI of 1.10/year [73].

Has Enough Time Elapsed to Evaluate the Impact of HIV and HAART on CV Morbidity and Mortality?

Given the lag time between the exposure to traditional cardiac risk factors and the development of atherosclerosis and cardiac events, it's unclear whether enough time has elapsed to allow for the evaluation of HIV disease and HAART on cardiovascular morbidity [13, 14, 61, 65]. The survival of HIV infected patients is just recently being lengthened by HAART, and the median duration on HAART in published studies ranging from less than two years [61] to barely over five years [14]. Finally, as mentioned below, the most recent studies are suggesting a waning of the PI effect on cardiovascular morbidity.

c. Pathogenesis of Cardiovascular Disease in HIV

i. Prevalence of "Traditional" Cardiovascular Risks in HIV Other than Dyslipidemia and Insulin Resistance

Do HIV and HAART Mediate CV Risk Through Induction or Worsening of Traditional Risk Factors or Through Other Pathways?

Are Other Cardiovascular Risk Factors More Prevalent Among HIV-Infected Patients than Among Uninfected Patients?

If the metabolic syndrome is not more prevalent among HIV patients than in the general population, it would be reasonable to speculate that if there is indeed an increase in cardiovascular morbidity in the HIV population – compared to age-matched uninfected subjects – then HIV disease induces this excess morbidity though pathways other than the traditional risk factors accounted for in the metabolic syndrome.
It has already been shown that HIV-infected patients are more likely to smoke than age- and gender-matched controls [74]. Indeed, tobacco smoking appears to not only independently predicts HIV infection, but also progression to AIDS [74]. A recent population-based cohort study in France [36], evaluated the distribution of risk factors for cardiovascular disease in HIV patient. The predicted CAD risk was greater among HIV-1-infected compared with the HIV-1-uninfected cohort. However, the estimated attributable risks due to smoking were 65% and 29% for HIV-1-infected men and women, respectively. Smoking was also the most prevalent cardiovascular risk factor among HIV-infected patients in the Swiss Cohort [71]. Smoking and other potential lifestyle differences can therefore account for at least part of the excess cardiovascular morbidity. There might also be other causes of increased cardiovascular risk inherently associated with HIV infection itself. This is indeed suggested by recent findings that delayed initiation of HAART was recently been found to be a risk factor for metabolic complications [75], and HAART discontinuation leads to increased incidence of cardiovascular events [76].

ii. Other Potential Mechanisms for Increased Cardiovascular Risk in HIV

What are other potential pathogenic mechanisms for the increased cardiovascular morbidity in HIV?

1. Impairment of Cholesterol Efflux

Also, several steps of HIV-1 replication critically depend on cholesterol. It has recently been demonstrate that HIV-1 impairs ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux from human macrophages [77]. Impairment of cholesterol efflux leads to accumulation of intracellular cholesterol a condition previously shown to be highly atherogenic.
Also, NRTIs have also been shown to alter the expression of both mitochondrial and lipid metabolism genes [27].

2. Endothelial Dysfunction

Recent data suggests that endothelial dysfunction, impaired fibrinolysis, and excess inflammation may contribute to increased cardiovascular risk in HIV-infected patients with or without HAART.[13, 78] Endothelial dysfunction may be caused by the infection itself, the immunologic responses due to the HIV virus, and also by the effects of HAART through their effects on both lipid and glucose metabolism. Although intriguing, the large number of potential confounders including viral and immunologic factors, as well as treatment factors significantly hampers the study of endothelial dysfunction in HIV-associated cardiovascular morbidity.[78, 79]

There is also evidence that coronary atherosclerotic disease can be revealed by means of carotid intimal medial thickness (IMT) assessments in specific groups of HIV patients. Carotid IMT is higher in HIV patients than in age-matched control subjects and progresses much more rapidly than previously reported rates in non-HIV cohorts. In HIV patients, carotid IMT is associated with classic coronary risk factors and with nadir CD4 count < or =200, suggesting that immunodeficiency and traditional coronary risk factors may contribute to atherosclerosis [80]. Again, multiple possible factors, including viral factors, immunologic conditions, and metabolic drug effects could affect the interpretation of these results [78].

VII. Management of Cardiovascular Risk in HIV

Over the past several years there has been a growing focus on minimizing cardiovascular risk by addressing dyslipidemia and other modifiable risk factors among patients with HIV infection. Even if as mentioned above, several

epidemiologic associations and pathogenic mechanisms are yet to be elucidated, there's nascent evidence that these efforts may be yielding a benefit. Several large cohort studies demonstrated that rates of myocardial infarction and coronary heart disease among HIV-infected adults seem to be stabilizing or declining [73, 81, 82]. This change has been attributed to changing patterns of antiretroviral use and increased attention to lipid-lowering and antihypertensive therapy. However there is room for improvement as noted in the Swiss HIV Cohort Study in which only one third of patients with dyslipidemia or hypertension were receiving lipid lowering or antihypertensive therapy [71].

The Infectious Diseases Society of the America recently published a set of evidence-based guidelines for the management of metabolic and cardiovascular complications in HIV-infected patients [83]. The authors however acknowledged that establishing management guidelines was seriously hampered by the "lack of standardized diagnostic criteria, as well as disparate study populations and research methods" leading to "conflicting data regarding the diagnosis and treatment of metabolic and body shape disorders associated with HIV infection." Nonetheless, emerging data show that multidisciplinary – medical and surgical – therapeutic approaches are efficacious and safe in the management of lipodystrophy [84].

a. Management of dyslipidemia in HIV

i. Lipid lowering therapy

In the absence of data specific to the HIV-infected population, the newly-revised National Cholesterol Education Project (NCEP) treatment guidelines have been revised and can be applied to persons with HIV infection [85, 86] However, previous studies designed to evaluate conventional therapies for the reduction of hyperlipidemia and elevated triglycerides have met with modest or limited success [87], particularly in the setting of continued use of antiretroviral therapies known to affect lipid metabolism.

Nonetheless, in some patients, the hypertriglyceridemia can be treated with gemfibrozil and a statin can be given for concurrent hypercholesterolemia. Patients should generally undergo evaluation and treatment on the basis of existing guidelines for dyslipidemia [83, 88]. A simultaneous use of different interventions including combination lipid-lowering medications, diet and exercise has been shown in one study to have potentially profound impact on serum cholesterol in 45 HIV infected patients taking protease inhibitors [87, 89].

ii. Antiretroviral therapy modification

With insight gained on the correlations between the use of different antiretrovirals and the development of dyslipidemia, as well as the elucidation of the pathogenic mechanisms of these lipid abnormalities, studies have been carried out to

evaluate the impact of a switch in antiretroviral therapy away from the likely offending medications. Lipid levels may improve with substitution of an NNRTI for a PI [90], with substitution of atazanavir for other PIs or NNRTIs [91] or with substitution of a non-thymidine analogue NRTI for a thymidine analogue NRTI [92, 93].

iii. Lifestyle modification

Again, following above NCEP guidelines, the IDSA recommends that patients should be counseled on lifestyle changes, including smoking cessation, adoption of a lipid-decreasing diet, and aerobic exercise, as appropriate for the individual. For patients who have not met desired lipid goals after 4–8 weeks, additional therapeutic options include change in antiretroviral regimen and initiation of lipid-decreasing therapy.

b. Management of Insulin resistance in HIV

i. Lifestyle modification and hypoglycemic agents

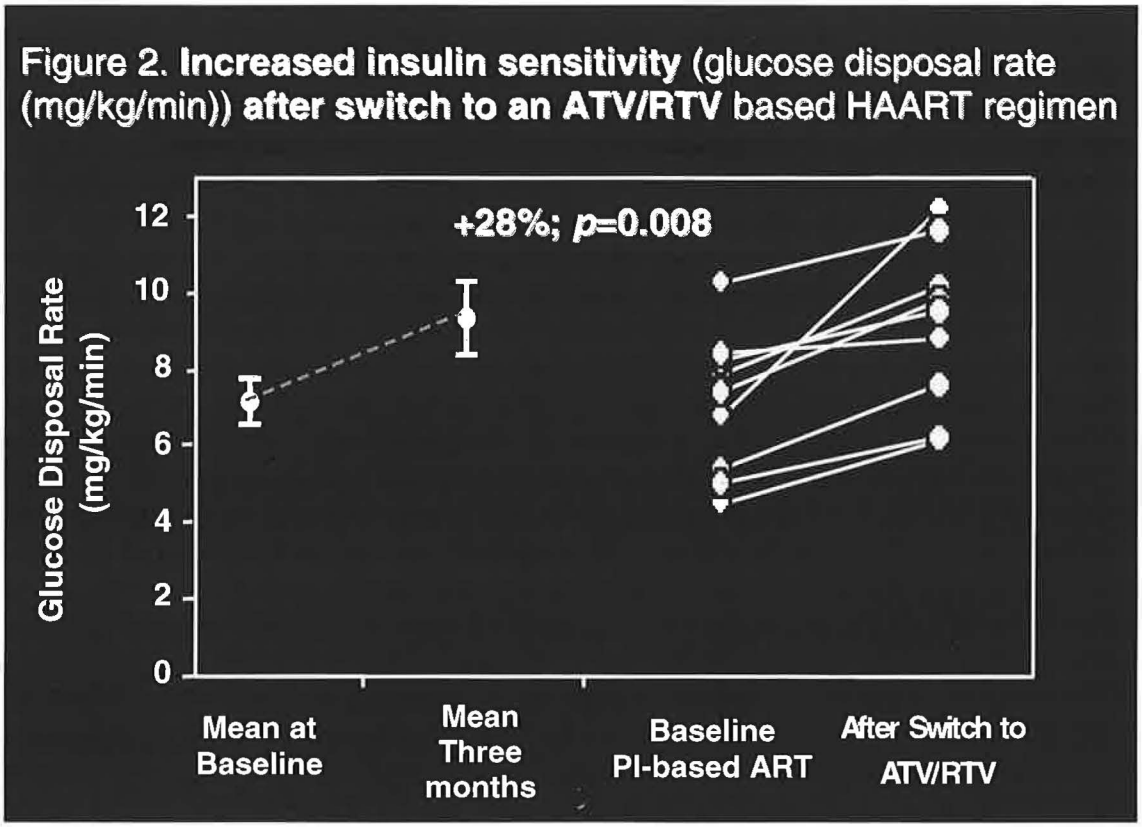
Although no available data specifically evaluating the impact of lifestyle modification among HIV-infected patients, guidelines established for the HIV-uninfected patient are used. Also, as mentioned above with other components of the metabolic syndrome, multidisciplinary approaches are efficacious [84, 89]. Metformin and thiazolidinediones should be preferred in patients with established diabetes, as it also improves features of lipodystrophy (see below).

ii. Antiretroviral substitution

Substitution of an NNRTI for a PI has been observed to increase insulin sensitivity in some—but not all—studies [94]. Also, newer protease inhibitors (PI) like Atazanavir (ATV) have been shown to be associated with fewer metabolic abnormalities in HIV+ patients. We recently carried out a prospective open-label study in 9 HIV+ patients with dyslipidemia on stable PI-containing antiretroviral therapy whose PIs were changed to ATV/RTV (300/100 mg once daily). Inclusion criteria were VL < 50 copies/mL, CD4 count > 200 cells/μL and triglycerides > 200 mg/dL. Whole-body insulin sensitivity was measured by 3 hr. hyperinsulinemic euglycemic clamp (200 mU/m2/min) and body composition by whole-body DEXA at baseline and after 12 weeks of ATV/RTV.

After 12 weeks, insulin sensitivity (glucose disposal rate, GDR) significantly improved (+28%; p=0.008) in all patients without change of body weight. Lipids improved with median changes in TC of +6%, TG of -35%, LDL -4%, and apoB of -12%. LDL size also increased. Switching to an ATV/RTV based ART regimen therefore resulted in a less atherogenic lipid profile.

These findings are not attributable to a change in body weight – which didn't change during the 12 weeks – and suggest that newer PIs like ATZ have a more neutral effect on glucose and lipid metabolisms. They are also consistent with recently published data [95].



Busti AJ, Bedimo, R, Margolis D et al. 8th International Workshop on Adverse Drug Interactions and Lipodystrophy in HIV. 24-26 September 2006, San Francisco, CA, USA.

c. Management of fat redistribution in HIV

As noted above, lipoatrophy and lipohypertrophy appear to be separate processes and should therefore be addressed independently in a given patient, if they co-exist. The evidence for the impact of their management on cardiovascular morbidity is however lacking. In addition to "standard methods" of weight reduction (diet and exercise) terventions include:

i. Antiretroviral therapy switch

Switching from a PI to an alternative antiretroviral agent has generally not been found to reverse lipohypertrophy or lipoatrophy . Recent data suggest that a switch from a thymidine analogue NRTI (zidovudine or stavudine) to either

abacavir, tenofovir or an NRTI-sparing regimen significantly increases abdominal subcutaneous fat, and partially reverses peripheral fat loss [93, 96, 97].

ii. Hypoglycemic agents

Studies on the effects of the insulin-sensitizing agents thiazolidinediones on subcutaneous fat in patients with HIV infection have produced mixed results. The effect is at best modest and has come at the expense of significant hypertriglyceridemia in some trials [98-100]. Metformin appears to promote a general loss of weight. In HIV, this might lead to not only the decrease insulin resistance and visceral adipose tissue (beneficial) but also the loss of lean body mass and worsening of lipoatrophy (unwanted).

iii. Surgical methods

Liposuction, temporary and permanent fillers are used by dermatologists and plastic surgeons for alleviation of features of lipoatrophy and lipohypertrophy. Subcutaneous injections of recombinant human growth hormone and TH9507, a growth hormone releasing factor analogue, have both shown promise in reducing visceral fat accumulation in phase II trials [101]

VIII. HCV Co-Infection and Metabolic Complications

a. Impact of HCV co-infection on HIV disease

Does Hepatitis C Co-Infection Worsen HIV Disaese?

Hepatitic C (HCV) co-infection is very prevalent among HIV-infected patients, reaching up to 70% in some series [102]. There has been a lot of speculation over whether HCV co-infection negatively impacts HIV disease progression and death, with earlier studies reporting conflicting data [103, 104]. Data from a longitudinal medical records review project conducted in over 100 US medical clinics from 1998 to 2004 and compiled by the CDC on this subject was recently published [105]. In that cohort, HCV did not increase the risk of death or AIDS-Opportunistic Infections, and did not affect the early immunological or virological response to initial HAART.

b. HCV co-infection and Metabolic Abnormalities in HIV

Does Hepatitis C Co-Infection Worsen HIV and HAART-Associated Metabolic Complications? What's the Impact of Race?

A non-exhaustive list of metabolic abnormalities in HIV that might be potentially worsened by HCV includes insulin resistance, fat redistribution including hepatic steatosis, dyslipidemias and Nonalcoholic Fatty Liver Disease (NAFLD).

i. HCV Co-Infection, Lipodystrophy and Insulin Resistance

HCV co-infection has been shown to be associated with higher rates of lipodystrophy and glucose intolerance among HIV-infected patients [106, 107]. In addition, recent epidemiological and laboratory studies have suggested a linkage between type 2 diabetes and chronic HCV infection [108, 109]. However, a definite relationship between HCV infection and other components of the metabolic syndrome – especially dyslipidemias – has not been established. This has often been attributed to the presence of additional factors in patients, such as obesity, aging or cirrhosis. In fact, among NHANES-III subjects, HCV was not associated with metabolic syndrome but associated with HOMA insulin resistance [109].

In a series by Duong et al.[106], insulin resistance was significantly more frequent, and dyslipidemia significantly less prevalent in HIV/HCV co-infected patients compared to HIV mono-infected patients. Three other retrospective analyses [110-112] and one prospective cohort [113] suggested that HCV co-infection is an independent factor preventing the emergence of treatment-limiting total cholesterol increase on HAART, possibly reflecting impaired total cholesterol synthesis in the liver or total cholesterol hypercatabolism.

ii. HCV Co-Infection and Dyslipidemia

As coinfection with HCV appears to decrease the prevalence of dyslipidemia in HIV infection, lower rates of dyslipidemia would be expected in HCV mono-infected patients. None of the previous studies, however, compared rates of dyslipidemia among HIV mono-infected, HCV mono-infected and HIV/HCV co-infected patients. In addition, the small numbers of patients enrolled in these studies prevented the analyses of potentially contributing factors such as age, duration of HAART therapy and age.

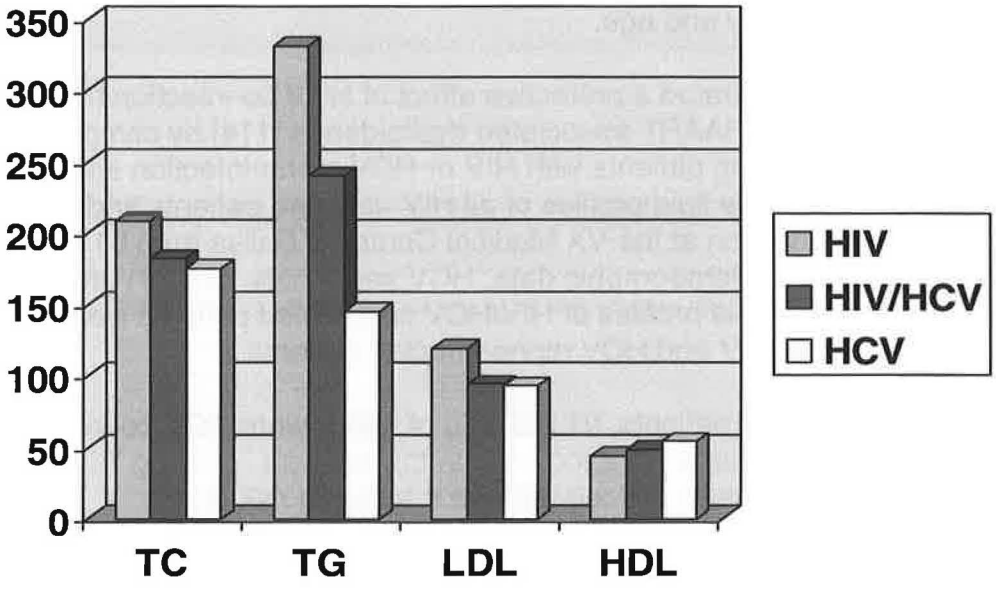
We have recently demonstrated a protective effect of HCV co-infection from the development of HIV- and HAART-associated dyslipidemia [114] by comparing rates of dyslipidemia among patients with HIV or HCV mono-infection and HIV/HCV co-infection. The lipid profiles of all HIV -infected patients and a subset of HCV patients seen at the VA Medical Center in Dallas from 01/2003 to 03/2004 were analyzed. Demographic data, HCV serostatus, and HIV treatment history were recorded. Lipid profiles of HIV/HCV co-infected patients were compared with those of HIV and HCV mono-infected patients.

A total of 359 HIV-infected patients, 91 (25.3%) of which were HCV co-infected; and 112 HCV-infected patients were included in the analysis. Among HIV patients, HCV co-infection was associated with a reduced risk of hypercholesterolemia (9.9% vs. 24.8%; RR=0.333; 95% CI= 0.158 – 0.699; $p<0.001$) and hypertriglyceridemia (48.4% vs. 60.3%; RR=0.616; 95% CI= 0.382 – 0.994; $p=0.031$). After controlling for duration of PI therapy, race, ALT and

platelet count HCV remained an independent predictor of hypercholesterolemia (RR = 0.369; p = 0.01) and any dyslipidemia (RR = 0.531; p = 0.019).
In addition, the rate of dyslipidemia was lower among HCV mono-infected than HIV/HCV co-infected patients (29.5% vs. 50.5; p = 0.002). White race was also an independent predictor of dyslipidemia (73.8 vs. 50.7%; %; RR = 2.32; 95% CI = 1.44 – 3.76; p = 0.001).

Our data show that HCV co-infection was an independent predictor of lower rates of dyslipidemia in general, and hypercholesterolemia in particular, among HIV-infected patients. Although HCV co-infection predicted lower rates of hypertriglyeridemia in univariate analysis, this did not remain in multivariate analysis controlling for age, race, platelet count and ALT.
HCV did not independently predict rates of lipodystrophy among HIV-infected patients and we did not have enough fasting blood sugar data to evaluate the effect of HCV on glucose intolerance in our study population. Previous studies showed that lipodystrophy and insulin resistance were significantly more frequent in HIV/HCV co-infected patients.[106, 107] Factors that independently predicted lipodystrophy in our cohort included longer duration on PI, older age and White race. These findings are in accordance with previously published observations.[11, 16, 24, 115, 116]

In summary, our results therefore confirm a growing body of evidence that HCV co-infection is associated with the development of dyslipidemia among HIV-infected patients [107, 110-113, 116, 117]. Also, patients with chronic HCV mono-infection have lower rates of lipid abnormalities than age- and sex-matched healthy subjects [118], and LDL concentrations were inversely correlated with the severity of liver disease [119].



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iii. HCV Co-Infection and Nonalcoholic Fatty Liver Disease

NAFLD is now recognized as one of the most important causes of chronic liver disease in Western Countries, and is the hepatic manifestation of metabolic syndrome [120]. Indeed, insulin resistance is the pathophysiological hallmark of NAFLD. NAFLD is characterized by excess fat in hepatocytes in patients without significant alcohol use. It can progress from steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis [121]. Studies have shown that visceral obesity and insulin resistance are integral to the pathogenesis of NAFLD. Patients with HIV are at greater risk of NAFLD. This is postulated to be due to the potentially additive effects of antiretroviral therapy and viral hepatitis co-infection. However, histological-based, longitudinal studies are still needed that address the interactions of HCV and HIV infections as well as antiretroviral therapy in the causation of NAFLD [121].

c. Dyslipidemia and HIV/HCV co-infection; Potential Mechanisms of Protective Effect of HCV

How Would Hepatitis C Infection Protect from Dyslipidemia?

As mentioned above, a dysregulation of fatty acid metabolism leading to increased lipolysis has been implicated as the cause of the HIV- and HAART-associated hyperlipidemia [47-50]. Mechanisms by which HCV co-infection might reduce hyperlipidemia in HIV may include a reduction in fatty acid flux, lower hepatic fatty acid synthesis and reduced TG secretion rates in the form of very low-density lipoprotein particles (VLDL).

If fatty acid metabolism in HIV is similar to that of uninfected, obese, insulin-resistant individuals, then elevated adipose fatty acid release would stimulate TG synthesis in the liver [122]. HCV infection might achieve the apparent protective effect from HIV- and HAART-induced dyslipidemias by either directly interfering with lipoprotein metabolism or through the hepatic dysfunction it induces. One potential mechanism is interference with excess adipose fatty acid flux. Reduced fatty acid clearance through decreased lipoprotein lipase activity may also play a role [123, 124]. Another potential explanation is that HCV infection downregulates lipoprotein receptor expression or lipoprotein transport into infected cells. Indeed, HCV particles bind to LDL receptors in vitro and are present in the LDL fraction isolated from plasma of infected patients. These data suggest an association of the viral particles with lipoproteins and the use of lipoprotein receptors for cell entry [125]. A better understanding of how HCV protects from the development of hyperlipidemia will result in the development of novel strategies to prevent and/or reverse dyslipidemia in HIV.

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