The risk of myocardial infarction during HIV infection treated with antiretroviral combinations. A review

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Abstract

Highly active antiretroviral therapy (HAART) has dramatically reduced morbidity and mortality associated with acquired immunodeficiency syndrome (AIDS), and human immunodeficiency virus (HIV) infection has become a chronic and manageable disease. Paralleling increased life expectancy, HIV-infected subjects may present many comorbidities, most notably cardiovascular diseases, and recent studies have identified an increased prevalence of traditional coronary risk factors in these patients. Moreover, additional investigations suggest that HIV itself may independently favour premature atherosclerosis, and antiretroviral agents also could directly or indirectly play a role in the atherosclerotic process. Dyslipidaemia, insulin resistance, inflammation, and fat redistribution are all likely to contribute to this pathogenetic pathway, and these abnormalities may be interrelated and due to either HIV infection, or the related inflammatory syndrome, or HAART-associated toxicity. Appropriate screening and assessment of cardiovascular risk and intensive strategies for prevention of cardiovascular events are suitable in HIV-infected patients, including lifestyle measures, switching antiretroviral drugs, and pharmacologic therapy of lipid and glucose metabolism alterations. This article reviews the correlation between HIV infection and myocardial infarction, and discusses the most appropriate clinical management of cardiovascular risk among HIV-positive individuals.

Key words: HIV infection, antiretroviral therapy, coronary heart disease, myocardial infarction, endothelial dysfunction

Introduction

The introduction of highly active antiretroviral therapy (HAART) has led to a dramatic decrease in morbidity and mortality associated with the human immunodeficiency virus (HIV) infection, with mortality declining from 20-30 deaths per 100 person-years before 1995, up to to 2-5 deaths per 100 person-years after 1997[1-3], with these figures continuing to decrease in recent years.

Since new antiretroviral regimens have led to a notable extension of life expectancy in HIV-positive patients, questions related to comorbidities and long-term adverse effects of HAART have recently emerged. An increasing concern is mounting particularly about the increased risk of coronary artery disease in HIV-infected subjects, as recently described in two large prospective studies[4,5]. Owing to the effectiveness of HAART and the increasing age of patients, more than 50% of deaths in HIV-positive population are now from causes other than acquired immune deficiency syndrome (AIDS), and the percentage of non-AIDS related deaths continues to increase. Particularly, the most frequent non-AIDS-associated causes of deaths are comparable in recent surveys and include malignancies, chronic liver disease and cardiovascular disease[6-8].

Several of the traditional risk factors for coronary artery disease are frequently reported in HIV-positive individuals, including factors related to the patients' lifestyle (such as cigarette smoking and drug addiction), and factors associated with HIV infection itself and antiretroviral drugs (such as dyslipidaemia, insulin resistance, diabetes mellitus, central adiposity, arterial hypertension, and direct effects of

the virus or antiretroviral agents on the vascular system). Moreover, some data suggest that endothelial dysfunction, impaired fibrinolysis, and increased inflammation are more common in HIV-positive patients than in general population, and may contribute to an increased cardiovascular risk[9,10]. At the same time, carotid intimal-media thickness and coronary calcification assessments suggest increased incidence of atherosclerotic disease and premature occurrence of arterial atherosclerotic lesions among HIV-infected individuals[11,12].

To the best of our knowledge, HIV and HAART may contribute to an increased risk of cardiovascular diseases in three principal ways: (1) HIV infection can identify a subgroup of the general population with a greater prevalence of traditional risk factors unrelated to HIV or HAART (eg, male sex, advancing age, higher smoking rate, alcoholism or drug addict); (2) HIV infection and HAART can indirectly favour the occurrence of traditional risk factors (eg, hyperlipidaemia, insulin resistance, diabetes mellitus, fat redistribution, or hypertension); (3) HIV and HAART can directly affect the pathogenesis of atherosclerotic disease (eg, through inflammation and endothelial dysfunction)[13].

The body of our knowledge suggest that all three above-mentioned mechanisms are plausible and contemporaneously affecting the risk of coronary artery disease in HIV-infected subjects. However, experimental and clinical data are often conflicting still today, and several questions remain as to the detection, pathogenesis, prevention and treatment of cardiovascular diseases and related risk factors. This review will assess the most recent literature data in order to explain next essential questions in HIV-positive population: (1) incidence of myocardial infarction and related risk factors; (2) incidence of premature atherosclerosis and related risk factors; (3) pathogenetic role of HIV infection; (4) pathogenetic role of antiretroviral therapy; (5) screening and diagnosis; (6) treatment and prevention. A more straightforward understanding of the cardiovascular complications associated with HIV disease is also advisable in order to design the most adequate clinical trials and to define the most appropriate guidelines for the clinical management of these long-term complications.

Myocardial infarction in hiv-infected patients

The first cases of acute myocardial infarction in HIV-positive individuals under combination antiretroviral treatment have been described in early year 1998. These initial case reports suggested an increased frequence of cardiovascular diseases in HIV-infected patients receiving combination antiretroviral therapy, raising the question of the association between cardiovascular complications and new, potent therapies including protease inhibitors (PIs)[14-16].

Subsequently, some retrospective and prospective studies have shown that the incidence of myocardial infarction in HIV-positive subjects treated with antiretroviral therapy tends to be higher than in the general population, particularly in those receiving a PI-based treatment[17]. However, reports from large observational studies demonstrate that considerable controversy exists until now about the association of HAART, particularly PI-based combinations, with increased incidence of coronary heart disease risk. The most large studies investigating incidence of cardiovascular events in HIV-positive subjects and their association with HAART are summarized in **Table 1**.

Table 1. Retrospective and prospective studies evaluating the relationship between risk of cardiovascular events and use of combination antiretroviral therapy.

Author, year [reference]	Type of study	N. of patients	Years of study	Events	N. of events	Event rate per 1000 person/years HIV+ group	Increased risk of CVD associated with CART
Jütte, 1999 [18]	R	1,324	1990-1998	MI	5	10.6	Yes (PIs)
Holmberg, 2002 [4]	P	5,672	1993-2002		21	1.42	Yes (PIs)
DAD Study Group [5, 24, 31]	P	33,347	1999-2007	MI	517	3.5	Yes (PIs, ABC, ddI)
Rickerts, 2000 [19]	R	4,993	1983-1998	MI	29	3.41	Yes
Klein, 2002 [20]	R	4,159	1996-2001	CVD	47	4.3	No
Currier, 2003 [21]	R	28,513	1994-2000	CVD	294	4.12	Yes
Mary-Krause, 2003 [22]	R	34,976	1996-1999	MI	49	4.9	Yes (PIs)
Escaut, 2003 [23]	R	840	1997-2002	MI	17	5.9	Yes
Obel, 2007 [25]	P	3,953	1995-2004	MI	11	2.3	Yes
Iloeje, 2005 [26]	P	7,542	1996-2003	CVD	112	11.5	Yes (PIs)
Bozzette, 2003 [28]	R	36,766	1993-2001	CVD	410	5	No
Triant, 2007 [30]	P	3,851	1996-2004	MI	189	11.13	No
SMART Study, 2008 [29, 32]	P	2,752	2004-2007	CVD	112	4.3	Yes (ABC)
Brothers, 2009 [33]	P	14,174	1997-2004	MI	18	2.3	No association with ABC

HIV, human immunodeficiency virus; CVD, cardiovascular diseases; CART, combination antiretroviral therapy; R, retrospective; P, prospective; MI, myocardial infarction; PIs, protease inhibitors; ABC, abacavir; ddI, didanosine

Jütte et al. retrospectively assessed the incidence of myocardial infarction among 1,324 HIV-infected individuals receiving antiretroviral therapy (951 without PI and 373 with PIs), and followed-up between 1990 and 1998. The myocardial infarction rate was significantly greater in PI-treated than in PI-untreated subjects (1.06 and 0.21 per 100 patient-years, respectively), showing a five-fold increased risk of coronary events in PI-treated patients compared with untreated controls[18].

Rickerts et al. performed a retrospective analysis of a cohort of 4,993 HIV-positive patients treated with different antiretroviral treatment strategies, between the years 1983 and 1998. The incidence of coronary heart disease increased significantly in this cohort after the introduction of HAART. Particularly, the incidence of myocardial infarction increased from 0.86 (in the period 1983-86)

to 3.41 per 1,000 patient-years (in the period 1995-98) (p=0.002). Increased age (higher than 40 years), homo- or bisexual mode of HIV transmission, previous AIDS diagnosis, and previous HAART were significantly associated with myocardial infarction in univariate analysis, and increased age and previous HAART remained significantly associated with coronary heart disease also in a multiple regression model[19].

Klein et al. examined data from the Kaiser Permanente Medical Care Program of Northern California to compare hospitalization rates for coronary heart disease among HIV-infected and HIV-uninfected subjects, before and after PI introduction. This data set identified 4,159 HIV-positive patients aged 35 to 64 years, followed from 1996 up to 2003, with a median total follow-up of 4.1 years. The age-adjusted coronary heart disease hospitalization rate was significantly higher in HIV-positive members than in HIV-negative ones (6.5 vs 3.8; p=0.003), and the difference in the myocardial infarction rate also was higher (4.3 vs 2.9; p=0.07). However, the age-adjusted rate of myocardial infarction in patients receiving PIs was not statistically greater than in patients not receiving PIs (4.0 vs 3.4 per 1,000 patient-years). Similarly, hospitalization rates for cardiovascular diseases were not significantly different before versus after PIs (6.2 vs 6.7 events per 1,000 patient-years), or before versus after antiretroviral therapy (5.7 vs 6.8)[20].

Currier et al. reviewed administrative claims data for the HIV-positive and HIV-negative individuals from the California Medicare population, and investigated the incidence and the relative risk for coronary heart disease using log-linear regression analyses between two groups. The incidence of cardiovascular events among young men (up to age 34) and women (up to age 44) was significantly higher in HIV-positive compared with HIV-negative persons. Moreover, the covariate-adjusted relative risk for the development of coronary heart disease in subjects receiving antiretroviral drugs compared with those not receiving medications was 2.06 (p<0.001) in HIV-infected patients aged 18-33 years. Notably, there were no statistically significant associations between antiretroviral exposure and cardiovascular complications in other age groups[21].

Mary-Krause et al. assessed the incidence of myocardial infarction among 34,976 HIV-infected male patients belonging to the French Hospital Database on HIV, who were followed up for a median of 33 months between years 1996 and 1999. Myocardial infarction was diagnosed in 60 men among 88,029 person-years, including 49 cases among men receiving PIs. The exposure to PIs was associated with a higher risk of cardiovascular diasease, and the myocardial infarction rates increased in relation to duration of PI therapy (10.8 events per 10,000 person-years in men with <18 months PI use; 33.8 events per 10,000 person-years in those with >30 months PI use). The standardized morbidity ratios relative to the French general male population were 0.8 for men exposed to PI for <18 months, 1.5 for men exposed for 18-29 months, and 2.9 for men exposed for over 30 months. These results have pointed to a duration-related effect relationship between PI and myocardial infarction, with a greater incidence of this cardiac complication among patients exposed to PI for 18 months or more[22].

Escaut et al. evaluated retrospectively the incidence of coronary artery disease among 840 HIV-positive individuals followed-up for 5 years. Incidence of coronary events was 5.9 per 1,000 person-years and a greater risk of these complications was found to be associated with HAART, metabolic disturbances, and a higher prevalence of tobacco smoking[23].

Moreover, recent prospective studies involving large cohorts of HIV-infected patients have documented an increased incidence of myocardial infarction and cerebrovascular diseases in association with a prolonged exposure to combination antiretroviral therapies, even if the absolute risk of cardiovascular events remains low, and should be balanced against the remarkable benefits from HAART in terms of improvement in immune function and related morbidity and mortality.

Prospective studies have recently been published which were specifically designed to evaluate the incidence of cardiovascular diseases in HIV-positive population. Prospective observational cohorts with more systematic assessment of cardiovascular disease risk factors and validation of outcomes provide more insight into the epidemiology of cardiac complications in the HAART era, and are certainly more generalizable.

In the HIV Outpatient Study (HOPS), Holmberg et al. described 21 cases of myocardial infarction among 5,672 patients from nine United States HIV Clinics during 17,712 patient-years of follow-up (performed between years 1993 and 2002). The frequency of myocardial infarction increased after the introduction of PIs in the year 1996; this cardiac complication occurred in 19 patients on PIs (1.42 per 10,000 patient-years) and in two subjects not on PIs (0.46 per 10,000 patient-years; odds ratio=7.1). In multivariate Cox proportional hazards models adjusted for smoking, gender, age, diabetes mellitus, hypertension, and dyslipidemia, the hazard ratio was 6.5, suggesting that use of PIs is associated with increased risk of myocardial infarction in subjects with HIV infection[4].

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study is a prospective, observational study of 11 previously established cohorts comprising 23,468 HIV-infected patients followed in 21 countries in Europe, United States and Australia. During this study, a total of 126 episodes of myocardial infarction were diagnosed, leading to a crude incidence rate of 3.5 per 1,000 patient-years. The authors showed that the incidence of myocardial infarction increased significantly with increasing exposure to combination antiretroviral therapy, and the adjusted risk rate per year of exposure ranged from 0.32 for no HAART use to 2.93 for ≥6 years of HAART use. This suggested that during the first four to six years of combination antiretroviral treatment there was approximately a 26% increase in the relative risk of suffering from a myocardial infarction, but the absolute risk of coronary events was low and must be balanced against the remarkable benefits from antiret-

roviral therapy. On the other hand, the incidence rate of myocardial infarction did not exceed that of what should be expected from the background population given the same cluster of cardiovascular risk factors. Other factors that also independently predicted myocardial infarction in the DAD study were increased age, current or past smoking, previous cardiovascular diseases, male sex, hypercholesterolaemia, hypertriglyceridaemia, and diabetes mellitus[5]. Increased exposure to PIs was associated with an increased risk of myocardial infarction, which is partly explained by dyslipidaemia, while no evidence of such an association for non-nucleoside analogues was found[24].

A case-control survey involving 3,953 HIV-infected patients and 373,856 persons in a population-based control group showed that after initiation of HAART the cardiovascular risk was significantly higher among HIV-infected subjects than among control subjects, but the relative risk did not further increase, and were stable in the initial 8 years of antiretroviral treatment[25].

Iloeje et al. estimated the risk of cardiovascular disease events with PI exposure in a prospective observational study involving a cohort of 7,542 HIV-infected patients (whose 77% exposed to PIs) followed-up between 1996 and 2003. The study population was derived from the Centers for Disease Control and Prevention HIV Outpatient Study (HOPS) and additional physician offices and Clinics funded by the sponsoring agency, Cerner Corporation. The median duration of follow-up was 3.5 years and 2 years for the PI and non-PI groups, respectively, and the median PI exposure in the first group was 1.7 years. The incidence of cardiovascular complications was significantly higher in subjects exposed to PIs: a total of 127 cardiovascular events were observed, with 112 in the PI group for an adjusted event rate of 9.8 per 1,000 person-years of follow-up, and 15 in the nonPI group for an adjusted event rate of 6.5 per 1,000 person-years of follow-up (p=0.0008). In the multivariate analyses, cumulative PI therapy for $\geq$60 days was associated with an increased risk of cardiovascular diseases and the cardiovascular event rates were also higher in the PI group among patients in the 35 to 65-year-old subset. Other independent risk factors were current or past smoking, hypertension, diabetes mellitus, and pre-existing cardiovascular diseases[26].

Kaplan et al. estimated the predicted risk of coronary heart disease among 2,386 HIV-infected and 1,675 HIV-uninfected patients on the basis of age, sex, lipid and blood pressure levels, presence of diabetes mellitus, and smoking. Among HIV-positive persons, antiretroviral therapy exposure, increased body mass index and low income level were associated with increased predicted risk of coronary disease[27].

In contrast, in a large retrospective study using the Veterans' Affairs Database (which included 36,766 patients followed up for an average of 40 months, between years 1993 and 2001), Bozzette et al. showed that PI therapy was not associated with an increased risk of coronary heart disease. Patient-level regression analyses indicated that there was no relation between the administration of nucleoside analogues, non-nucleoside analogues, or PIs and the hazard of cardiovascular or cerebrovascular events. On the contrary, in this study the use of antiretroviral therapy was associated with a decreased risk of death from any cause. However, the median duration of exposure to PIs was only 16 months, and the true cardiovascular disease rate may have been underestimated, because many patients with acute myocardial infarction may not have been admitted to Veterans' Affairs hospitals[28].

Another important concern about the risk of coronary events in HIV-positive subjects has emerged from the Strategies for Management of Antiretroviral Therapy (SMART) study. This trial randomized 5,472 HIV-infected patients with CD4+ cell counts above 350 cells/mm^3 to intermittent antiretroviral therapy versus continuous antiretroviral therapy, and compared clinical outcomes. A total of 477 participants were evaluated during a mean follow-up of 18 months and the hazard ratio for risk of cardiovascular diseases for patients allocated to discontinuous therapy versus continuous therapy was 1.57. Although total and LDL cholesterol levels were usually reduced during discontinuations of HAART, the reasons for this higher cardiovascular risk associated with intermittent therapy are unclear still today[29].

Triant et al.[30] compared myocardial infarction rates (based on hospital claims data) among 3,851 HIV-infected subjects and 1,044,589 HIV-uninfected controls receiving longitudinal care in two tertiary care hospitals between 1996 and 2004. Incidence of myocardial infarction and prevalence of cardiovascular risk factors (hypertension, diabetes, and dyslipidaemia), were found to be higher in HIV-positive compared with HIV-negative persons, particularly among women.

Concern has also been raised regarding the potential cardiovascular risk associated with nucleoside reverse transcriptase inhibitors (NRTIs), and particularly with abacavir. The DAD study group used Poisson regression models to assess the relation between recent and past use of NRTIs and occurrence of myocardial infarction in 33,347 patients with 157,912 person-years of follow-up. Recent (within 6 months) or current, but not cumulative or past use (last use > 6 months) of abacavir or didanosine was associated with an increased risk of myocardial infarction (relative risk, 1.9 with abacavir and 1.49 with didanosine). The excess risk did not seem to be explained by underlying established cardiovascular risk factors, but the heightened risk of myocardial infarction with recent abacavir or didanosine exposure was accentuated in subjects with pre-existing risk factors for coronary artery disease[31]. A second study confirmed these data. An analysis of 2,752 patients assigned to the continuous antiretroviral therapy arm of the SMART study showed that current use of abacavir was associated with an excess risk of cardiovascular disease compared with other NRTIs (relative risk for myocardial infarction, 4.3). Even in this study, the highest risk was concentrated in individuals with five or more known cardiovascular risk factors[32].

In contrast to these two observational sudies, data from GlaxoSmithKline-sponsored trials found no increased cardiovascular risk in patients recently exposed to abacavir.

In a recent report, data from 52 clinical trials including 14,174 HIV-positive adults on HAART (9,502 abacavir recipients compared with 4,672 participants who did not receive abacavir) for at least 24 weeks were analysed. In this pooled summary, myocardial infarction rates were comparable among subjects exposed or not to abacavir-containing regimens (incidence of 2.09 and 2.57 per 1,000 person-years, respectively)[33].

Taken together, the above mentioned studies have shown that HIV-infected adults appear to have an increased relative risk of cardiovascular diseases compared with non-HIV patients, but they also have noted a higher prevalence of conventional cardiovascular risk factors (such as smoking, dyslipidaemia, diabetes mellitus, and arterial hypertension) in HIV-positive population, and it is often very difficult to determine the exact pathogenetic role of HIV infection per se, exposure to HAART, and traditional risk factors[13].

Moreover, data obtained from retrospective and prospective studies suggest that a small but significantly increased risk exists for myocardial infarction in association with HIV infection and combination antiretroviral therapy (and particularly with PIs, abacavir, and didanosine), regardless of traditional risk factors. Although conflicting data exist regarding risk of myocardial infarction associated with some NRTIs, the magnitude of the increased risk among the subset of individuals at high risk of coronary artery disease should not be ignored, and alternatives to abacavir and didanosine should be considered in persons at higher risk for cardiovascular complications. Certainly, data are not fully unanimous and larger, prospective studies evaluating cardiovascular risks of HIV disease are certainly requested, with appropriate design and statistical consideration of the effects of HAART and other, concomitant risk factors.

Premature atherosclerosis in hiv-infected patients

Investigation of subclinical atherosclerosis using evaluation of intima-media thickness and endothelial function have led new insights on the pathogenesis of structural and functional changes of arterial vessels observed in HIV-infected subjects. However, contradictory reports have been published concluding that HIV infection and antiretroviral therapy do or do not promote atherogenesis.

Endothelial dysfunction, reduced flow-mediated arterial dilatation and premature atherosclerotic lesions have been reported among HIV-infected patients receiving HAART, and newly available data highlight the incidence of cardiovascular events in this population. However, whether the increased cardiovascular risk in HIV-positive subjects is due to HIV infection itself, to antiretroviral therapy, or to a synergistic interaction between these factors, remains to be established. Although both HIV disease and HAART are associated with a lipid and glucose profile known to increase the risk of coronary and cerebrovascular complications, these metabolic factors do not fully account for the premature atherosclerotic lesions observed in these patients, suggesting that other mechanisms or mediators might be involved.

The association between antiretroviral therapy and premature atherosclerosis has been shown in some studies. Lai et al.[34] evaluated the association between PIs and accelerated atherosclerosis in 98 black adult HIV-infected patients aged 25 to 45 years. Subjects taking PIs had significantly higher plasma levels of total and LDL cholesterol, and those treated with ritonavir, nelfinavir or saquinavir were more likely to have a higher coronary artery calcium score than those on non-PI regimens.

Maggi et al.[11] evaluated 293 HIV-positive subjects, receiving PIs (n=105) or naive to PI therapy (n=188), by an epiaortic vessel colour-Doppler ultrasonography. Vascular lesions (including intima-media thickness >1 mm and/or atheromatous plaques), were detected in 52.4% of the PI-treated patients, while only 14.9% of the PI-naive individuals presented acquired lesions of the vascular wall. Antiretroviral therapy, age, cigarette smoking, and CD4 T-cell count were the main predictive risk factors for vascular lesions, but the highest significance value was found to be linked with the administration of PIs[35]. Moreover, in a study involving 110 HIV-positive patients and 91 HIV-negative patients, Maggi et al.[36] showed that HIV-infected subjects had a significantly higher number of hypoechogenic lesions (not fibrous or calcified), that had homogeneous parietal and endoluminal portions along with a smooth or slightly irregular surface. Ultrasonographic structure of the epi-aortic lesions in HIV-infected patients substantially differed from those of plaques in atherosclerotic individuals, although they shared similar features with patients affected by arteritis. These authors suggested that the pathogenetic mechanism responsible for carotid lesions associated with HIV infection may be more similar to an inflammatory process than the classical atherogenesis[36-38].

Jericò et al. investigated the relationship between combination antiretroviral therapy and subclinical carotid atherosclerosis according to cardiovascular risk in 132 HIV-infected patients who underwent a carotid high-resolution B-mode ultrasonography. Antiretroviral treatment exposure and a 10-year coronary risk estimated ≥10%, were found to be independent variables associated with subclinical carotid atherosclerosis[12].

Similarly, de Saint Martin et al.[39] assessed 154 HIV-infected individuals and confirmed the occurrence of premature atherosclerosis, which not only correlated with the usual risk factors (such as serum triglyceride, cholesterol, and glucose levels), but also with the PI exposure, especially the use of lopinavir/ritonavir. Moreover, Stein et al.[9] demonstrated impaired flow-mediated dilatation of the brachial or carotid artery (an early surrogate marker for endothelial dysfunction and subsequent plaque formation), among HIV-positive subjects receiving PIs, in comparison with PI-naive patients.

In a case-control survey involving 292 HIV-positive subjects and 1168 age- and sex-matched controls, Lorenz et al.[40] demonstrated that HIV infection and HAART were independent risk factors for early carotid atherosclerosis. In the carotid bifurcation, the intima-media thickness values were 24.4% higher in HIV patients, and premature carotid lesions correlated with the use of combination antiretroviral therapy.

A cross-sectional evaluation of HIV-positive participants and controls without pre-existing cardiovascular risk factors from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study showed an increased prevalence of atherosclerosis measured by the intima-media thickness in HIV-positive subgroup, even after adjustment for traditional risk factors[41].

The association of HIV infection and cumulative exposure to HAART with the presence of subclinical coronary atherosclerosis was investigated by assessing the presence and extent of coronary artery calcification in a cross-sectional study of 947 male (332 HIV-negative and 615 HIV-positive) participants from the Multicenter AIDS Cohort Study. After adjustment for age, race, family history, smoking, hypertension, HDL and LDL cholesterol levels, both HIV infection and long-term HAART use were associated with a higher prevalence of coronary artery calcification. However, the extent of calcification was significantly reduced among HAART users compared with HIV-negative controls[42].

In a cross-sectional study including 130 HIV-infected patients receiving HAART, treatment for 2 or more years with a PI-based regimen compared to an NNRTI-based combination was associated with a greater carotid intima-media thickness[43]. Another case-control study of 77 HIV-infected men and 52 controls showed that HIV infection was independently associated with increased carotid intima-media thickness and arterial stiffness, while antiretroviral treatment was associated only with increased stiffness of the femoral artery[44].

In a recent report by McComsey et al.[45], a greater prevalence of carotid atherosclerotic lesions was found also in HIV-infected children treated with antiretroviral therapy. Higher levels of carotid intima-media thickness and some cardiac markers (such as HOMA-IR, waist-to-hip ratio, cholesterol and triglycerides), were found in 31 HIV-positive children receiving HAART when compared to 31 matched HIV-negative controls. These results are certainly worrying, because they suggest that HIV-infected children receiving antiretroviral therapy may be at increased risk of cardiovascular complications.

In contrast to the above studies, other published investigations have failed to find a direct effect on the arterial wall of antiretroviral therapy. Depairon et al.[46] studied 168 HIV-infected persons, 136 of whom had received PIs. The prevalence of plaque lesions in the carotid or femoral arteries was significantly higher in HIV-positive group in comparison with HIV-negative individuals (55% versus 38%), but PI treatment did not independently predict vascular lesions, whereas traditional risk factors (including age, male gender, cholesterol levels, and smoking), were associated with premature atherosclerosis. Talwani et al.[47] showed that the rate of coronary atherosclerosis assessed by coronary artery calcium among 60 HIV-infected patients was not associated with short-term antiretroviral therapy with or without PIs. Hsue et al.[48] reported also a significantly higher rate of intima media thickness progression over one year in 121 HIV-positive subjects versus 27 HIV-negative controls, but in this study PI therapy did not correlate with atheromatous plaques. Mercié et al.[49] noted that conventional risk factors were major determinants of intima-media thickness evolution and premature atherosclerosis was not associated with type or duration of HAART among 346 HIV-positive subjects in a 12-month prospective cohort study.

These findings were corroborated by Currier et al.[50] in a prospective matched cohort study involving 134 HIV-infected and uninfected individuals, who underwent an ultrasonographic evaluation of the intima media thickness of the carotid artery. No association was found between PI exposure or HIV infection and carotid lesions, while significant predictors of higher carotid intima media thickness in a multivariate model included HDL cholesterol, triglycerides, age, and body mass index.

Mangili et al.[51] performed a cross-sectional analysis of 242 men and 85 women with HIV infection and found a more elevated prevalence of abnormal surrogate markers of cardiovascular risk (such as waist circumference, blood pressure, high-sensitivity C-reactive protein and body mass index). However, HAART administration was not associated with abnormal surrogate markers and increased risk of coronary heart disease. A recent study by Lebech et al.[52] involving 25 non-smoking HIV-positive persons, has found no sign of accelerated atherosclerosis by evaluation of carotid artery intima-media thickness, and premature carotid lesions correlated with HDL cholesterol but not LDL cholesterol. Traditional risk factors for cardiovascular diseases did overshadow the role of HAART in other studies[53,54], and a low CD4+ T-cell count was found to be the most robust risk factor for increased intima-media thickness in HIV-positive patients by Kaplan et al.[54].

In a recent cross-sectional study, Hsue et al.[55] measured carotid intima-media thickness in 494 patients, including 93 HIV-negative controls and 401 HIV-positive patients. HIV-positive group included patients treated with HAART and patients naïve to HAART with detectable or undetectable plasma HIV RNA. Premature atherosclerosis was associated with presence of HIV infection rather than viral load or CD4+ T cell count, and with antiretroviral drug exposure. This study showed that carotid intima-media thickness was higher among all groups of HIV-positive subjects compared to uninfected persons, irrespective of antiretroviral therapy or the level of viremia.

A recent systematic review evaluated the evidence for subclinical atherosclerosis among HIV-positive patients from six cross-sectional, seven case-control, and 13 cohort studies including 5,456 HIV-infected and 3,600 HIV-uninfected patients. Subclinical atherosclerosis was diagnosed by ultrasonographic evaluation of carotid intima-media thickness, focal plaque incidence, or coronary artery calcium detection. The weighted mean carotid intima-media thickness was 0.04 mm thicker among HIV-positive patients versus HIV-negative ones, and HIV infection was not associated with carotid plaques or presence of coronary calcium. Similarly, PI exposure did not significantly affect carotid intima-media thickness, carotid plaques, or coronary artery calcium. These authors concluded that HIV infection and PI therapy are not strong independent risk fac-

tors for subclinical atherosclerosis, and that confounding may contribute to over-estimation of the risk associated with HIV seropositivity and PI exposure[56].

In conclusion, the real impact of HIV infection and antiretroviral therapy on the development of subclinical atherosclerosis is still incompletely understood, even though most studies seem demonstrate in this population premature atherosclerosis and increased intima-media thickness. Similarly, the full clinical implications of surrogate markers of premature vascular lesions (including biochemical factors and vascular imaging findings), have not been completely evaluated. The contradictory findings in existing research are likely related to different study designs or populations, limitations of observational methods to control confounding factors, limited follow-up periods, different methods of atherosclerosis evaluation, and frequent absence of HIV-seronegative controls.

The most important reports evaluating the association of HIV infection and PIs with accelerated atherosclerosis are summarized in **Table 2**.

Table 2. Cross-sectional and prospective studies evaluating the association of premature atherosclerosis with HIV infection, antiretroviral therapy, and traditional risk factors

Authors, years [references]	Type of study	Outcome	N. of HIV-positive patients	N. of HIV-negative patients	Association with HIV infection	Association with PIs	Traditional risk factors associated with premature atherosclerosis
Lai, 2003 [34]	P	CAC	98	-	-	Yes	Total and LDL cholesterol
Maggi, 2004 [11, 35]	CS	CIMT	293	-	-	Yes	Age, smoking, CD4 cell count
Jericò, 2006 [12]	CS	CIMT	132	-	-	Yes	Age, hypertension, hyperlipidaemia
De Saint Martin, 2006 [39]	CS	CIMT	154	-	-	Yes	Age, hypertension, triglycerides
Lorenz, 2008 [40]	CS	CIMT	292	1168	Yes	Yes	Age, body mass index, smoking, hypertension
Kingsley, 2008 [42]	CS	CAC	615	332	Yes	Yes (HAART)	Age, smoking, race, family history, insulin resistance, hyperlipidaemia
Sankatsing, 2009 [43]	CS	CIMT	130	-	-	Yes	Framingham risk, body mass index, HDL cholesterol
van Vonderen, 2009 [44]	CS	CIMT	77	52	Yes	No	Age, smoking, hyperlipidaemia
Depairon 2001 [46]	CS	CIMT	168	68	Yes	No	Smoking, hyperlipidaemia
Talwani, 2002 [47]	CS	CAC	60	180	No	No	Smoking
Hsue, 2004 [48]	CS	IMT	148	63	Yes	No	Age, smoking, hypertension, race, LDL cholesterol, low CD4 cell count
Mercié, 2005 [49]	P	CIMT	346	-	-	No	Age, sex, smoking
Currier, 2005 [50]	P	CIMT	88	44	No	No	Age, body mass index, triglycerides, HDL cholesterol
Mangili, 2006 [51]	CS	CIMT	327	-	-	No	Age, body mass index, hypertension, high C-reactive protein
Lebech, 2007 [52]	CS	CIMT	25	14	No	No	HDL cholesterol
Bongiovanni, 2008 [53]	P	CIMT	186	54	No	No	Age, body mass index, triglycerides, glucose, high homocysteine
Kaplan, 2008 [54]	P	CIMT	1931	859	No	No	Age, smoking, hyperlipidaemia, low CD4 cell count
Hsue, 2009 [55]	CS	CIMT	401	93	Yes	Yes	Age, smoking, LDL cholesterol, triglycerides, lipid lowering therapy, glucose, hypertension, high C-reactive protein

HIV, human immunodeficiency virus; PIs, protease inhibitors; P, prospective; CS, cross-sectional; CAC, coronary artery calcification; CIMT, carotid intima media thickness; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HAART, highly active antiretroviral therapy.

The role of hiv infection

Recent data support the hypothesis that both HIV infection and antiretroviral treatment promote atherosclerosis and its clinical manifestations through inflammatory mechanisms involving arterial wall and endothelial cells, either directly or indirectly, also by the metabolic alterations they induce[57,58].

During the last decades, inflammation was demonstrated to play a major role during all stages of atherosclerosis, and the incidence of cardiovascular diseases was found to be increased in patients with chronic inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's disease, and vasculitis[59,60]. In general, activation of leucocytes and increased concentrations of cytokines and other inflammatory mediators associated with exacerbations of inflammatory disorders may produce detrimental effects on the arterial wall. Particularly, atherogenic effects of a systemic inflammation can manifest at three different levels: (1) endothelial dysfunction; (2) secondary dyslipidaemia; (3) activation of the coagulation cascade[60].

If an inflammation systemic state participates pivotally in all stages of atherosclerosis, from fatty streak formation up to plaque progression and destabilization, soluble biological markers of inflammation should provide independent diagnostic and prognostic value by reflecting and underlying the disease state. Recent studies suggest that several inflammatory biomarkers such as C-reactive protein (CRP), fibrinogen, secretory phospholipase A2, interleukin (IL)-1, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), soluble CD40 ligand, E-selectin, P-selectin, matrix metalloproteinases (MMPs), myeloperoxidase (MPO), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1) may have a potential role for the prediction of risk for developing coronary artery disease and may correlate with severity and mortality of atherosclerotic disease, also in HIV-positive subjects[61-63]. Although the circulating concentration of these inflammatory biomarkers usually correlate with increased cardiovascular risk in general population, few are ready for clinical practice with the exception of CRP, which strongly and independently predicts adverse cardiovascular events[64].

In conjunction with the above-mentioned general effects of systemic inflammation, there are additional pathologic mechanisms anchored within the pathophysiology of individual inflammatory diseases that are specific to that particular disorder, such as HIV infection. Numerous mechanism exist as to how HIV can directly damage endothelium, which is continuosly exposed to a number of viral-induced trigger, including HIV-infected cells, freely circulating HIV virions, HIV proteins released upon host cell lysis, actively secreted viral proteins, and viral-induced proinflammatory cytokines.

Endothelial cells have been shown to be variably permissive for HIV infection. HIV itself is able to penetrate coronary artery and brain microvascular endothelial cell membrane, and to initiate inflammatory and biochemical intracellular reactions. Endothelial activation may also occur either by cytokines secreted in response to mononuclear or adventitial cell activation by HIV virus, or by the effects of gp120 and Tat, two secretory HIV-associated proteins[65,66].

The activation of endothelium induced by either HIV infection itself or by a leucocyte-mediated inflammatory cascade triggered by the same virus leads to the increased expression of endothelial cellular adhesion molecules, such as ICAM-1, VCAM-1, E-selectin, P-selectin, thrombomodulin, tissue plasminogen activator (tPA), and plasminogen activator inhibitor 1 (PAI-1)[67,68].

HIV-infected antiretroviral-naïve patients display markers of endothelial activation. Increased serum levels of ICAM-1, VCAM-1, E-selectin, von Willebrand factor, PAI-1, and thrombomodulin were demonstrated in patients with advanced HIV infection and opportunistic diseases, and higher levels of these markers were found in these patients compared with healthy controls. Moreover, soluble markers of endothelial dysfunction positively correlate with anti-p24 antibody levels, reduction of CD4 lymphocyte count, and disease severity[69-71]. This up-regulation of cell adhesion and endothelial activation molecules in HIV-positive patients naïve to antiretroviral treatment suggests that the virus activates and dysregulates endothelial cells.

Experimental evidence show that HIV-1 proteins affect the endothelium in both specific and overlapping ways. Tat protein is the principal transactivator for HIV-1 replication, is actively secreted by infected cells, and is probably involved in HIV-induced endothelial dysfunction. Low concentrations of Tat protein significantly impair endothelium-dependent vasorelaxation in isolated pig coronary arteries without affecting smooth muscle cell function[72]. In vitro and in vivo studies have shown that endothelial cells of diverse origin (umbilical vein, pulmonary artery, aorta, and brain) release MCP-1 and induce expression of VCAM-1 in response to Tat[73,74]. Finally, Tat interacts with three known receptors to gain access to endothelium: the integrins $\alpha_5\beta_3$ and $\alpha_5\beta_1$ through Tat's Arg-Gly-Asp (RGD) motif, and the vascular endothelial growth factor receptor-2 (VEGFR-2) through Tat's basic domain. Activation of these receptors initiates endothelial signal transduction cascades regulating several processes such as cytoskeletal dynamics, endothelial permeability, MMP activation, chemotaxis, and apoptosis. Particularly, Tat-mediated activation of p21-activated kinase-1 (PAK-1) increases endothelial oxidative stress through NADPH oxidase activation and through decreased antioxidant capacity[75].

Similarly to Tat, gp120 glycoprotein induces the expression of ICAM-1 in human coronary artery, lung, brain, umbilical vein, and dermal microvascular endothelial cells, and significantly increases the adhesion of monocytes and lymphocytes to the endothelium[76,77]. Furthermore, gp120 promotes apoptosis in human coronary endothelial cells, and negatively affects endothelial function through the production of potent vasoconstrictors, such as endothelin-1. Like Tat, reactive oxygen species (ROS) have also implicated in gp120-induced toxicity of endothelium, and

the molecular mechanism by which gp120 exerts its endothelial damage may involve protein kinase C and p38 mitogen-activated protein kinase signaling[78-80]. Moreover, recent data show that gp120 activates signal transducers and activators of transcription (STAT) pathway, and induces IL-6 and IL-8 secretion in human brain microvascular endothelial cells[81].

The effects of other HIV-1 accessory proteins on endothelial cell biology, are considerably less well-known. In vitro data suggest that Nef alters vascular homeostasis by affecting endothelial cells and macrophages through distinct pathways. Enhanced Nef-mediated macrophage activation and superoxide generation may contribute to vascular dysfunction, but Nef probably plays an additional role by altering cholesterol metabolism. In particular, Nef increases cholesterol biosynthesis, binds to newly created cholesterol in order to enrich lipid rafts at the plasma membrane, and favours the macrophage transformation into a lipid-loaded foam cell[82,83]. Vpu seems up-regulate the tumor necrosis factor receptor family molecule CD40, inducing VCAM-1 expression and adhesion of B-lymphoma cells to the endothelium[84].

Endothelial dysfunction is also associated with an increase in oxidative stress, and ROS play an important role in dysregulating the endothelium by oxidatively damaging cellular macromolecules, inactivating enzymatic systems, and altering transcription factor activation[85]. Multiple cell types of arterial wall may produce ROS, including activated macrophages, T lymphocytes, vascular smooth muscle cells, and endothelial cells. HIV infection is associated with increased free radical production and chronic oxidative stress, suggesting a role for ROS in HIV-induced endothelial damage. In fact, elevated ROS levels have also been reported in peripheral blood monocytes from HIV-infected subjects, and antioxidant restoration via dietary supplements improves cardiovascular health in HIV-positive patients[86,87].

The HIV-induced endothelial dysfunction is clinically demonstrated by some studies assessing the flow-mediated dilatation (FMD) of the brachial artery, which is often used as an indicator of endothelial function in humans. Blum et al. evaluated brachial artery diameter in 24 HIV-positive subjects and found that HIV viral load correlated inversely with endothelial function[88]. Similarly, in a cross-sectional analysis including 75 HIV-infected patients compared with 223 HIV-negative controls, a significant association between reduced brachial artery FMD and HIV viremia was found, particularly among injection drug users[89]. In conclusion, in these reports HIV-positive, HAART naïve individuals have significant impairment of endothelial function when compared with HIV-negative controls.

The role of antiretroviral therapy

The ability of HAART to accelerate atherosclerosis and increase cardiovascular risk in HIV-positive subjects has been controversial in that some studies have found an association and other studies have not found an association. Numerous mechanism exist as to how antiretroviral treatment can protect or damage the vascular endothelium, as showed by experimental and clinical data, and the global effect is still unknown.

The remarkable decrease in viral replication and plasma HIV viral load induced by combination antiretroviral therapy should improve T-cell function and reduce the HIV-associated endothelial dysfunction. In fact, several authors have reported a significant decrease in serum concentrations of VCAM-1 and ICAM-1 after the first months of HAART, suggesting that the reported reversion of endothelial activation is mediated by control of viral replication obtained by potent antiretroviral treatment[89,90]. Similarly, the SMART study showed that the risks for all-cause mortality (including mortality for cardiovascular diseases) were higher in participants randomized to treatment interruption than in those who received continuous antiretroviral therapy[29].

However, HAART may also indirectly or directly induce endothelial dysfunction. It has early been assumed that use of several antiretroviral agents (mostly PIs, stavudine, efavirenz) favours the occurrence of multiple metabolic and morphologic abnormalities, including dyslipidaemia, insulin resistance, diabetes mellitus, subcutaneous fat loss, visceral fat accumulation, and metabolic syndrome, which are associated with an increased risk of premature atherosclerosis and myocardial infarction. Lipid abnormalities occur early in HIV infection, with reduction in HDL and LDL cholesterol and increase in triglycerides, but they became very common after the introduction of PI-based combination therapy[91,92].

PI-related dyslipidaemia has been attributed to inhibition of lipid metabolism and adipocyte regulatory proteins that have partial homology to the catalytic site of HIV-1 protease, to which PIs bind. These regulatory proteins include the cytoplasmic retinoic acid-binding protein type 1 (CRABP-1), which is critical for maturation and proliferation of adipocytes, and the LDL-receptor related protein (LRP), an hepatic cell receptor which cleaves fatty acids from circulating triglycerides[93,94]. Several other pathogenetic mechanisms have been described: PIs could inhibit proteasomal degradation of nascent apolipoprotein B (the main protein component of triglycerides and cholesterol rich plasma lipoproteins), promote intracellular accumulation of cholesterol in macrophages, induce foam cell formation by an upregulation of CD36 in peripheral blood mononuclear cells, and alter the function of pre-existing adipocytes leading to hypertriglyceridaemia[91,95,96]. Human studies have suggested that PIs may decrease the function of lipoprotein lipase and reduce the clearance of very low density lipoprotein (VLDL)-triglycerides from plasma, preventing the generation of new adipocytes, and severely limiting the function of existing adipocytes[97].

The PI-induced metabolic disturbances may also are associated with a reduced secretion of adiponectin. Adiponectin is an anti-diabetic and anti-inflammatory protein producted in adipose tissue, and its levels decrease in association with insulin resistance, obesity, and increased expression of endothelial adhesion molecules in the general population. Preliminary data suggest that reduced

adiponectin concentrations may increase the risk of coronary heart disease, event though this relationship has not been yet evaluated in HIV-positive subjects[98]. Recently, studies use 3T3-F442A cells and mice have found that HIV protease inhibitors decrease adiponectin mRNA levels and secretions[99].

Although several clinical studies have established that HAART promote endothelial dysfunction indirectly by inducing lipid and glucose metabolism alterations, data obtained from experimental investigations on animal models have also proved a direct effect of HAART on endothelial cells and function.

The molecular mechanism of PI damage in endothelium has been described in detail, and many in vivo and in vitro experiments suggest an oxidative stress in PI-related endothelial dysfunction. In fact, PIs reduce the excretion of urinary nitrate, a stable degradation product of nitric oxide, and decrease the expression of endothelial nitric oxide synthase. In addition to decrease in nitric oxide production and impairment in endothelium-dependent vasodilatation capacity, PIs have been reported to increase superoxide production and subsequently oxidative stress. Moreover, PIs decrease mitochondrial membrane potential, increase mitochondrial production of ROS, increase endothelial cell permeability, and favour leukocyte adhesion in cell culture models[75,97,100].

Clinical evidence for NRTI-induced vascular toxicity is difficult to assess because NRTIs are not prescribed as monotherapy. In vitro studies showing a direct endothelial toxicity related to NRTIs are not numerous, but some experimental evidences support a direct role for this class in endothelial dysfunction. In general, mitochondrial toxicity caused by nucleoside analogues is responsible for abnormal oxidative phosphorylation, aberrant cellular respiration, and cellular toxicity also in endothelium[75]. Particularly, aortas from mice treated with zidovudine have a significant reduction in maximum endothelial-dependent relaxation, as well as a remarkable decrease in acetylcholine sensitivity. Most recent studies show that zidovudine increases aortic endothelium superoxide levels in animal models, implicating ROS in NRTI-related endothelial dysfunction[101,102].

The recent association of the use of the nucleoside analogue abacavir with an increased risk of myocardial infarction was investigated in several studies, in order to find plausible pathogenetic mechanisms. In the SMART study, serum high sensitivity CRP and IL-6 levels were significantly higher for patients receiving abacavir, and a direct role of this drug in vascular inflammation was suggested[32]. Similar results were found in a cohort study including 61 antiretroviral-treated patients with undetectable HIV RNA, which showed a significant lower flow-mediated dilatation of the brachial artery in abacavir-treated subjects, associated with an impaired endothelial function[103]. Abacavir has been shown to induce cardiomyopathy in mice and rats, and it is metabolised intracellularly to carbovir, which has the potential to be cytotoxic[31,104]. However, serum levels of inflammatory markers (such as TNF-α, IL-6, IL-8, and MCP-1), did not significantly increase in 41 HIV-infected patients after 1 year of abacavir-based therapy[105], and the biological mechanism of possible endothelial damage associated with abacavir is still unknown.

Finally, a possible contribution of cell-mediated immune responses to the pathogenesis of the atherosclerosis associated with HIV infection was also supposed. Post-ischaemic flow-mediated dilatation of the brachial artery was found to be significantly associated with percentage of "naïve" CD4+ 45RA+ T cells, while plasma lipid and insulin concentrations did not correlate with endothelial function among 48 patients assessed by Nolan et al.[106]. On the other hand, increased carotid intima-media thickness was associated with depletion of circulating myeloid dendritic cells in 36 HIV-positive subjects on suppressive HAART[107].

To conclude, antiretroviral therapy should reduce the endothelial damage by controlling HIV infection, but it would also induce endothelial dysfunction by a direct effect or by deranging both lipid and glucose metabolism. Further enlarged studies are certainly needed in order to better define this complex interaction between antiretroviral drugs and endothelium.

Screening and assessment of cardiovascular risk

With an increase in cardiovascular disease rates and aging of HIV-infected patients, screening and appropriate assessment of cardiovascular risk in this population assumes increasing importance. A founding element of preventing cardiovascular diseases is that the intensity of risk-reducing interventions should be based on the level of cardiovascular risk. Patients with established cardiovascular disease or high cardiovascular risk qualify for the most aggressive risk factor management, with special focus on strategies able to prevent myocardial infarction and death.

Insufficient data currently exist to recommend a screening strategy different from that for HIV-negative subjects, but currently available cardiovascular risk prediction equations were not developed and approved in HIV-positive adults and children. In the general population, presently available prediction models of coronary heart disease risk were derived from the Framingham Heart Study and estimate the risk for an initial coronary event in a population of middle-aged adults with minimal coronary heart disease risk at the beginning of the observation period[108,109].

To date, the estimates of the relative effects of traditional risk factors on cardiovascular outcomes appear similar between HIV- and non-HIV-infected individuals, and the Framingham coronary heart disease risk predictions have performed reasonably satisfactory when applied to HIV-positive population. However, specific cardiovascular risk factors were found in HIV-infected subjects, and the above-mentioned equations may not provide suitable predictions for young people living with HIV infection[110]. Particularly, HIV and antiretroviral therapy may directly and indirectly promote endothelial dysfunction, as discussed above, in association with metabolic disturbances and adipose tissue redistribution. Moreover, HIV-positive persons are different in terms of both demographic characteristics (younger and more racially diverse) and prevalence of

substance abuse (mostly tobacco and recreational drugs). At the same time, other medications, lifestyle/behavioural choices (diet, physical inactivity, alcoholism and substance abuse) may deeply affect the global cardiovascular risk in this population.

The Framingham risk equation includes age, sex, blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus, and cigarette smoking to calculate a 10-year coronary heart disease risk[108]. This algorithm has been applied to HIV-infected people and investigated in the DAD study and has been shown to perform reasonably well, although it somewhat underestimates cardiovascular risk[111].

New HIV-specific algorithms for prediction of coronary heart disease risk have recently proposed by the DAD investigators. The DAD-derived HIV-specific prediction models incorporated traditional risk factors (such as age, blood pressure, lipid profile, diabetes mellitus and smoking) associated with exposure to antiretroviral agents, and captured cardiovascular events as the dependent variable[112-114]. The Framingham equation predicted remarkably well the risk, but tended to underestimate coronary events in HIV-positive smokers and overestimate cardiovascular risk in non-smokers. Moreover, predicted rates of myocardial infarction increased in a parallel fashion with increased duration of combination antiretroviral therapy, suggesting that the observed increase in cardiovascular risk may at least in part be explained by HAART-induced changes in traditional risk factors[112]. Further external validation of the DAD prediction algorithm is warranted to assess whether it is applicable to people living with HIV infection. Larger, multicenter, prospective study including both traditional and HIV-specific risk factors are consequently needed in order to determine the optimal specific algorithm to predict coronary heart disease risk in HIV-positive population.

All HIV-infected patients should be carefully evaluated at their first clinical visit for categorical risk factors for coronary events that are summarized in **Table 3**. Laboratory parameters for identifying alterations in lipid and glucose metabolism should include total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glycaemia (obtained after a minimun of eight hours of fasting). The lipid and glucose panel should be repeated every 3-4 months if patients are assuming stable antiretroviral treatment, or annually if patients are not being treated and have normal lipid and glucose values. For subjects with serum triglyceride levels >200 mg/dL, the measurement of serum lipid profile should be repeated within 1-2 months after starting antiretroviral therapy. Risk factors more specific to HIV-positive patients should also be collected, including lifestyle (alcoholism, cocaine, and other psychotropic substances), drugs interfering with glucose and lipid metabolism (such as growth hormone, estrogens, corticosteroids, thyroid hormones), body mass index, abdominal circumference, duration and type of HAART, HIV viral load, nadir and CD4 lymphocyte count, and chronic hepatitis C[115-117].

Table 3. Categorical risk factors for coronary heart disease that determine the 10-year risk of myocardial infarction and the target levels of LDL cholesterol

Risk factors	Definition
Age	≥45 years for men ≥55 years for women
Family history of premature CHD	Male first-degree relative <55 years old or female first-degree relative <65 years old
Arterial hypertension	Blood pressure ≥140/90 mmHg, or receipt of antihypertensive treatment
Cigarette smoking	-
Low HDL cholesterol*	<40 mg/dL

CHD, coronary heart disease
* An elevated HDL cholesterol concentration (≥60 mg/dL) is considered a "negative" risk factor and, if present, it subtracts one factor from the above-mentioned risk factor total.

It is useful for an electrocardiogram to be performed at the beginning of HAART, while in patients with several cardiovascular risk factors or established cardiovascular disease a periodic electrocardiogram, an echocardiography, and a doppler-echographical examination of supra-aortic vascular trunk are advisable. In patients with basal glycaemia on an empty stomach above 100 mg/dL, insulinemia, HOMA test calculation, and oral glucose tolerance test (OGTT) should be performed[117].

The number of categorical risk factors for coronary heart disease determines the target level of LDL cholesterol and the aggressiveness of lipid-lowering treatment. The patient's absolute 10-year risk of myocardial infarction or cardiac death should be calculated using the Framingham risk factor calculator, which can be found at http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm[118,119]. High-risk patients are subjects with established coronary heart disease or those with a coronary risk "equivalent", such as cerebrovascular disease, peripheral vascular disease, diabetes mellitus, or two or more risk factors that predict a 10-year risk of myocardial infarction or cardiac death >20%. Moderate-risk patients are those with two or more risk factors but a 10-year risk ≤20%. Finally, low-risk patients are those with 0 or 1 risk factor for coronary heart disease.

Finally, newer inflammatory biomarkers, such as high-sensitivity C-reactive protein (HS-CRP) and adiponectin, may proved useful also for identifying HIV-infected patients at risk for coronary heart disease, but to date the specificity of such markers for the assessment of coronary risk in HIV-positive subjects remains unclear. Although the Prevention/American Heart Association guidelines recommend measuring of HS-CRP in HIV-negative patients at intermediate risk for cardiovascular diseases, this strategy requires validation in HIV-positive population in whom C-reactive protein levels are frequently increased. Similarly, long-term data on the clinical significance of reduced adiponectin level in HIV-positive subjects with fat redistribution syndrome are not available. Other surrogate markers for coronary heart disease, including intimal-medial thickness, computed tomographic angiography, and coronary

artery calcification have been investigated but not validated as independent predictors of coronary heart disease outcomes in HIV-infected population[92]. Future researches are certainly needed in order to determine the optimal screening strategy and risk stratification algorithm for HIV-positive individuals, and to define sensitivity and specificity of new diagnostic tests for coronary disease, including inflammatory and surrogate markers.

Prevention strategies to reduce cardiovascular risk

As with HIV-negative persons, the most important principle to prevent cardiovascular diseases in HIV-positive population is that risk-reducing strategies should be based on the level of coronary heart disease risk and whether the presence of cardiovascular diseases has been established.

HIV-infected patients clearly have a significant risk of atherosclerosis given their underlying traditional risk factors. Early intervention to reduce these risks is recommended in all HIV-infected patients and include smoking cessation, blood pressure management, weight loss, and correction of lipid and glucose metabolism abnormalities.

Prevalence of cigarette smoking is great among HIV-positive patients, ranging from 47% to 71%, and higher than in general population. Aside from a diagnosis of cardiovascular disease, current cigarette smoking is the most powerful predictor of cardiovascular events among individuals with HIV infection, and a significant reduction in cardiovascular risk and total mortality associated with smoking cessation has been demonstrated in non-HIV population. Preventing HIV-positive individuals (particularly educating teenagers) from starting smoking is critical, because stopping smoking remains a very difficult challenge[120].

Arterial hypertension is also a powerful predictor for cardiovascular events in general population. The best evidence suggests that HAART may be associated with a modest increase in blood pressure and prevalence of hypertension, that has not been established with certainty among HIV-positive patients, but usually ranges from 12% to 20% among individuals <40 years old and from 35% to 41% among those ≥40 years old[121,122]. Among HIV-negative patients, dietary interventions are effective for reducing blood pressure, and one study showed also that HIV-positive patients who completed an intensive lifestyle intervention that included dietary changes and regular physical activity experienced a significant reduction in blood pressure values. Drug therapy for hypertension significantly decreases cardiovascular risk in general population, but specific researches are needed in order to evaluate pharmacodinamic interactions between commonly used antihypertensive agents and antiretroviral drugs, owing to the overlap in metabolic pathways affected by antiretroviral agents (mostly PIs and NNRTIs) and certain antihypertensive drugs[123].

The Infectious Disease Society of America (IDSA) and Adult AIDS Clinical Trials Group (AACTG) have updated specific guidelines for evaluation and management of HAART-related hyperlipidaemia[116]. These recommendations are based on those provided by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, which adjust the intensity of risk reduction therapy to the patient's risk of developing an acute coronary event[118,119].

Except for subjects with triglycerides >500 mg/dL, in whom the primary goal is to reduce triglyceride concentration and prevent pancreatitis, the primary target is reduction of LDL cholesterol levels. Lipid goals and cutoffs for lifestyle modification and drug therapy are summarized in **Table 4**. When patients have triglycerides >200 mg/dL, the cholesterol content of triglyceride-rich lipoproteins is increased and the estimated LDL-cholesterol underestimates the number of atherogenic particles. In this case, non-HDL cholesterol (calculated as total cholesterol minus HDL cholesterol) becomes the secondary target of medical intervention; the non-HDL cholesterol goals are simply the LDL cholesterol goals plus 30 mg/dL. It is very important to consider the non-HDL cholesterol concentration or its mathematical equivalent (the total cholesterol/HDL cholesterol ratio) when assessing hyperlipidaemia in HIV-infected patients, because such individuals frequently have hypertriglyceridaemia or mixed hyperlipidaemia, and the LDL cholesterol concentrations usually underestimate the overall atherogenic lipoprotein burden[116-119].

Table 4. ATP III LDL-cholesterol goals and cutpoints for therapeutic lifestyle changes and lipid-lowering therapy in different risk categories [118, 119].

Risk category	LDL-C goal	Initiate TLC	Consider drug therapy
High risk: CHD or CHD equivalents[1] (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL
Moderately high risk: ≥2 risk factors[2] (10-year risk 10% to 20%)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
Moderate risk: ≥2 risk factors[2] (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Low risk: 0-1 risk factor[2]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL

LDL-C, low-density lipoprotein cholesterol; TLC, therapeutic lifestyle changes; CHD, coronary heart disease.
(1)CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia; CHD equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease, diabetes, and 2 or more risk factors with 10-year risk for hard CHD >20%.
(2)Risk factors include: cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein (HDL) cholesterol (<40 mg/dL), family history of premature CHD, and age (men ≥45 years, women ≥55 years).

Treatment of HAART-associated dyslipidaemia includes three levels of medical intervention: lifestyle changes and diet therapy, modification of current antiretroviral regimen, and lipid-lowering drugs.

Non-drug therapies should generally be instituted first and given a thorough trial before starting drug therapies. Apart from stopping smoking, patients with HIV infection and receiving antiretroviral therapy should regularly perform moderate aerobic activity for a minimum of 30 minutes five times per week, with a goal of 60 minutes, to

be carried out 5 to 7 times per week. This routine physical exercise usually improves trunk adiposity and plasma lipid parameters, and might therefore be beneficial to reduce cardiovascular disease risk. At the same time, patients who are overweight should also restrict calories to achieve their ideal body weight. Improvement of cardiovascular outcomes has been associated with substitution of non-hydrogenated unsaturated fats for saturated fats and trans-fats, increased intake of omega-3 fats from fish, fish oil, or plants, and eating a diet that is high in fruits, vegetables, nuts, and whole grains but low in refined grains. Dietary and exercise intervention resulted in a significant 11-25% decrease in total cholesterol and triglyceride levels in HIV-infected patients[116,124].

Several studies have showed that an antiretroviral regimen in which a PI is replaced with nevirapine or abacavir in patients with long-lasting viral suppression usually maintains optimal antiviral acitivity. Moreover, as compared with PIs, these agents reduce serum lipid abnormalities, offer more convenient dosing regimens, involve fewer pills, and result in fewer potentially serious drug-drug interactions, reduced side effects, and improved adherence to antiretroviral therapy. However, the rate of virological failure might eventually increase among patients who have previously received prolonged non-suppressive antiretroviral treatment, such as single or dual NRTI therapy, as a result of the re-emergence of archived viral resistance. Significant improvement in serum lipid concentrations was also reported after switching from stavudine or zidovudine to abacavir or tenofovir, or after replacing current PI with atazanavir, an azapeptide PI which is usually associated with a more favourable plasma lipid profile[125-127].

Lipid-lowering therapy becomes suitable when lifestyle modifications, dietary changes, physical activity, and switching treatment are ineffective or not applicable, and for patients with urgent need of drug intervention (such as those with coronary heart disease or equivalent, and those with extreme elevation in serum lipid levels). Drug therapy for dyslipidaemia in HIV-infected patients receiving HAART is problematic, because of potential drug interactions, toxicity, intolerance, and reduced patient adherence to multiple pharmacologic regimens.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co A) reductase inhibitors, or statins, are considered the current first-line therapy for primary hypercholesterolaemia. Most of these compounds are metabolized by the cytochrome P450 3A4 and may cause clinically relevant interactions with other agents that are changed by this enzymatic complex, such as PIs and NNRTIs. Simvastatin, lovastatin, and atorvastatin are extensively metabolized by CYP 3A4: these notable drug interactions cause elevated plasma levels of statins, leading to a significantly increased risk of liver and skeletal muscle toxicity (acute hepatitis, myopathy and rhabdomyolysis). On the other hand, fluvastatin is metabolized by CYP 2C9 and pravastatin is not significantly metabolized by the CYP enzyme system, with a very low risk of drug interactions.

Consequently, it is reasonable to recommend the use of pravastatin (20-40 mg daily starting dose) or atorvastatin (10 mg daily starting dose) as first-line treatment for hypercholesterolaemia in PI-treated patients, and the use of fluvastatin (20-40 mg starting dose), as second-line regimen. On the other hand, simvastatin and lovastatin should be avoided, because they present a great risk of pharmacological interactions with PIs[128,129].

Rosuvastatin is a new HMG-Co A reductase inhibitor that showed the highest dose-to-dose potency in lowering total and LDL cholesterol levels, compared with other currently available statins. Moreover, pharmacokinetic studies have demonstrated that its metabolism is not dependent on the cytochrome P450 3A4 isoenzyme, and its use could be considered in PI-treated individuals as a result of the low risk of drug-drug interactions[130]. In a small, observational, pilot study involving 16 HAART-treated patients with hypercholesterolaemia, a 24-week treatment with 10 mg daily of rosuvastatin reduced significantly total cholesterol and triglyceride levels and was associated with a favourable tolerability profile[131].

However, recent results showed a significant increase in rosuvastatin plasma levels in HIV-negative and HIV-positive subjects who are being treated with lopinavir/ritonavir, while the PI levels were not affected by the lipid-lowering drug. Therefore, the combination of rosuvastatin and lopinavir-ritonavir should be used with caution (at the lowest dosage of rosuvastatin) until safety and efficacy of this treatment have been confirmed in further studies[132,133].

Fibrates represent the cornerstone of drug therapy for hypertriglyceridaemia and mixed hyperlipidaemia. These compounds are also metabolized by hepatic cytochrome P450 enzymes, but they appear to primarly affect only CYP 4A, and do not show clinically rilevant interactions with PIs. However, concomitant use of both fibrates and statins can increase the risk of skeletal muscle toxicity and should be avoided. Treatment with gemfibrozil (600 mg twice daily), bezafibrate (400 mg daily), or fenofibrate (200 mg daily), generally results in a significant reduction in serum triglyceride and cholesterol levels in HIV-infected patients receiving a PI-containing therapy, with a more evident improvement of hypertriglyceridaemia[133,134].

Second-line lipid-lowering agents include fish oils in patients with hypertriglyceridaemia, ezetimibe in those with increased LDL-cholesterol levels, and niacin in those with mixed hyperlipidaemia. However, these compounds have not yet been studied in detail in HIV infected patients. Moreover, niacin and ezetimibe require monitoring of hepatic transaminases, and niacin may be associated with hyperglycaemia, hyperuraemia, and skin rash[116]. Recommendations for choice of initial drug therapy for dyslipidaemia are listed in **Table 5**.

Prevalence of impaired fasting glucose (defined as fasting blood glucose > 100 mg/dL), and impaired glucose tolerance (defined as a 2-hour glucose >140 mg/dL after a 75-g glucose load), is increased in patients with HIV infection and higher in those exposed to HAART[135,136]. The initial management approach for the HAART-related hyperglycaemia includes increased physical exercise and dietary

therapy. If diet and physical activity fail to achieve the desired level of glucose (defined by fasting glucose concentrations <126 mg/dL or random levels <200 mg/dL) after eight weeks, patient should be sent to a diabetes specialist and pharmacologic therapy should be considered.

Table 5. Recommendations for choice of initial pharmacologic treatment for hyperlipidaemia in HIV-infected patients receiving HAART

Lipid alterations	First choice therapy (rating)	Alternatives (rating)
Elevated LDL cholesterol or elevated non-HDL cholesterol with triglyceride level of 200-500 mg/dL	Statin (B1): - pravastatin, 20-40 mg daily - atorvastatin, 10 mg daily - fluvastatin, 20-40 mg daily	Fibrate (C1) or niacin (C3)
Triglyceride level > 500 mg/dL	Fibrate (B1): - gemfibrozil, 1200 mg daily - fenofibrate, 200 mg daily - bezafibrate, 400 mg daily	Niacin (C3) or fish oils (C3)

Ratings:
- strength of recommendation: B, moderate evidence to support a recommendation; C, poor evidence to support a recommendation;
- quality of evidence: 1, evidence from ≥1 properly randomized controlled trials; 2, evidence from ≥1 well-designed clinical trials without randomization, case-controlled analytic studies, or multiple case-series; 3, evidence from opinion of respected authorities [116].

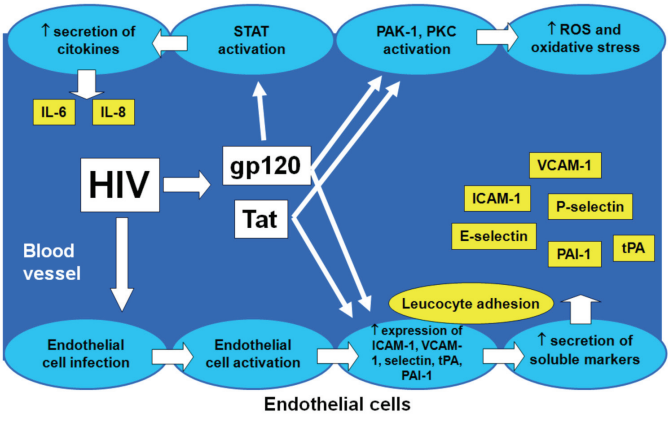
Since alterations in glucose metabolism associated with HAART resemble those seen in type 2 diabetes mellitus, drug therapy in HIV-positive patients with hyperglycaemia should be that recommended for type 2 diabetes and started with an oral hypoglycaemic agent, which may reduce glycaemia and improve insulin sensitivity. However, there are very few data about efficacy and safety of these medications in HIV-positive patients, but the insulin-sensitizing compounds seem to be preferable because they can ameliorate insulin resistance and visceral fat accumulation.

Metformin was generally well tolerated and only mild gastrointestinal adverse effects were rarely observed. Since this biguanide is not metabolized by the liver, there are no risks of drug interactions with PIs, but it should be employed with caution in patients receiving NRTIs, because of the increased risk of mitochondrial toxicity and lactic acidosis. However, at least over three months, metformin did not result in any increase of transaminase or lactic acid levels in recent trials[137,138], even though metformin may seriously enhance the risk of lipoatrophy in such patients[139].

The insulin-sensitizing compounds thiazolidinediones have been shown to improve insulin sensitivity and hyperglycaemia in patients with type 2 diabetes, and also promote adipocyte differentiation in vitro. They have obtained promising results because of their potential to ameliorate insulin resistance, decrease visceral adiposity, and increase subcutaneous adipose tissue. On the other hand, in a recent randomized, placebo-controlled trial, rosiglitazone did not produce significant changes in body fat composition, although seemed to ameliorate insulin resistance and decrease live fat content[140,141]. However, rosiglitazone appeared to have some detrimental effects on lipid profiles[129]. The major cytochrome P450 3A4 isoenzymes are involved in the hepatic metabolism of pioglitazone, which is associated with the risk of potential drug interactions with other drugs metabolized by CYP 3A4 (such as PIs). Rosiglitazone, in contrast, is mostly metabolized by CYP 2C8 and presents lower risks of drug-drug interactions. However, little is known about its pharmacological interactions with antiretroviral drugs, and treatment with 4 mg daily of rosiglitazone has been associated with a reduced bioavailability of nevirapine[142].

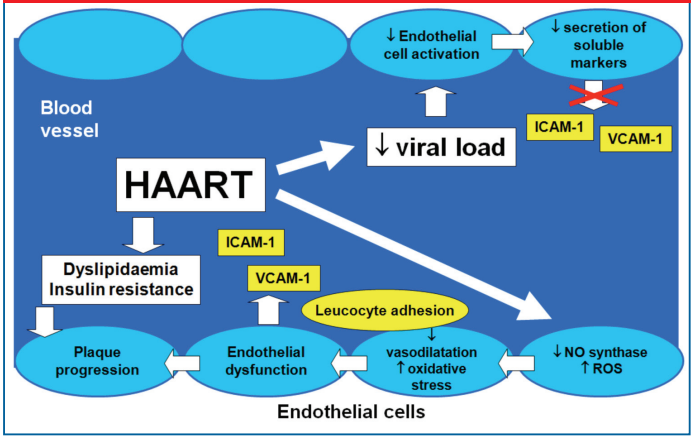
If fasting plasma glucose level of <126 mg/dL are not achieved with oral antidiabetic monotherapy, oral combination treatment consisting of a sulfonylurea with metformin or rosiglitazone should be considered. Finally, in subjects who are severly hyperglycaemic at baseline (fasting glycaemia >300 mg/dL), or who are symptomatic, insulin therapy alone or in combination with an oral hypoglycaemic agent (such as metformin or rosiglitazone) should be prescribed[143].

Figure 1



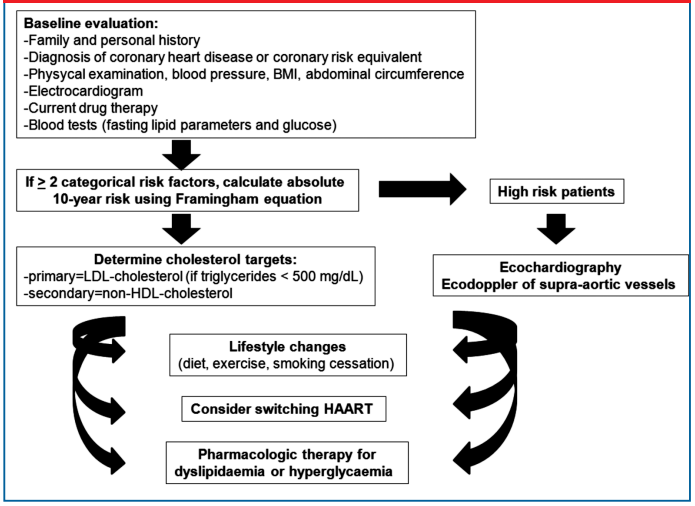
Hypothetic pathogenetic mechanisms of HIV-induced endothelial dysfunction which may lead to inflammatory alterations of endothelium and premature atherosclerosis (IL-6, interleukin-6; IL-8, interleukin-8; STAT, signal transducers and activators of transcription; PAK-1, p21-activated kinase-1; PKC, protein kinase C; ROS, reactive oxygen species; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1).

Figure 2



Possible protective and detrimental effects of antiretroviral therapy on endothelial cells (HAART, highly active antiretroviral therapy; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; NO, nitric oxide; ROS, reactive oxygen species).

Figure 3



Screening and treatment algorithm to assess and reduce cardiovascular risk in HIV-infected patients (BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; HAART, highly active antiretroviral therapy).

Conclusions

The use of combination antiretroviral therapy has converted HIV infection into a chronic disease, leading to the progressive occurrence of several comorbidities, such as atherosclerosis and coronary heart disese. Atherosclerosis in HIV-positive subjects is clearly multifactorial in origin, and ensues from traditional cardiac risk factors, HIV itself, and antiretroviral therapy. However, the absolute risk of cardiovascular events among HIV-infected subjects remains low and must be balanced against the remarkable benefits from HAART in terms of improvement in immune function and related morbidity and mortality.

Nonetheless, as HIV-infected patients live longer on new potent antiretroviral combinations, cardiovascular events could become increasingly frequent and cardiovascular risk evaluation should be performed regularly in these subjects, especially after initiation or change of antiretroviral regimen.

Lifestyle modification strategies (including cigarette smoking cessation, dietary changes, and regular exercise), should be rigorously encouraged, obtaining frequently a significant improvement in lipid and glucose metabolism abnormalities and reducing cardiovascular disease risk. Moreover, the choice of antiretroviral agents with a less detrimental effect on lipid and glucose profile should be considered in subjects with cardiovascular risk factors.. Pharmacological treatment of dyslipidaemia (usually with statins or fibrates) and diabetes (with biguanides or thiazolidinediones), becomes mandatory when lifestyle changes and switching therapy are ineffective or not applicable, and when increases in lipid and glucose concentrations are severe or persist for a long time. However, preliminary guidelines regarding pharmacological therapy of metabolic alterations associated with HAART can be made from a limited number of studies. Moreover, the benefit of aggressive management of hyperlipidaemia and diabetes must be balanced with the risk of additional medications, potential drug interactions, additional pill burden, compromise in patient adherence, and potential compromise of optimal HIV infection control.

Maintaining virological suppression should be considered still today the main concern in HIV-infected patients treated with HAART, because short-term rates of cardiovascular complications remain quite low and are significantly lower than death rates for AIDS-related conditions in subjects with virological failure and immunological impairement. However, HIV and HAART should be routinely considered among the more traditional risk factors in assessing a patient for coronary heart disease, and a more aggressive intervention to reduce cardiac risk factors in persons with HIV infection is today mandatory.

Further, enlarged, prospective studies are certainly needed in order to better evaluate the cardiovascular disease risk in HIV-positive individuals receiving HAART, and to define specific guidelines for the management of HAART-related metabolic abnormalities.

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