First Italian Consensus Statement on Diagnosis, Prevention and Treatment of Cardiovascular Complications in HIV-infected Patients in the HAART Era (2006)

G. Carosi, E. Quiros-Roldan, C. Torti, A. Antinori, M. Bevilacqua, R.C. Bonadonna, P. Bonfanti, A. Castagna, R. Cauda, A. d'Arminio-Monforte, P. Di Gregorio, G. Di Perri, R. Esposito, F. Fatuzzo, C. Gervasoni, C. Giannattasio, G. Guaraldi, A. Lazzarin, S. Lo Caputo, P. Maggi, F. Mazzotta, M. Moroni, T. Prestileo, R. Ranieri, G. Rizzardini, R. Russo, M. Galli, members of the Italian Cardiovascular Risk Guidelines Working Group

Abstract

The present document contains recommendations for assessment, prevention and treatment of cardiovascular risk for HIV-infected patients. All recommendations were graded according to the strength and quality of the evidence and were voted on by 73 members of the Italian Cardiovascular Risk Guidelines Working Group which includes both experts in HIV/AIDS care and in cardiovascular and metabolic medicine. Since antiretroviral drug exposure represents only one risk factor, continued emphasis on an integrated management is given. This should include prevention and treatment of known cardiovascular risk factors (such as dyslipidaemia, diabetes, insulin resistance, healthy diet, physical activity, avoidance of smoking), but also rational switch of antiretroviral drugs. A rational switch strategy should consider both metabolic and anthropometric disturbances and effectiveness of antiretroviral regimens.

Infection 2007; 35: 134–142
DOI 10.1007/s15010-007-6295-5

Introduction

Highly active antiretroviral therapy (HAART) allows virological, immunological and clinical control of HIV infection. Notwithstanding, several adverse events are emerging. Among them, insulin resistance, hyper-lipidaemia and blood hypertension merit attention since they may increase patients' cardiovascular (CV) risk, so as to compromise the beneficial effects of HAART on patients' morbidity and mortality [1].

In managing this problem, that part of HIV-infected patients that will present with acute myocardial infarction (IMA), *ictus cerebri* or other serious CV events in the future should be identified. Then, rational algorithms to prevent and treat cardiovascular risk should be used. With

G. Carosi *(corresponding author)*, **E. Quiros-Roldan, C. Torti**
Clinica di Malattie Infettive e Tropicali, Università degli Studi di Brescia, P.le Spedali Civili, 1, 25123 Brescia, Italy; Phone: (+39/030) 3995671, Fax: 303061, e-mail: torti.carlo@libero.it
A. Antinori
Istituto Nazionale di Malattie Infettive, Rome, Italy
M. Bevilacqua
Unità Endocrinologia Ospedale L. Sacco, Milan, Italy
R.C. Bonadonna
Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona, Verona, Italy
P. Bonfanti, G. Rizzardini
I Divisione Malattie Infettive Ospedale L. Sacco, Milan, Italy
A. Castagna, A. Lazzarin
IRCCS, S. Raffaele, Milan, Italy
R. Cauda
Clinica Malattie Infettive, Università Cattolica del Sacro Cuore, Rome, Italy
A. d'Arminio-Monforte
Clinica di Malattie Infettive e Tropicali, Azienda Ospedaliera S. Paolo, Milan, Italy
P. Di Gregorio
UO Malattie Infettive, Spedale Cannizzaro, Catania, Italy
G. Di Perri
Clinica Malattie Infettive, Università di Torino, Turin, Italy
R. Esposito, G. Guaraldi
Clinica di Malattie Infettive e Tropicali, Università di Modena, Modena, Italy
F. Fatuzzo
Medicina Specialistica AO, Universitaria Ferrarotto S. Bambino, Catania, Italy
C. Gervasoni, M. Moroni, M. Galli
Clinica di Malattie Infettive e Tropicali, Università di Milano, Milan, Italy
C. Giannattasio
Clinica Medica 9, Ospedale S. Gerardo Nuovo, Monza (Milan), Italy
S. Lo Caputo, F. Mazzotta
UO Malattie Infettive, Ospedale SM Annunziata, Florence, Italy
P. Maggi
Clinica Malattie Infettive, Policlinico di Bari, Bari, Italy
T. Prestileo
UO Malattie Infettive, Ospedale Casa del Sole, Palermo, Italy
R. Ranier, R. Russo
Clinica Malattie Infettive, Università di Catania, Catania, Italy

Members of the Italian Cardiovascular Risk Guidelines Working Group are listed in acknowledgments.

Received: October 20, 2006 • Revision accepted: February 26, 2007

Table 1
Levels of evidence and grading of recommendations.

Strength of recommendation	Quality of evidence
A – good	I – properly randomized controlled trials
B – moderate	II – other published studies
C – poor	III – expert opinion

this objective in mind, it is useful for groups of experts to assess periodically how the results of studies can be utilized in daily clinical practice for improving the identification of patients who are most at risk. A strict collaboration between clinicians in HIV care and specialists in cardiovascular or metabolic medicine is, therefore, necessary.

The objectives of the present consensus conference are as follows: (a) to review data on cardiovascular risk, its prevention and management in HIV-infected patients; (b) to derive a set of practical recommendations useful for clinicians; (c) to facilitate collaboration between specialists in metabolic diseases and cardiovascular medicine and specialists in infectious diseases who take care of HIV infected patients in Italy.

Methods

A consensus workshop of Italian HIV-treating physicians and experts in the field of metabolic and cardiovascular medicine has been held, in order to review the current knowledge, with a view to developing this consensus statement. Statements were graded for their strength and quality using a system based on the one adopted by the Infectious Diseases Society of America (IDSA), as previously explained (Table 1) [2].

Briefly, the method of a nominal group meeting was used. Six experts in the field prepared a draft of the consensus statements, grading the quality of each evidence after a careful review of the current literature and their clinical experience. Specific studies in the HIV population were privileged. However, in absence of specific studies, knowledge was derived from studies conducted in the general population.

Four main topics were addressed by the six experts: (1) Cardiovascular risk factors in HIV infections. Classification and prevention criteria; (2) HIV and cardiovascular risk factors. Clinical and laboratory monitoring; (3) impact of antiretroviral therapy on cardiovascular risk factors. Switch strategy, and interruption due to toxicity; (4) treatment of cardiovascular risk in HIV infection.

In a 2 day workshop, after two lectures held by leading experts in the field, the statements were presented, and after a plenary discussion these statements were reviewed and re-formulated by a working group of 10–15 HIV-treating physicians for each group of statements. On the second day, the revised statements were presented in a plenary session by a tutor from each group, modified if necessary after a plenary discussion, and voted by all participants using a tele-voting system. All the participants voted on their degree of agreement with the statements and the strength of the recommendation. Participants ranked their agreement on a scale of one (complete disagreement) to nine (complete agreement). Statements were accepted only when all the ranks of agreement were between seven and nine, otherwise they were re-formulated and re-voted. This report summarizes the main conclusions and recommendations from the consensus workshop.

Table 2
Parameters to be evaluated at baseline for assessment of cardiovascular (CV) risk.

Genetic	Gender, age, ethnicity, relatives affected by CV pathologies, previous cerebro-vascular diseases
Behavioral	Atherogenetic diet, physical inactivity, cigarette smoking, alcohol abuse, cocaine or psychotropic substances use, therapies with estrogen substitutes, testosterone or growth hormone
Laboratory and instrumental	Blood pressure, glycaemia, triglycerides, total cholesterol, c-HDL, c-LDL, hepatotropic viruses, nadir CD4+ T-cell count, electrocardiogram
Anthropometric and combined	Weight, height, body mass index, abdominal circumference, Framingham score

Cardiovascular Risk Factors in HIV Infections. Classification and Prevention Criteria

Introduction

This topic addresses the issue of cardiovascular risk associated with the presence of HIV infection, independently from HAART. Table 2 reports major factors for CV complications ranked into four categories (i.e., genetic, behavioral, laboratory/instrumental and, anthropometric/combined). On the one side, HIV patients are frequently exposed to behavioral risks (such as smoking, cocaine abuse, sedentary life style). On the other side, HIV by itself, or the immune disequilibrium caused by HIV, or the opportunistic infections can damage the endothelium and this can provoke or aggravate cardiovascular diseases [3]. Recent data have shown that interruption of HAART is associated with increased risk of myocardial infarction, providing one of the best evidences that HIV could indeed aggravate cardiovascular diseases (via direct or indirect mechanisms) [4].

Statement 1.1

The case histories of HIV-infected patients must include the collection of information useful for identifying those who are most at risk for CV complications. The risk factors can be ranked into those which are common to the general population and those which are more specific to the HIV-positive population, as indicated below.

Factors common to the general population include: advanced age, male gender or female gender after menopause, relatives affected by CV pathologies, diabetes, hyperlipidaemia, previous CV events, obesity, lifestyles (active or ex-smoker –Since? When? How much? atherogenic diet, physical inactivity) (A-I). Factors more specific to HIV-positive patients include: lifestyle (alcohol abuse, cocaine and other psychotropic substances), drugs interfering with the glucose and lipid metabolisms (growth hormone, ther-

Table 3
Assessment of cardiovascular (CV) risk and follow-up.

Assessment		Timing
Biochemical parameters	Glycaemia, triglycerides, total cholesterol, c-HDL, c-LDL	Baseline, start of antiretroviral therapy (ART), after 1–2 months and after 3–4 months thereafter or annually in patients not treated with ART
Instrumental parameters	Blood pressure	Baseline and every follow-up examination thereafter
	Electrocardiogram	Baseline. To be repeated in patients with CV risk factors
	Supra-aortic trunk Doppler ecography	In case of previous CV events or in patients with CV risk factors
	L4-L5 CAT scans or abdominal MRI	In case of adipose tissue central accumulation

apies with estrogen substitutes or testosterone), duration and type of HAART (B-I), nadir CD4+ T-cell count (B-II). Moreover, co-infection with hepatitis C virus (HCV) has also been suggested as possible risk factor in HIV mono-infected patients, although this has not been confirmed by others (B-II) [5, 6].

Statement 1.2

Laboratory parameters for identifying alterations in the glucose and lipid profiles should also be evaluated. In particular, total cholesterol values must be calculated, c-HDL, c-LDL, triglycerides and glycaemia (on fasted conditions) (A-I).

Statement 1.3

Arterial hypertension or silent ischemic heart disease should always be identified by:

- Measuring blood pressure using specific guidelines (A-I) [7, 8].
- An electrocardiogram (B-II), especially in cases where antiretroviral drugs that may cause prolongation of the Q-T interval are prescribed.

Assessment of endothelial damage indicators of HIV-infected patients is not advised at present for routine use during routine screening of CV risk.

Statement 1.4

Obesity or alterations in adipose tissue distribution contributing to CV risk (e.g., central fat accumulation) should also be identified by means of: body composition through measurements of weight, height, BMI, abdominal circumference (A-II) [8–11]. L4–L5 computerized tomography (CAT) scans (B-II) and abdominal magnetic resonance images (MRI) (B-II) are not necessary at initial screening unless further clinical studies will demonstrate their clinical utility.

Statement 1.5

The presence of metabolic syndrome will be diagnosed using the National Cholesterol Educational Program (NCEP) 2001 criteria (A-I) [12].

Statement 1.6

Despite the well-known limitations observed in the general population, the use of the Framingham score (available at http://www.cardiology.org/tools/medcalc/fram/) is advisable in all HIV-infected patients (B-I). It would also be advisable, however, for the results of the Framingham score to be compared with at least another risk algorithm (e.g., European or Italian, the latter being available at http://www.cuore.iss.it) (C-III).

HIV and Cardiovascular Risk Factors. Clinical and Laboratory Monitoring

Introduction

This topic addresses the issue of cardiovascular risk monitoring. Specific algorithms dedicated to HIV infected patients do not exist so far. More studies are necessary to understand what is the predictive marker for cardiovascular risk assessment in HIV infected populations. The necessary diagnostic procedures and a possible time frame are illustrated in Table 3.

Statement 2.1

Triglycerides, total cholesterol, c-HDL, c-LDL and basal glycaemia tests should be repeated at the following intervals (B-III):

- Annually, if patients are not being treated with antiretroviral drugs and have normal lipid and glucose values.
- Before the initiation of antiretroviral therapy; 1–2 months after the initiation of new antiretroviral drugs.
- Every 3–4 months if patients are assuming stable antiretroviral therapy.

In patients with hyper-triglyceridaemia, assessment of apoprotein B might be considered an additional risk indicator (C-III). In patients with cardiovascular risk factors, PCR assessment might also be considered [13]. In the case of abnormal PCR values, it is advisable to perform the test again after 3 weeks for further confirmation (C-III).

Table 4
Major metabolic and anthropometric complications, risk factors and proposed switch strategies.

Complication	Major risk factors	Results from switch studies
Dyslipidaemia	Advanced HIV infection (increase in triglycerides, decrease in HDL cholesterol), protease inhibitor exposure – except from atazanavir without ritonavir booster[a] (increase in triglycerides, total and LDL cholesterol), stavudine (increase in triglycerides, total and LDL cholesterol), efavirenz > nevirapine (increase in triglycerides, total and LDL cholesterol, but also HDL cholesterol)	Stavudine → tenofovir Non nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI)→ Atazanavir unboosted[a] PI → NNRTI (nevirapine)
Diabetes and insulin resistance	Family history of diabetes, lipodystrophy, older age, indinavir, HCV co-infection, obesity	Hypothesis: *switch* to atazanavir unboosted[a] (ritonavir *booster* could increase the risk)
Central fat accumulation	Obesity, low CD4+ T-cell count nadir, older age	PI interruption did not generally lead to significant benefits in terms of improvement in central obesity
Blood hypertension	High *body mass index*, older age, lipodystrophy syndrome (especially central obesity), cholesterol increase, insulin resistance, low CD4+ T-cell count, length of exposure to antiretroviral drugs (>2 years), the role of specific drugs is currently uncertain [31–34]	No data

[a] Currently not registered in Italy

Statement 2.2

Additional assessment to better define cardiovascular risk should include body mass index (BMI) and abdominal circumference [11]. These measurements should be performed at the first examination, before initiation of antiretroviral therapy, annually when undergoing stable therapy and before any change in treatment should occur (B-II).

Statement 2.3

Arterial blood pressure should be measured in accordance with JNC 7 or other official guidelines [7, 8] at the first examination and at every examination along the follow-up (A-I). Holter pressure monitoring can give additional information in cases of borderline hypertension, as well as to monitor responses to anti-hypertensive therapy (C-III).

It is useful for an ECG to be performed at the beginning of ART (BII). Electrocardiogram should also be repeated in patients with CV risk factors (C-II). It is useful for a doppler-echographical examination of supra-aortic vascular trunk to be performed in patients with cardiovascular or equivalent diseases or where several CV risk factors exist (B-I).

Longitudinal assessment of central fat accumulation may be taken into consideration using L4–L5 CAT scans or abdominal MRI (C-II).

Statement 2.4

Risk estimation of possible CV complications should be performed on the following occasions, using standard algorithms (such as Framingham score): at the first examination, at the beginning of antiretroviral therapy and then annually. Also, at these points in time, the NCEP 2001 criteria should be used to diagnose the metabolic syndrome. Such evaluations have also to be performed when antiretroviral regimens are modified, after the onset of a cardiovascular events and following patient lifestyle modifications (B-III).

Statement 2.5

In cases of glucose intolerance or diabetes discovered by measuring basal values, integrated patient management is always advisable (infectious disease experts plus diabetes specialists). As in the case of the general population, in HIV-positive patients with basal glycaemia on an empty stomach >110 (100) mg/dl (data confirmed by a second assessment), an oral glucose tolerance test (OGTT) should be performed (A-I) [14].

With glycaemia at 120 min >140 mg/dl or basal glycaemia >110 mg/dl, modifications in lifestyle (diet, giving up smoking, physical exercise) are strongly recommended (A-II) and, if necessary, the OGTT should be performed again after 3 months (B-II).

Despite some problems in the standardization of methods, insulinaemia quantification and HOMA calculations are useful indicators for diagnosing insulin resistance (C-III), especially in populations at a high risk of insulin resistance, such as HIV/HCV co-infected patients [15, 16].

Impact of Antiretroviral Therapy on Cardiovascular Risk Factors. Switch Strategy, and Interruption Due to Toxicity

Introduction

Nowadays, the benefits of HAART in terms of survival and reduction of opportunistic infections seem to overweight the impact of CV risk [17]. Notwithstanding, several studies suggest that the choice of drugs should be optimized in order to minimize metabolic complications which may then increase CV risk.

Statement 3.1

HIV-infection by itself is associated with alterations of lipid parameters, in particular, an increase in triglycerides levels and a drop in HDL cholesterol levels (A-II). HIV-infection also causes a series of alterations in the vascular wall which could foster the onset of the endothelial lesions (C-II) [3].

Statement 3.2

Antiretroviral therapy can induce alterations in the plasmatic lipids (A-I), even if the role of each single drug has yet to be completely defined (B-I). Protease inhibitors (PIs) are held responsible for an increase in triglycerides, total cholesterol and c-LDL (A-I) [18]. Treatments including ritonavir (even at a booster dosage) are involved in these alterations (A-I), while atazanavir not boosted with ritonavir appears to be the PI least involved in altering the plasmatic lipids (B-I) [19]. However, similarly to what has been reported after NNRTI drug regimens, treatments containing PIs can cause an increase in HDL cholesterol (B-I), thus perhaps counteracting part of the cardiovascular risk deriving from elevated LDL cholesterol. So far, this has been demonstrated particularly for regimens containing LPV/r [20].

Statement 3.3

Regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs) are seen to have less impact on the lipid alterations than those containing PIs. In some studies, however, efavirenz was seen to have an effect on cholesterol and on triglyceride levels similar to that of PIs (B-I). NNRTIs frequently cause an increase in c-HDL; such effect was found more pronounced in regimens containing nevirapine (A-I) [21].

Statement 3.4

Diverse evidence concurs in attributing to nucleoside analogues (NRTIs), in particular to thymidine analogues (stavudine more than zidovudine) a major responsibility in metabolic alterations (A-I). Therapeutic regimens containing stavudine cause a higher increase in cholesterol and triglyceride values than combination therapies containing other NRTIs (A-I). Switching from stavudine to tenofovir can improve lipid abnormalities, even in the presence of ritonavir-boosted PIs (A-I) [22].

Statement 3.5

Antiretroviral drugs may induce insulin resistance. Cases of type II diabetes after antiretroviral treatment have been observed, although at a very low prevalence (A-II). PIs (indinavir in particular) seem to have a role in inducing insulin resistance (B-II) [23].

The role of the other classes of drugs is less well documented. Regimens containing stavudine appeared to be involved to a greater degree than other NRTIs, although the length of exposure to thymidine analogue drugs as a class is also a very important risk factor (B-II). The pathogenesis of insulin resistance is complex phenomenon since genetic factors, HCV co-infection, behavioral (e.g., sedentary lifestyle) and anthropometric characteristics (e.g., central fat accumulation) are also involved (A-II) [24].

Statement 3.6

Some observational studies revealed an incidence of CV events in HIV-infected patients, greater than that found in the general population (B-II) [1]. However, the incidence of CV events in HIV-infected patients is still low, especially in the short term after HAART, while there are considerable benefits in terms of survival deriving from HAART [17]. For this reason, the prospect of HAART must take precedence over any other considerations when choosing an antiretroviral regimen (A-II).

Statement 3.7

In the decision to start HAART and for the choice of antiretroviral drugs it is worth considering that prolonged exposure to antiretroviral treatment (B-II), in particular to regimens containing PIs (C-II), constitutes an additional risk factor for CV events.

In patients with previous cardiovascular events or *cerebro-vascular heart disease risk equivalent* (such as diabetes), a PI-sparing therapeutic regimen without thymidine analogues might be a preferred option (C-II).

Statement 3.8

In case of high CV risk, when further possible therapeutic options exist and if diet and change of life style are not effective, the antiretroviral regimen should be modified (C-III). However, viro-immunological and clinical effectiveness should not be compromised through a careful assessment of the pharmacological history, and compliance

of the patient to the treatment is a priority. Careful assessment and comparison of the CV risk and toxicity profile of drugs used are also important (B-III). Table 4 summarizes the major risk factors and possible switch interventions aimed at improving metabolic alterations and minimizing CV risk. A selection of data supporting the following recommendations (see Statement 3.9) have recently been reviewed by *Negredo* et al. [25].

Statement 3.9

The substitution of a PI with abacavir is able to cause a significant drop in cholesterol and triglycerides levels. However, such changes may increase the risk of virologic failure, especially in patients with previous NRTI treatment failures (B-I).

The substitution of a PI with nevirapine is able to cause a significant drop in cholesterol and triglycerides levels. The substitution of a PI with Efavirenz is not necessary associated with a significant drop in lipid levels and insulin resistance (B-II).

Switching to unboosted atazanavir (currently not registered in Italy) may limit lipid alterations (C-II) even if such strategy should be experimented more in depth as far as the durability of the virological response is concerned (B-I).

The substitution of stavudine by tenofovir or abacavir causes an improvement in HAART-induced dyslipidemia (especially hyper-triglyceridaemia) (A-I).

Statement 3.10

Therapeutic drug monitoring could be theoretically used to adjust drug dosage in order to prevent or treat metabolic toxicity. However, the actual relationship between plasma drug levels and metabolic toxicity has yet to be defined. Therefore, the utility of this strategy cannot be recommended at present (C-III).

Treatment of Cardiovascular Risk in HIV Infection

Introduction

Treatment of metabolic alterations in HIV infected patients is a challenging intervention. In fact, when lipid-lowering drugs are prescribed, increasing pill burden could decrease patient adherence to medications, as well as interactions between lipid lowering drugs and antiretrovirals may arise. For this reason, treatment of these complications should include, in the first instance, correction of patient life style.

Statement 4.1

The prevention of CV risk in HIV-positive patients must follow the same guidelines used in the general population. Lifestyle modifications must be advised, especially if patients have concomitant risk factors for CV risk (advanced age, familiarity cerebro-vascular ischemic diseases, previous cerebro-vascular ischemic diseases):

- Propose giving up smoking (A-I).
- Propose increasing physical activity (A-I). For example, aerobic exercise (such as walking briskly for 30–60 min/day) may reduce CV risk by 30–50% and this correlates with reduction in plasmatic lipid concentrations and reduction of abdominal circumference.
- Modifications in diet, through dietetic counseling (B-I). For example, a diet rich in fish, vegetables, fruits, cereals and low in-saturated fats may decrease cholesterol levels by 10–20%.

Statement 4.2

Special attention should be paid to the individualization of antiretroviral therapy (*tailor therapy to patient needs*), but achieving and maintaining HIV replication under control are important priorities. Prevention of CV risk should be managed through collaboration of the following professional figures (B-III):

- Expert in infectious diseases
- Cardiologist/specialist in internal medicine
- Endocrinologist/diabetes specialist
- Psychologist
- Dietitian

Statement 4.3

Treatment of insulin resistance should follow the same guidelines and the same types of treatment as for the general population [14]:

- Lifestyle modifications (diet, physical exercise);
- Start of treatment if glycemia >125 mg/dl (confirmed data);
- Specific treatment with anti-diabetic drugs should be prescribed, while paying attention to possible drug-drug interactions (specifically, with antiretroviral drugs);
- There are no guidelines regarding the pharmacological treatment in the case of hyperinsulinaemia in presence of normal glycaemia found on an empty stomach. In this circumstance, patients should be monitored very closely (C-II).

Statement 4.4

In the case of use of oral anti-diabetic drugs, the following evidences should be noted: (a) metformin appears to have the lowest risk of interactions with antiretrovirals (B-III); (b) the role of glitazonic drugs is currently being defined; (c) metformin and rosiglitazone may improve lipoatrophy, insulin resistance (B-I) and could diminish blood pressure (B-III) [26]; (d) rosiglitazone may cause an increase in cholesterol and triglycerides and is therefore to be used with caution (A-I) [27].

Statement 4.5

The treatment of hypercholesterolemia must follow the same guidelines and the same types of treatment as in the case of the general population, with some remarks specific to HIV infection [12, 28]:

- Interventions are recommended when cLDL is >130 mg/dl (B-II).
- Pharmacological treatment is recommended after 3 months from modifications in lifestyle (stop smoking, exercise, diet) without benefits (B-III).
- The following pharmacological treatments may be used:
  - pravastatin 20–40 mg/day (A-I),
  - fluvastatin 20 40 mg/day (B-II),
  - rosuvastatin 20– 40mg/day (B-II) (no interactions with PIs, good results in reducing cLDL have been demonstrated, but further studies are necessary).
- Atorvastatin 10 mg/day (B-II) could have relevant pharmacokinetic interactions with PIs and NNRTIs, while use of simvastatin and lovastatin (B-II) is not recommended because of the unfavorable interactions with PIs.
- Regardless of the cLDL cholesterol target level achieved, statins probably diminish cardiovascular morbidity and mortality (A-II).
- The statin plasmatic concentrations are reduced by simultaneous administration of NNRTIs, thereby the effect of statins could be reduced (A-II) [29].

Statement 4.6

The treatment of hypertrigliceridaemia must follow the same guidelines and the same types of treatment as in the case of the general population, with some remarks specific to HIV infection [12, 28]:

- Modification in lifestyle (stop smoking and alcohol abuse, exercise, diet) is the recommended intervention when triglycerides >150 and <500 mg/dl.
- If triglycerides values >500 mg/dl or they are not reduced by modifications in lifestyle, pharmacological treatment is recommended (A-II).
- The following pharmacological treatments may be used:
  - fibrates are the first choice drugs at the following dosages: gemfribozil (600 mg bid), fenofibrates (50–160 mg qd) (B-I),
  - niacin is contraindicated (C-III), especially in the case of insulin resistance (C-II),
  - omega 3 (fish oil) drugs may reduce trigliceridemia but with a risk of increasing cLDL (B-II),
  - leptin would appear to give interesting results in HIV-positive patients with lipodystrophy (C-III),
  - the simultaneous treatment of statins + fibrates is associated with a increased risk of rhabdomyolysis; therefore, their combined use is recommended solely in cases of hypercholesterolaemia refractory to pravastatin (C-III).

Statement 4.7

Treatment of blood hypertension should follow the same guidelines and the same types of treatment as in the case of the general population, with some remarks specific to HIV infection [7, 30]:

- Advices of a cardiologist or internal medicine specialist are needed,
- Modifications in lifestyle are first line treatments (stop smoking, exercise, reduction of salt intake),
- Anti-hypertensive treatment is taken into consideration when systolic blood pressure is >140 mmHg and diastolic blood pressure is >90 mmHg,
- When choosing anti-hypertensive drugs, any possible interactions with antiretroviral drugs (e.g., beta blockers and calcium antagonists) are to be considered. There is lack of data on drug–drug interactions between antiretroviral drugs and other classes of anti-hypertensive drugs (e.g., sartanic drugs),
- Utilization of low dose acetyl salicylic acid should be considered in the case of accumulation of >2 risk factors for CV diseases (C-III).

Acknowledgments

The organization of the meeting was supported by an unrestricted grant form Abbott S.p.A. Italy, held under the auspices of the Italian Society for Infectious and Tropical Diseases (Società Italiana di Malattie Infettive e Tropicali, SIMIT).

The following doctors are members of the Italian Cardiovascular Risk Guidelines Working Group: C. Abeli, A. Aliffi, B. Argenteri, G. Ballardini, F. Barchiesi, C. Bellacosa, G. Bevacqua, S. Bonora, M. Brandolini, P. Castelli, B.M. Celesia, G. Cenderello, D. Cibelli, P. Cicconi, L. Cordier, R. Cuomo, M. De Marco, F. Di Lorenzo, M. Di Pietro, S. Galvagna, M. Gargiulo, S. Giancotti, E. Granelli, P. Grima, M. Guffanti, R. Iardino, L. Maiocchi, S. Marcotullio, C. Martinelli, A. Masala, G. Mazzarello, M.C. Moioli, R. Morandi, M.T. Mughini, M. Nigro, R. Pisapia, R. Piscopo, P. Pizzaferri, L. Pusterla, C.M. Regnery, A. Ruggieri, P. Sette, C. Sfara, L. Sighinolfi, N. Squillace, M. Trezzi, M. Villa.

References

1. The Data Collection on Adverse Events of Anti-HIV-Drugs (DAD) Study Group: Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 2003; 349: 1993–2003 (Erratum, N Engl J Med 2004; 350: 955).
2. Carosi G, Torti C, Andreoni M, Angarano G, Antinori A, Bonora S, Borderi M, Castagna A, Castelli F, Cauda R, Chiodo F, D'arminio-Monforte A, De Luca A, Di Perri G, Dianzani F Filice G, Galli M, Lazzarin A, Maggiolo F, Maserati R, Mazzotta F, Moroni M, Perno CF, Vullo V: Key questions in antiretroviral therapy: Italian consensus workshop (2005). J Antimicrob Chemother 2006; 57: 1055–1064.
3. Grinspoon S, Carr A: Cardiovascular risk and body fat abnormalities in HIV infected adults. N Engl J Med 2005; 352: 48–62.
4. Carr A, Grund B, Neuhaus J, El-Sadr W, Grandits G, Gibert C, Neaton J, Prineas R: ART and asymptomatic ischemic heart disease in HIV-infected adults: a cross-sectional analysis of patients enrolling in the SMART trial. In: Program and abstracts in the 13th Conference on Retroviruses and Opportunistic Infections; 5–8 February 2006; Denver, Colorado. Abstract 736.
5. Vassalle C, Masini S, Bianchi F, Zucchelli GC: Evidence for association between hepatitis C virus seropositivity and coronary artery disease. Heart 2004; 90: 565–566.

6. Arcari CM, Nelson KE, Netski DM, Nieto FJ, Gaydos CA: No association between hepatitis C virus seropositivity and acute myocardial infarction. Clin Infect Dis 2006; 43: e53–e56.
7. Hemmelgarn BR, McAlister FA, Grover S, Myers MG, McKay DW, Bolli P, Abbott C, Schiffrin EL, Honos G, Burgess E, Mann K, Wilson T, Penner B, Tremblay G, Milot A, Chockalingam A, Touyz RM, Tobe SW: The 2006 canadian hypertension education program recommendations for the management of hypertension: Part I—blood pressure measurement, diagnosis and assessment of rish. Can J Cardiol 2006; 22: 573–581.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: The Seven Report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report. JAMA 2003; 290: 2560–2572.
9. Yusuf S, Hawken S, Ounpuu S, On behalf of the INTERHEART Study Investigators: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). Lancet 2004; 364: 937–952.
10. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S: Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 953–962.
11. Haffner SM, Despres JP, Balkau B: Waist circumference and body mass index are both independently associated with cardiovascular disease: The International Day for the Evaluation of Abdominal Obesity (IDEA) survey. J Am Coll Cardiol 2006; 47 (4 Suppl A): 358A (Abstract 842–846).
12. Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults. Executive summary of the third report of national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001; 285: 2486–2497.
13. Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836–843.
14. Lebovitz HE, Austin MM, Blonde L, Davidson JA, Del Prato S, Gavin JR, Handelsman Y, Jellinger PS, Levy P, Riddle MC, Roberts VL, Siminerio LM: ACE/AACE consensus conference on the implementation of outpatient management of diabetes mellitus: consensus conference recommendation. Endocr Pract 2006; 12 (Suppl 1): 6–12.
15. Duong M, Petit JM, Piroth L, Grappin M, Buisson M, Chavanet P, Hillon P, Portier H: Association between insulin resistance, and hepatitis C virus chronic infection in HIV-hepatitis C virus coinfected patients undergoing antiretroviral therapy. J Acquir Immune Defic Syndr 2001; 27: 245–250.
16. Palacios R, Merchante N, Macias J, Gonzalez M, Castillo J, Ruiz J, Marquez M, Gomez-Mateos J, Pineda JA, Santos J: Incidence and risk factors for insulin resistance in treatment naïve HIV-infected patients 48 weeks after starting highly active antiretroviral therapy Antiviral Ther 2006;11:529–535.
17. Law M, Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Calvo G, El-Sadr W, De Wit S, Sabin CA, Lundgren JD: Modelling the 3-year risk of myocardial infarction among participants in the Data collection on adverse events of anti-HIV drugs (DAD) study. HIV Med 2003; 4: 1–10.
18. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, Tarr PE, Vernazza P, Battegay M, Bucher HC: Lipid profiles for antiretroviral naive patients starting PI and NNRTI based therapy in the Swiss HIV Cohort study. Antivir Ther 2005; 10: 585 –591.
19. Sax PE, Kumar P: Tolerability and safety of HIV protease inhibitors in adults. J Acquir Immune Defic Syndr 2004; 37: 1111–1124.
20. Montes ML, Pulido F, Barros C, Condes E, Rubio R, Cepeda C, Dronda F, Antela A, Sanz J, Navas E, Miralles P, Berenguer J, Perez S, Zapata A, Gonzalez-Garcia JJ, Pena JM, Vazquez JJ, Arribas JR: Lipid disorders in antiretroviral naïve patients treated with lopinavir/ritonavir based HAART: frequency, characterization and risk factors. J Antimicrob Chemother 2005; 55: 800–804.
21. van Leth F, Phanuphak P, Stroes E, Gazzard B, Cahn P, Raffi F, Wood R, Bloch M, Katlama C, Kastelein JJ, Schechter M, Murphy RL, Horban A, Hall DB, Lange JM, Reiss P: Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral therapy naive patients infected with HIV. Plos Med 2004; 1: e19.
22. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, Lu B, Toole JJ, Cheng AK: Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral naïve patients: a 3-year randomized trial. JAMA 2004; 292: 191–201.
23. Lee GA, Lo JC, Aweeka F, Schwarz JM, Mulligan K, Schambelan M, Grunfeld C: Single dose lopinavir-ritonavir acutely inhibits insulin mediated glucose disposal in healthy volunteers. Clin Infect Dis 2006; 43: 658–660.
24. Brown TT, Li X, Cole SR, Kingsley LA, Palella FJ, Riddler SA, Chmiel JS, Visscher BR, Margolick JB, Dobs AS: Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicentre AIDS Cohort Study. AIDS 2005; 19: 1375–1383.
25. Negredo E, Bonjoch A, Clotet B: Benefits and concerns of simplification strategies in HIV-infected patients. J Antimicrobiol Chemother 2006; 58: 235–242.
26. Mulligan K, Yang Y, Koletar S, Wininger D, Parker R, Alston-Smith B, Basar M, Grinspoon S: Effects of metformin and rosiglitazone on body composition in HIV-infected patients with hyperinsulinemia and elevated waist/hip ratio: a randomized, placebo-controlled trial. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections (Denver). Abstract 147.
27. Carr A, Workman C, Carey D, Rogers G, Martin A, Baker D, Wand H, Law M, Samaras K, Emery S, Cooper DA: No effect of rosiglitazone for treatment of HIV-1 lipoatrophy: randomized double blind, placebo-controlled trial. Lancet 2004; 363: 429–438.
28. Stein JH: Managing cardiovascular risk in patients with HIV infection. J Acquir Immune Defic Syndr 2005; 38: 115–123.
29. Gerber JG, Rosenkranz SL, Fichtenbaum CJ, Vega JM, Yang A, Alston BL, Brobst SW, Segal Y, Aberg JA: Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin. Results of the AIDS Clinical Trials Group 5108 Study. J Acquir Immune Defic Syndr 2005; 39: 307–312.
30. Khan NA, McAlister FA, Rabkin SW, Padwal R, Feldman RD, Campbell NR, Leiter LA, Lewanczuk RZ, Schiffrin EL, Hill MD, Arnold M, Moe G, Campbell TS, Herbert C, Milot A, Stone JA, Burgess E, Hemmelgarn B, Jones C, Larochelle P, Ogilvie RI, Houlden R, Herman RJ, Hamet P, Fodor G, Carruthers G, Culleton B, Dechamplain J, Pylypchuk G, Logan AG, Gledhill N, Petrella R, Tobe S, Touyz RM: The 2006 canadian hypertension education program recommendations for the management of hypertension: part II—therapy. Can J Cardiol 2006; 22: 583–593.
31. Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, Filice G: Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. J Hypertens 2003; 21: 1377–1382.

32. Palacios R, Santos J, Garcia A, Castells E, Gonzalez M, Ruiz J, Marquez M: Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients. A prospective study in a cohort of naïve patients. HIV Med 2006; 7: 10–15.
33. Thiebaur R, El-Sadr WM, Friis-Moller N, Rickenbach M, Reiss P, Monforte AD, Morfeldt L, Fontas E, Kirk O, De Wit S, Calvo G, Law MG, Dabis F, Sabin CA, Lundgren JD: Predictors of hypertension and changes of blood pressure in HIV-infected patients. Antivir Ther 2005; 10: 811–823 (Erratum in: Antiviral Ther 2005; 10: 969).
34. Crane HM, van Rompaey SE, Kitahata MM: Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. AIDS 2006; 20: 1019–1026.