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Cardiovascular Risk in Patients with HIV Infection

Impact of Antiretroviral Therapy

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Contents

Abstract

Increased coronary heart disease risk in HIV-positive patients using antiretroviral therapy (ART) has been a controversial topic since 1998 when the dyslipidaemic effect of protease inhibitors (PIs) was recognised. Accumulating evidence suggests an association between ART and increased coronary heart disease risk. In 2003, the large, prospective D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study reported a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4–6 years of use. As the HIV-population grows older, infectious disease specialists have to consider unfamiliar areas of internal medicine such as lipid-lowering therapy and smoking cessation. Moreover, the ART regimen itself may be a modifiable risk factor, as there are both class differences and within-class differences in the tendency to increase lipids. Most nucleoside reverse transcriptase inhibitors (NRTIs), including the newer agents tenofovir disoproxil fumarate and emtricitabine, have little or no effect on lipid levels or glucose metabolism. One exception is the highly effective NRTI stavudine, which has a dyslipidaemic profile and a negative effect on glucose metabolism. In contrast the non-nucleoside reverse transcriptase inhibitor nevirapine may increase the 'good cholesterol' high-density lipoprotein (HDL) cholesterol and thus reduce the total cholesterol **:** HDL cholesterol index.

Most of the PIs have some dyslipidaemic effect, especially ritonavir (alone or in combination with other PIs), fosamprenavir and the novel PI tipranavir. Only atazanavir, and to some extent saquinavir, seem to have little effect on lipid levels and glucose metabolism.

Studies on blood pressure in HIV-positive patients have been contradictory. Apart from a recent report from the D:A:D study where lower blood pressure was found in patients receiving NNRTIs, the influence of the individual drugs on blood pressure is unknown. When hypertension is detected in a HIV-positive patient, creatinine clearance (CL_{CR}) should be calculated and the urine checked for proteinuria. When CL_{CR} is <30 mL/min, tenofovir disoproxil fumarate is not recommended. Many hypertensive HIV-positive patients have proteinuria and an ACE inhibitor or an angiotensin II receptor antagonist is a better choice than a thiazide diuretic or calcium channel antagonist in these patients. In addition, physicians treating patients with ART should be especially aware of the long list of possible interactions between PIs and anti-hypertensive- and lipid-lowering drugs.

This review discusses important clinical aspects of treating middle-aged HIV-positive patients who have an increased risk of experiencing a cardiovascular event.

Combined antiretroviral therapy (ART) was widely introduced in people with HIV infection in the Western world around 1996. Today this combination consists of at least three different drugs; two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI). HIV-infection is still not a curable disease, but with this treatment the immune system may be preserved for decades. The annual mortality rate among HIV-infected patients has been dramatically reduced in cohorts where this treatment is available. EuroSIDA is a prospective study[1] of approximately 11 000 patients with HIV-1 infection in 80 centres across Europe, Israel and Argentina. In the EuroSIDA cohort the mortality rate declined from 16% to 3% between 1994 and 2001. Today, <50% of the HIV-infected patients die from AIDS-defining events. A recent French study[2] reported that cardiovascular disease was the fourth largest cause of death (7%) among HIV-infected patients, following AIDS-defining events (47%), hepatitis B-associated or C-associated liver disease (11%) and non-HIV-related malignancies (11%). The change of life expectancy and attitude to these patients is illustrated by the fact that the first HIV-infected transplant patient was successfully given a new heart in 2001, receiving a combination of ART and ciclosporin (cyclosporine).[3] Hence, long-term adverse effects of ART have to be taken into account. Globally, still less than one in ten people who need ART receive it,[4] but as one of the goals of WHO has been 'HAART to 3 million within 2005', the adverse effects of these drugs are also an important issue in the nondeveloped world. This paper focuses on dyslipidaemia, cardiovascular risk, class differences and within-class differences, and which agents to use in patients with underlying risk factors.

1. Risk of Coronary Heart Disease (CHD) in HIV-Positive Patients Receiving Antiretroviral Therapy (ART)

The first studies presenting data on coronary event rates in ART patients could not find any increased myocardial infarction (MI) risk in patients receiving PIs,[5,6] but in 2003 the D:A:D (Data collection on Adverse events of anti-HIV Drugs) study[7] stated that ART was associated with a 26% relative increase in the rate of MI per year of exposure during the first 4–6 years of use. D:A:D is a large, international, prospective study where MI rates and important coronary heart disease (CHD) risk factors are systematically assessed. Consequently, the common opinion today is that ART

increases CHD risk. To understand the clinical importance of this increased risk, it is important to understand the difference in absolute and relative risk. Relative risk is used to compare risk in two different groups of people. For example men have an increased risk of MI compared with women. If we call the women's MI risk '1', and the men have a relative risk of 1.50, relative risk is increased by 50% in men compared with women. Absolute risk is defined as the chance of a person developing a specific disease over a specified time-period. For example, a young, HIV-positive, nonsmoking woman's 10-year absolute risk of MI is <1/100. That is to say, less than one young nonsmoking woman in every 100 will develop MI over a 10-year period. Consequently, although relative MI risk in patients receiving ART is increased compared with ART-naive patients, the absolute MI risk in a young, ART-experienced woman is usually microscopic. Details about the different cohort studies are discussed in this section and presented in table I.

In the Veterans administration cohort[5] the rate of admissions for cardio- and cerebrovascular events (CCVE) decreased from 1.7 to 0.9 per 100 patients between 1995 and 2001, and investigators found no relation between the use of PIs or NNRTIs and CCVE (table I). This study was not adjusted for possible confounding variables. The patients had been receiving ART for a short time (median 16 months in the PI group, 9 months in the NNRTI group), thus the effect of any dyslipidaemia on the vascular bed would be expected to be minimal. In The Kaiser Permanente Medical Care Program in North California, USA[6] the PI group had a median of 3 years PI-exposure time, but the investigators did not find any differences in CHD and MI hospitalisation rates before and after PIs (6.2 vs 6.7 events per 1000 person-years) or before and after ART (5.7 vs 6.8). This study was adjusted for age, but other CHD risk factors were not included in the analysis. In another US study, Currier et al.[9] found that in young individuals aged 18–33 years, adjusted relative risk was 2.06 ($p < 0.001$) in ART-treated

Table I. Cardiovascular risk in HIV: clinical endpoint studies

Study	No. of patients	Study peroid	Events	Coronary heart disease risk
Retrospective studies				
Bozzette et al.[5] Veterans administration cohort	36 766	January 1993–June 2001	1 207 admissions for CCVE	No relation between PI or NNRTI and CCVE
Klein et al.[6] Kaiser Permanente	4 159	January 1996–June 2001	72 hospitalisations for CHD events	No increase before vs after PI Increased in HIV+ vs HIV−
Coplan et al.[8] Meta-analysis of 30 randomised trials	10 986	1996–9	29 MIs	No increase in PI treated vs NRTI-only therapy
Currier et al.[9] California Medicaid cohort	28 513	July 1994–June 2000	1 360 CHD events	Increased in young ART+ vs ART− Increased in young HIV+ vs HIV−
Mary-Krause et al.[10] French hospital database	34 976	January 1996–December 1999	60 MIs	Increased risk in PI treated vs non-PI treated
Prospective studies				
Barbaro et al.[11] Italian cohort	1 551	September 1999–October 2002	25 CHD events	Increased risk in PI treated vs non-PI treated
Holmberg et al.[12] HOPS	5 672	January 1993–January 2002	21 MIs	Increased risk in PI treated vs non-PI treated
D:A:D study group[7]	23 468	December 1999–February 2002	126 MIs	Increased risk with increased exposure to PI

ART = antiretroviral therapy; **CCVE** = cardio- and cerebrovascular events; **CHD** = cardiovascular heart disease; **D:A:D** = Data Collection on Adverse Events of Anti-HIV Drugs study; **HOPS** = HIV OutPatient Study; **MIs** = myocardial infarctions; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside (nucleotide) reverse transcriptase inhibitors; **PI** = protease inhibitor.

versus those not receiving ART. The study included administrative claims data for HIV-positive and HIV-negative patients from the California Medicaid population. Of 3 083 209 individuals, 28 513 were HIV-infected, and approximately 50–60% of them were ART experienced. The multivariate model included recognised CHD risk factors such as diabetes mellitus, hyperlipidaemia, renal failure and hypertension. A limitation of most of these studies is the dependence of hospitalisation rates and health registers that may be influenced by unknown economic and social factors. Other retrospective, observational studies have demonstrated an increased MI risk in patients receiving PIs versus those who aren't. The French hospital HIV database[10] found that exposure to a PI was associated with a higher risk of MI (hazard ratio [HR] 2.56).

This is in contrast with three prospective studies where an increased risk of MI in patients taking PIs compared with those not receiving PIs was found in all the studies. An Italian study[11] included ART-naive patients between January to September 1999, and compared MI incidence in PI-treated versus NNRTI-treated subjects. The annual incidence of MI was found to be 5.1/1000 in the PI group and 0.4/1000 in the NNRTI group ($p < 0.001$). Of the 23 PI recipients who developed coronary artery disease, all 23 had hypertriglyceridaemia and hypercholesterolaemia. There were no significant differences in any demographic or clinical characteristics between the two groups at baseline.

In HOPS (HIV OutPatient Study), [12] the investigators found an increased risk of MI in patients receiving a PI compared with those who were not. In a multivariate model that examined smoking, sex, age, diabetes mellitus, hyperlipidaemia and hypertension, investigators showed that PI use was still strongly, but not significantly, associated with the incidence of MI (HR = 6.51; $p = 0.065$). In 2003, data from the large, international, prospective D:A:D study[7] including HIV-positive patients from 11 cohorts and 20 countries situated in Europe, USA and Australia was published in the *NEJM*. The writing group of the D:A:D study reported that ART was associated with a 26% relative increase in the rate of MI per year of exposure during the first 4–6 years of use. In addition to well documented risk factors, such as age, sex, smoking, diabetes and total cholesterol, they found a significant association between elevated triglycerides and MI risk. In the multivariate model they did not include plasma lipid levels, which could potentially be on the causal pathway from drug exposure to MI. This is an important aspect, as true differences can wrongly become insignificant if factors on the causal pathway are included in the multivariate model. Hence, the inclusion of dyslipidaemia in the multivariate model of HOPS[12] may explain why the association between MI and use of PI became (possibly incorrectly) insignificant. The D:A:D study showed that the incidence of MI in patients who had been receiving ART for >4 years was 5.5 per 1000 person years. Later reports from the D:A:D study[13] showed that not only the MI incidence but also the total incidence of CCVE was positively associated with the duration of ART (figure 1).

Predictive markers of elevated CHD risk such as abnormal levels of circulating adhesion molecules and other signs of endothelial dysfunction are demonstrated in HIV-positive patients.[14,15] Studies assessing carotid intima-media thickness (IMT) and increased arterial stiffness have been somewhat conflicting.[16,17] In a recent French IMT study,[18] the investigators found premature atherosclerosis that correlated with usual risk factors, but also with PI

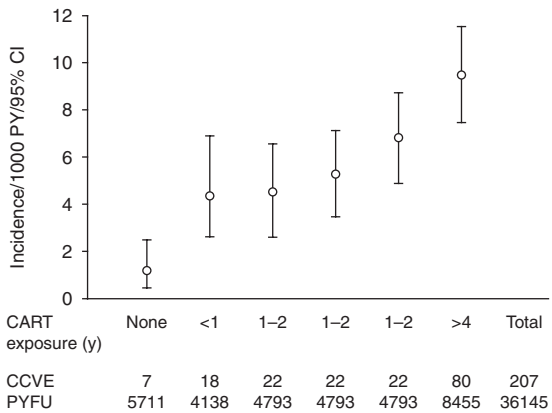

Fig. 1. Incidence of cardio- and cerebrovascular events relative to duration of highly active antiretroviral therapy. The incidence of cardio- and cerebrovascular events (CCVE) was assessed according to cumulative duration of combination antiretroviral therapy (CART) since initiation, stratified in 1-year intervals from 0–4 years, an interval of >4 years exposure and an interval for no exposure (reproduced from d'Arminio et al.,[13] with permission). **PYFU** = person years follow up; p-value for trends < 0.00001.

exposure, especially lopinavir. However, the changes were small and the clinical impact low. In another French study[19] that included 364 patients, investigators could not find any association between IMT and type or duration of ART. In addition, studies concerning coronary-artery calcifications (CAC) have been inconclusive. Risk factors for elevated CAC scores are advanced age, male sex, hypertension, diabetes and chronic coronary heart disease. In one study, CAC was more common in patients receiving PI-treatment than in patients receiving non-PI treatment,[20] whereas another study did not show any clinically significant difference in CAC between ART-treated men and matched, HIV-negative controls.[21]

There are different scoring systems for estimating CHD risk in HIV-negative patients. The European model for calculating fatal cardiovascular disease risk,[22] including both coronary and cerebrovascular events could be useful in these patients, but no studies in HIV-positive patients have been published so far. In addition, risk-estimates including triglycerides could be valuable tools when evaluating ART-treated patients.[23] However, the American model based on the Framingham study[24] is the main model applied to studies of HIV-positive patients.[25-27] In a prospective study[25] comparing 219 ART-treated, 64 ART-naive and 428 HIV-negative age- and sex-matched controls, we showed that the prevalence of estimated 10-year CHD risk of >20% in ART-treated patients was more than twice as high as in HIV-negative controls. The main contributors to the increased CHD risk in patients receiving ART were a high prevalence of daily smoking, somewhat higher total cholesterol and lower high-density lipoprotein (HDL) cholesterol. In ART-naive patients the prevalence of elevated CHD risk was similar to HIV-negative controls. The high prevalence of smoking and low HDL cholesterol in the ART-naive patients was counterbalanced by their low total cholesterol and low blood pressure. Grover et al.[26] compared changes in estimated Framingham risk after 32 weeks of therapy with nelfinavir or atazanavir, each in combination with stavudine and lamivudine. Levels of total cholesterol and low-density lipoprotein (LDL) cholesterol increased significantly more among patients who used nelfinavir (+24% and +28%) than among those who used atazanavir (+4% and +1%). This dyslipidaemia increased the risk of coronary disease by 50% over 10 years. The absence of dyslipidaemia was estimated to preserve life expectancy 0.15–1.53 additional years depending on a patient's age, sex and other risk factors. The morbidity and mortality due to CHD has decreased since the Framingham model was developed and it is now shown to overestimate CHD risk in HIV-negative patients.[28,29] However, the D:A:D study found a 3-year MI incidence of 1.0%, which was close to the upper limit of their 3-year Framingham risk estimate; 0.4–1.1%. Hence, today the Framingham model seems to be useful in HIV-positive populations but further studies are needed to confirm these findings.

2. Risk Factors for CHD in HIV-Positive Patients

In 1998, 2 years after the broad introduction of ART, Carr et al.[30] described a syndrome of body fat changes, increased visceral fat, increased triglycerides, increased total cholesterol and insulin resistance. The syndrome mimicked inherited lipodystrophies[31,32] and was initially associated with the new antiretroviral drugs, PIs, especially indinavir. Still, 8 years after the first description of HIV-associated lipodystrophy, there are many controversies about this syndrome. Less controversial is the fact that dyslipidaemia is common in individuals with HIV and patients receiving ART, and that dyslipidaemia has an influence on cardiovascular risk.

Dyslipidaemia is a well known CHD risk factor in the HIV-negative population, and it does not seem reasonable that this factor induces less CHD risk in HIV-positive patients. In the pre-ART era hypertriglyceridaemia was associated with disease progression in AIDS patients,[33] and acquiring HIV-infection *per se* is still associated with a reduction in total, HDL and LDL cholesterol levels by 0.8, 0.6 and 0.3 mmol/L, respectively.[34] The underlying mechanism is unclear but interestingly hypocholesterolaemia has also been demonstrated in patients with hepatitis C.[35,36] Because total, HDL and LDL cholesterol levels are reduced in HIV-positive, ART-naive patients, some of the elevation of cholesterol induced by ART may represent a normalisation back to pre-HIV levels.[34] Few studies have

compared lipid levels in HIV-positive patients receiving ART with ART-naive and HIV-negative patients. In our study from 2000–2001[25] we found that the prevalence of total cholesterol ≥6.2 mmol/L was 36% in HIV-positive patients receiving ART, 9% in ART-naive and 22% in HIV-negative patients. The prevalence of fasting triglycerides ≥1.7 mmol/L was 55% in HIV-positive patients receiving ART, 23% in ART-naive and 25% in HIV-negative patients.[37]

The D:A:D study[27] found similar results; 27% of patients receiving a PI regimen had total cholesterol ≥6.2 mmol/L compared with 8% in ART-naive patients. HIV-negative controls were not included. In patients receiving a quadruple regimen (two NRTIs, one or two PIs and a NNRTI), 43% had total cholesterol ≥6.2 mmol/L. Prevalence of triglycerides ≥2.3 mmol/L was 40% in PI recipients versus 15% in ART-naïve patients. Approximately 36% of these measurements were fasting values, 24% were nonfasting and the remaining lacked information regarding fasting status. The prevalence of HDL cholesterol ≤0.9 mmol/L was 23% in patients receiving PIs compared with 16% for NNRTI recipients, and studies have shown that NNRTIs increase the level of HDL cholesterol more than most PIs.[38,39] Both class differences and within-class differences exist between the various antiretroviral regimens[40] (figure 2), and these differences are discussed in detail in section 3.3, with main focus on the newer antiretroviral drugs.

Some of the ART regimens induce hypertriglyceridaemia and also hypercholesterolaemia.[41,42] The mechanisms underlying the dyslipidaemia are probably multifactorial, including genetic disposition, age, race, sex, the effect of HIV-infection itself and ART. There is growing evidence that the core problem is disturbances in the metabolism of peripheral adipocytes. One possible mechanism is inhibition of adipogenic differentiation factors such as the peroxisome proliferator activator receptor (PPAR)-γ, sterol-regulatory-element-binding-protein (SREBP)-1 and CCAAT-enhancer binding protein.[43]

Inhibition of PPARγ by increased tumour necrosis factor (TNF)-α is another possibility, as TNFα may be elevated in HIV-positive patients,[44] and is known to induce hyperlipidaemia and insulin resistance.[45,46] A naturally occurring TNFα polymorphism has also been found to enhance the progression of lipoatrophy.[47] Dysregulation of other adipocytokines (proteins produced by adipose tissue) such as interleukin-2, adiponectin and leptin may also contribute to the development of metabolic complications in HIV. Another plausible explanation for apoptosis of peripheral adipocytes is mitochondrial toxicity. NRTIs induce depletion of mtDNA and mitochondrial dysfunction by inhibition of DNA-polymerase γ.[48] This in turn may induce disturbances in the metabolism of muscle cells, liver cells and adipocytes.

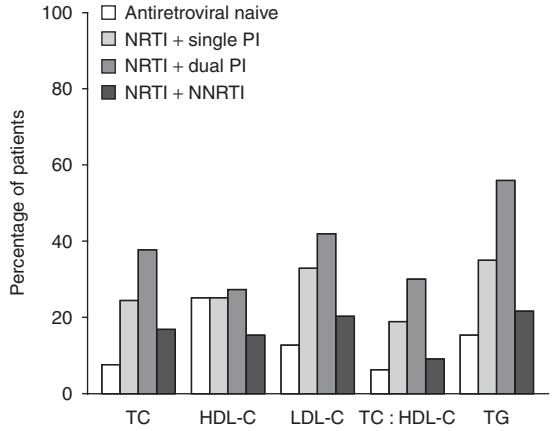

Fig. 2. Prevalence of dyslipidaemia in patients enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs study, by type of antiretroviral regimen received at initiation of the study. Dyslipidaemia is defined as total cholesterol (TC) level ≥6.2 mmol/L, high-density lipoprotein-cholesterol (HDL-C) level ≤0.9 mmol/L, low-density lipoprotein-cholesterol (LDL-C) level ≥4.1 mmol/L, TC : HDL-C ratio ≥6.5 or triglyceride (TG) level ≥2.3 mmol (reproduced from Fontas et al.,[40] with permission). **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor.

Increased peripheral lipolysis and reduced uptake of fatty acids imply increased level of circulating lipids. When limited quantities of lipids are stored in peripheral fat depots, they accumulate in sites with high capacities for energy uptake; skeletal muscle, central fat deposits and liver.[49] In the liver increased fat enhances the synthesis of triglycerides and very LDL (VLDL) particles. In plasma, cholesterol and triglycerides are transported as VLDL (56% triglycerides), LDL cholesterol (48% cholesterol) or HDL cholesterol particles (46% phospholipids). In a study in which lipoproteins

were ultrasentrifugated,[50] 76% of ART-treated patients with lipoprotein disorders had elevated VLDL cholesterol with a normal LDL cholesterol level (Frederickson's type IV hyperlipidaemia). The VLDL composition resembled familial hypertriglyceridaemia with large VLDL particles, which means lower CHD risk than hyperlipidaemia caused by small LDL cholesterol particles as in Frederickson's type II. The authors suggested that a large proportion of ART-treated patients could have a lower cardiovascular risk than generally expected.

The high rate of concomitant infections in HIV-positive patients such as chlamydial and cytomegalovirus infections may also contribute to increased CHD risk.[51] Other risk factors in this population are the use of illicit drugs such as cocaine, amphetamines and anabolic steroids.[52] These drugs increase CHD risk, but are infrequently included in large cohort studies and could be important confounders when comparing HIV-positive and HIV-negative populations.

3. Managing CHD Risk in HIV-Positive Patients

Important factors relevant for estimating CHD risk should be assessed before initiating ART, for example, fasting lipids, fasting glucose, body measurements, blood pressure, kidney function, ECG and information about cigarette smoking, family history, previous diseases and relevant symptoms (table II). The physician should refer patients with dyslipidaemia to a dietician for advice regarding diet, exercise and smoking cessation. CHD risk should be calculated[53,54] in patients with elevated lipids, glucose or blood pressure. Drug therapy should be considered if the goals (table II and table III) are not reached by lifestyle intervention.

3.1 Diet

In HIV-negative patients an association between diet and lipid levels has been verified.[56] Dietary intervention alone has shown little lipid-lowering effect in dyslipidaemic patients receiving ART,[57,58] but a combination of dietary intervention and exercise may reduce total cholesterol, triglyceride levels and insulin resistance.[59,60] Reduction of visceral fat with exercise has also been demonstrated in patients receiving ART.[61] A negative aspect of a low-fat diet and exercise in already lipoatrophic patients is the reduction of peripheral fat. Increased intake of unsaturated fat is therefore recommended in lipoatrophic patients with dyslipidaemia. On the other hand, weight reduction in obese HIV-positive patients is crucial, as even modest reductions in bodyweight improve dyslipidaemia, hypertension and impaired glucose metabolism. Increased levels of HDL cholesterol have been associated with high alcohol consumption both in HIV-negative and HIV-positive patients.[62,63] Conversely, reduced intake of alcohol is important in patients with hypertriglyceridaemia. According to these various needs (fat atrophy or fat accumulation, different patterns of dyslipidaemia) individual dietary guidance, primarily made by a dietician, is required for patients receiving ART.

3.2 Cessation of Smoking

The most important CHD risk factor in the HIV-positive population seems to be smoking cigarettes, thus smoking cessation is essential to reduce CHD risk in patients receiving ART. Little research has been done on smoking cessation in this patient group, and the creation of innovative and individual cessation programmes is needed. In a pilot study from the Swiss HIV Cohort Study[64] 34 of 417 HIV-positive smokers from Basel participated in a smoking cessation programme. Fifty percent stopped smoking and 32% were still nonsmokers 12 months later. Today, smoking cessation often includes nicotine patches or oral bupropion. The combination of ART and these drugs is not contraindicated, but the reduction of seizure threshold seen with bupropion may exclude some HIV-patients from using it.

3.3 Dyslipidaemia

3.3.1 ART Regimen

In patients who already have lipid disturbances at baseline, regimens with low lipid-elevating effect should be preferred. However, many of these options may be restricted by individual resistance profiles, interactions with other components of regimens and serious adverse effects of the 'low lipid' ART regimens.[65-67] Nevertheless, individual tailor-

Table II. Clinical assessment before initiating antiretroviral therapy

Parameter	Goal	Lifestyle changes	Consider drug therapy
Fasting lipid levels[a]			
Triglycerides	<2.3 mmol/L; <200 mg/dL	≥2.3 mmol/L; ≥200 mg/dL	≥10.0 mmol/L ≥900 mg/dL
HDL cholesterol	>1 mmol/L; >40 mg/dL	<1 mmol/L;<40 mg/dL	
Total cholesterol	<6.2 mmol/L; <240 mg/dL	≥6.2 mmol/L; ≥240 mg/dL Calculate CHD risk	≥8.0 mmol/L; ≥312 mg/dL Consider other risk factors table III
LDL cholesterol[b]	<2.6 mmol/L; <100 mg/dL	≥2.6 mmol/L; ≥100 mg/dL Calculate CHD risk	≥4.9 mmol/L; ≥190 mg/dL Consider other risk factors table III
Fasting glucose levels			
Glucose	<6.2 mmol/L; <100 mg/dL	Elevated fasting glucose ≥6.2 mmol/L; ≥100 mg/dL On two separate occasions	DM >7.0 mmol/L; >130 mg/dL on two separate occasions
Body measures			
BMI (weight ÷ height^2)	<25 kg/m^2	Overweight: ≥25 kg/m^2	Obese: ≥30 kg/m^2
Umbilical waist	Men: <102cm, <40 inches Women: <88cm, <35 inches	Men: ≥102cm, ≥40 inches Women: ≥88cm, ≥35 inches	
Blood pressure			
Blood pressure (mm Hg)	<140/90; <130/80 if DM	≥140/90 or ≥130/80 if DM	≥140/90 or ≥130/80 if DM after lifestyle changes
Renal function			
Proteinuria			
Creatinine clearance[c]			
Cardiovasular			
ECG			
Anaemnestic information			
Cigarette smoking, adrenergic illegal drugs			
History/family: hypercholesterolaemia, hypertension, diabetes mellitus, cerebrovascular disease, peripheral vascular disease			
Premature CHD in first degree relative and age at event			
Drugs: lipid-, blood pressure- or glucose-lowering drug, smoking device, NSAIDs, anabolic steroids, oestrogen			
Symptoms: angina pectoris, dyspnoea, intermittent claudication			

a To convert total, HDL and LDL cholesterol from mmol/L to mg/dL we multiplied by 39. To convert triglycerides from mmol/L to mg/dL we multiplied by 89.

b When the triglyceride level is >4.2 mmol/L the LDL cholesterol level cannot be calculated by the Friedwald formula and has to be measured directly.

c Calculated by the Cockroft-Gault formula (figure 3).

BMI = body mass index; **CHD =** coronary heart disease; **DM** = diabetes mellitus; **HDL =** high-density lipoprotein; **LDL** = low-density lipoprotein.

ing of the ART regimen should be tried in patients with elevated CHD risk.

3.3.2 Nucleoside (Nucleotide) Reverse Transcriptase Inhibitors

When the lipodystrophy syndrome was discovered in 1998, the newly introduced PIs were the main suspects.[30] This made sense as mono- and dual NRTI therapy had been used for many years without emerging lipid changes. Later studies have shown that in combination regimens, stavudine may increase triglyceride and total cholesterol level and induce insulin resistance.[68]

Abacavir has undeniably a superior lipid profile than stavudine,[69] but its use has been somewhat restricted because of the potentially life-threatening hypersensitivity syndrome seen in 5% of recipients. This problem may be more easily handled in the future as an association between the hypersensitivity

syndrome and the haplotype HLA-B*5701 has been detected.[70] Rapid and accurate methods for haplotype HLA-B*5701 screening have been developed and validated,[71] and will probably be available for clinical use within short time. Abacavir plus lamivudine in combination with a PI or NNRTI is thus a good NRTI choice in dyslipidaemic patients. In contrast, the inferior efficacy of triple NRTI regimens as monotherapy such as abacavir/lamivudine/zidovudine is now well documented in the ACTG 5095 study and should not be used.[72]

Tenofovir disoproxil fumarate (tenofovir DF) is a once daily nucleotide analogue with little or no effect on blood lipids.[73] It has similar effect to lamivudine, including an effect on viral hepatitis. The efficacy and safety of tenofovir DF versus stavudine in ART-naive patients is shown in a 3-year randomised trial.[74] Through to 144 weeks, the regimen including tenofovir DF was comparable with stavudine and had a better lipid profile; triglyceride levels increased 0.01 mmol/L with tenofovir DF versus 1.5 mmol/L with stavudine ($p < 0.001$), total cholesterol increased 0.8 mmol/L versus 1.5 mmol/L ($p < 0.001$), direct LDL cholesterol increased 0.36 mmol/L versus 0.67 mmol/L ($p < 0.001$), and HDL cholesterol increased 0.23 mmol/L versus 0.15 mmol/L ($p = 0.003$). Thus, tenofovir DF may be a useful choice in patients with dyslipidaemia, except in patients with significantly impaired renal function (see section 3.5).

Emtricitabine (FTC) is a new nucleoside agent with activity against both HIV and hepatitis B virus. Just like tenofovir DF, emtricitabine is very similar to lamivudine with respect to its activity, convenience, safety and resistance profile. The now available combination of emtricitabine with tenofovir DF in the same pill makes it an attractive backbone combination to use in conjunction with other antiretroviral drugs.[75,76]

3.3.3 Protease Inhibitors

Most PIs alter the lipid profiles of HIV-positive patients. In a study including 679 ART-naive HIV-infected patients who initiated PI therapy between August 1996 and January 2002,[77] the investigators found a 22% increase in triglycerides and a 24% increase in total cholesterol after 12 months. The elevating effect of ritonavir on triglyceride levels is well documented,[41,78] including boosting other PIs with ritonavir 100mg.[40] The highly effective combination of lopinavir/ritonavir is often the drug of choice when a PI regimen is needed, but this combination is shown to significantly increase triglyceride levels, VLDL cholesterol and free fatty acids levels, even in HIV-negative men.[79]

The novel PI atazanavir has a less dyslipidaemic profile than nelfinavir[78] and lopinavir,[80] and it does not seem to affect insulin sensitivity.[81] In a recent 96-week comparison of once daily ritonavir boosted atazanavir and twice daily lopinavir/ritonavir, Johnson et al.[80] found the combinations to have similar efficacy in treatment-experienced

Table III. National Cholesterol Education Program treatment decision based on low-density lipoprotein cholesterol (LDL-C) and/or non-high-density lipoprotein cholesterol (HDL-C) levels[55]

Treatment decision; mmol/L (mg/dL)	CHD, type 2 diabetes mellitus, dialysis, stroke, PAD or 10y risk ≥20%	≥2 Risk factors[a]		0–1 Risk factors
		10y risk 10–20%	10y risk <10%	
Goal				
LDL-C	<2.6 (100)	≥3.4 (130)	<3.4 (130)	<4.1 (160)
Non-HDL-C	<3.4 (130)	≥4.1 (160)	<4.1 (160)	<4.9 (190)
Lifestyle changes				
LDL-C	≥2.6 (100)	≥3.4 (130)	≥3.4 (130)	≥4.1 (160)
Non-HDL-C	≥3.4 (130)	≥4.1 (160)	≥4.1 (160)	≥4.9 (190)
Consider drug therapy				
LDL-C	≥3.4 (130)	≥3.4 (130)	≥4.1 (160)	≥4.9 (190)
Non-HDL-C	≥4.1 (160)	≥4.1 (160)	≥4.9 (190)	≥5.7 (220)

a For risk factors, see table III.

CHD = cardiovascular heart disease; **Non-HDL-C** = total cholesterol minus HDL-C; **PAD** = peripheral arterial disease.

patients; mean reductions from baseline in HIV RNA were −2.29 and −2.08 $\log_{10}$ copies/mL, respectively. Low-lipid, once daily regimens may become attractive options if the efficacy of such regimens is verified. In the European AIDS Clinical Society Conference in Dublin 2005, preliminary 24-week results from a study including a once daily regimen was presented.[82] This was a single-arm, open-label study combining atazanavir/ritonavir (100 mg/300 mg) plus tenofovir DF/emtricitabine.[82] In an intention-to-treat analysis including 23 patients, the percentages of patients with an HIV-1 RNA <50 and <400 copies/mL were 56% and 94%, respectively. Five patients discontinued the study, two of them as a result of adverse events.

Tipranavir is a new PI approved by the US FDA in June 2005 as rescue therapy in highly treatment-experienced patients. In the two phase III RESIST (Randomised Evaluation of Strategic Intervention in multidrug reSistant patients with Tipranavir)-1 and -2 studies,[83] tipranavir/ritonavir achieved better virological response after 24 weeks than standard comparable ritonavir-boosted PIs. Tipranavir had a more dyslipidaemic profile than the standard boosted regimens; prevalence of grade 2 and 3 lipid abnormalities was 3% vs 0.3% for total cholesterol and 21% vs 11% for triglycerides. Details about the grade 2 and 3 abnormality cut-offs are not available.

Fosamprenavir in combination with ritonavir is an improved way to administrate amprenavir, with fewer pills and better efficacy. In a small study presented by Gathe et al.[84] fosamprenavir/ritonavir had a potency similar to nelfinavir, but more patients in the fosamprenavir/ritonavir arm developed grade 3 hypertriglyceridaemia; 5% vs 2%. Similar results were found in patients receiving amprenavir in the D:A:D study; median (interquartile range) triglycerides 2.4 mmol/L in amprenavir recipients versus 1. 7 mmol/L in patients receiving nelfinavir.[40] Consequently, fosamprenavir should not be used in dyslipidaemic patients if any other choices are available and is in any case restricted to PI-naive patients.

3.3.4 Non-Nucleoside Reverse Transcriptase Inhibitors

Data presented at Conference on Retroviruses and Opportunistic Infections 2006 by the D:A:D study[85] showed no association between increased NNRTI exposure and increased MI risk. By 2005, the D:A:D cohort included 23 400 HIV-infected patients, thus this study settles much of the discussion around the influence of NNRTIs on CHD. However, the NNRTI recipients in this study had fewer years of experience than those receiving PIs, and the risk reducing effect of switching from a PI-based to a NNRTI-based regimen is still not very well documented. Changing from a PI regimen to a NNRTI regimen may improve the lipid profile by increasing HDL cholesterol levels and thus lowering the total cholesterol **:** HDL cholesterol ratio,[38,39] but it does not necessarily reduce the level of triglycerides or total cholesterol.[86]

3.3.5 Lipid-Lowering Therapy

The benefits of lipid-lowering drugs on CHD in ART-treated patients have not been documented, but lipid-lowering diet and drugs are recommended in dyslipidaemic ART-patients with manifest CHD disease, diabetes or estimated CHD risk ≥20%.[55] Useful web-based risk calculators for estimating Framingham risk,[54] and special guidelines for evaluation and treatment of dyslipidaemia in HIV-positive patients[55] are available and should be consulted before initiating lipid-lowering drugs in dyslipidaemic ART-treated patients.

3.3.6 Drug Treatment of Hypertriglyceridaemia

Elevated triglycerides are the main problem for ART-treated patients, and in the multivariate model of the D:A:D study elevated triglycerides were an independent factor for increased CHD risk. On the other hand, there is limited evidence that correcting the laboratory abnormality of hypertriglyceridaemia will reduce coronary events, thus triglycerides are not a primary treatment target in the National Cholesterol Education Program guidelines[87] (table III). The level of triglycerides is first of all associated with glucose metabolism, and patients with elevated triglycerides should be asked about their consumption of alcohol, sweets and sodas before changes in ART regimens are considered. In severe hypertriglyceridaemia (>10 mmol/L), life-threatening pancreatitis may occur, and institution of diet and lipid-lowering therapy is important. Isolated hypertriglyceridaemia can be treated with omega-3 fatty acids or fibric acid derivatives (fibrates) such as gemfibrozil.[88]

3.3.7 Drug Treatment of Hypercholesterolaemia

Selected lipid-lowering drugs, such as the HMG-CoA reductase inhibitors (statins) pravastatin or atorvastatin, appear to be safely used in ART-treated patients.[58,67] Pravastatin has less effect on the liver metabolism than atorvastatin, but possibly also less effect on coronary atherosclerosis.[89] Simvastatin and lovastatin are contraindicated because of potential interactions.[90] A combination of diet, statins and fibrates are usually needed to reach the lipid goals. Nicotinic acid (niacin) has so far largely been avoided in ART-treated patients because of a negative influence on the glucose metabolism. Results from the ACTG 5148 study presented by Dube and Aberg[91] in Dublin 2005 showed that diet and extended-release nicotinic acid reduced triglycerides and total cholesterol significantly. Unfortunately (but as expected), insulin resistance increased significantly, thus care is needed when nicotinic acid is introduced in this patient group. In addition, the novel lipid-lowering drug ezetimibe[92] could be used to improve a lipid-lowering regimen. In a recent study presented at Interscience Conference on Antimicrobial Agents and Chemotherapy 2005,[93] 22 HIV-positive patients receiving ART and pravastatin with LDL cholesterol >3.3 mmol/L were included. By adding ezetimibe, triglycerides and LDL cholesterol levels were significantly reduced (nearly 20%) after 6 weeks, but at the final follow-up at week 24 the reduction was 8% only. Therefore, further studies of ezetimibe are needed before conclusions may be drawn.

3.4 Diabetes Mellitus

Fasting glucose levels should be monitored in patients receiving ART, as some of the drugs may induce alterations in the glucose metabolism. Indinavir has been shown to directly induce insulin resistance by reducing the selective intrinsic transport activity of glucose transporter 4.[94,95] The HIV-infection *per se* may also influence glucose metabolism. The HIV-1 accessory proteins, for example viral protein R (Vpr), may act as a co-activator for the glucocorticoid receptor and thus increase tissue sensitivity to corticosteroids.[96] This association to corticosteroid sensitivity seems reasonable as many characteristics of the lipodystrophy syndrome are similar to those of Cushing's syndrome. In addition, increased fat content in central fat deposits and skeletal muscle is found to be strongly associated with insulin resistance in lipodystrophic patients.[97]

An elevated prevalence of the metabolic syndrome and insulin resistance in patients receiving ART, especially in patients with lipodystrophy, has been described previously.[98-100] In a recent study,[37] we found that non-overweight ART-treated patients had a higher prevalence of metabolic syndrome (15% vs 2%) and insulin resistance (39% vs 19%) than non-overweight HIV-negative controls. The prevalence in non-overweight ART-treated patients with lipodystrophy was even higher; 21% had metabolic syndrome and 49% were insulin resistant. Independent of weight, only 2% of the ART-naive patients fulfilled the criteria for metabolic syndrome. In contrast to these findings, other studies have not demonstrated any significant difference in insulin resistance between lipodystrophic HIV-patients and HIV-negative controls.[101]

The D:A:D study did not find any increased risk of diabetes among patients with HIV receiving ART compared with ART-naive patients, but diabetes was an independent risk factor for MI.[7]

Cardiovascular risk is increased in people with diabetes, and regulation of blood glucose and lipid levels is important in these patients. First-line therapy in patients with type 2 diabetes is metformin with or without sulfonylurea. Although the combination with NRTIs may increase the risk of lactacidosis, this is uncommon in clinical practice. A novel (and expensive) group of antidiabetic drugs, the thiazolidinediones (glitazones), showed promising results in patients with inherited lipoatrophic diabetes by improving metabolic control and increasing subcutaneous body fat.[102] Thiazolidinediones are PPARγ agonists, thus promoting adipocyte differentiation *in vitro* and increasing insulin sensitivity *in vivo*, possibly by enhanced expression of adiponectin. In two randomised, double-blind, placebo-controlled studies where patients with HIV-associated lipoatrophy were given rosiglitazone 8 mg/day for 24 or 48 weeks, improvements in insulin sensitivity but not fat atrophy were seen; however, an alarming increase in total cholesterol and triglyceride levels was induced.[103,104] In a similar study,[105] treatment with rosiglitazone 4 mg/day for 3 months improved insulin sensitivity, increased

adiponectin levels, decreased free fatty acid levels and improved peripheral fat deposition. Also in this study, total and LDL cholesterol increased significantly, but triglycerides did not. Serum glitazone concentrations in combination with other antidiabetic agents may be decreased by ritonavir and nelfinavir, which induce cytochrome P450 enzyme CYP2C9. Another PPARγ agonist, pioglitazone, has recently showed an effect on limb lipoatrophy in HIV-infected patients.[106] In this study no significant lipid changes were found, thus the effect of different PPARγ agonist on HIV-infected patients deserves further investigation.

3.5 Hypertension

Studies of blood pressure in HIV-positive patients have so far been contradictory.[107-111] This may reflect both differences in age, sex, race and ART medication in the different cohorts. Only one study[112] so far includes blood pressure measures before and after initiating ART, and no randomised studies of antihypertensive drugs used in HIV-positive patients exist. In a Norwegian study[113] from 2000 to 2001 that included 721 patients, we found that the prevalence of hypertension was similar in HIV-positive patients receiving ART and matched HIV-negative controls. In the HIV-positive patients, hypertension was associated with age, male gender, waist/hip ratio, total cholesterol and triglyceride levels, but not with body mass index, HIV-related factors or ART. Few comparable studies including HIV-negative controls have been published, and these were either aimed at studying patients with lipodystrophy[110] or included especially healthy HIV-negative controls.[111] In a cohort including 5504 HIV-positive men, Seaberg et al.[114] found that ART for >2 years increased the risk of hypertension significantly. These findings are in contrast with recent cohort studies[115,116] that do not find any evidence for an independent deleterious effect of any class of antiretroviral drugs or cumulative duration of treatment on blood pressure. Somewhat surprisingly, the D:A:D study[116] found that use of NNRTIs was associated with a lower risk of development of hypertension, but these findings have to be confirmed in prospective, randomised studies.

However, as HIV-positive patients age they become hypertensive whether using antiretroviral drugs or not. When hypertension is detected (≥140/90mm Hg or ≥130/80mm Hg in patients with diabetes), a urine sample should be examined for proteinuria. In a recent German cohort study,[115] investigators found that 41% of hypertensive HIV-patients had persistent, glomerular proteinuria compared with 3% of the normotensive HIV-patients. Secondly, creatinine clearance (CL_{CR}) should be estimated using the Cockroft-Gault[117] or Modification of Diet in Renal Disease equations[118] (figure 3). CL_{CR} calculators are available at different websites.[119] If CL_{CR} is ≤50 mL/min, dose adjustments are needed in patients receiving tenofovir DF. When CL_{CR} is ≤30 mL/min tenofovir DF is not recommended. The renal effect of indinavir is well known, thus indinavir should be avoided when renal function is impaired.

Generally, guidelines for blood pressure reduction in HIV-negative patients are useful in HIV-positive patients as well. However, physicians treating hypertensive ART-treated patients should be especially aware of possible unfavourable lipid effects of thiazide diuretics, and interactions between ART and different antihypertensive drugs.[90] Valuable information about ART interactions is available at the HIV Site/Database of ART interactions,[120] MICROMEDEX and package inserts of the actual drugs. The potential increase in serum concentrations of calcium channel antagonists during concomitant use of atazanavir and ritonavir could lead to hypotension and bradycardia.[121] On the other hand, the serum concentration, and thus the antihypertensive effect, of calcium channel antagonists

Cockcroft-Gault:

$$CL_{CR}\ (\text{mL/min}) = \frac{[140 - \text{age (y)}] \times \text{weight (kg)}\ [\times 0.85 \text{ if female}]}{72 \times \text{serum creatinine (mg/dL)}}$$

Simplified MDRD:

$$\text{GFR (mL/min/1.73m}^2) = 186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age (y)}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if Black}]$$

Fig. 3. Cockroft-Gault[117] and modification of diet in renal disease (MDRD)[118] equations for predicting creatinine clearance (CL_{CR}). **GFR** = glomerular filtration rate.

can be decreased by concomitant nevirapine. The effect of β-adrenoceptor antagonists (β-blockers) may be enhanced by atazanavir, ritonavir and nelfinavir. A clinical illustration of such an interaction is a recent case report by Izzedine et al.[122] that describes hypotension, leg oedema and skin blood flow vasomotion in a patient receiving felodipine who started nelfinavir as part of a post-exposure prophylaxis regimen.

As in type 2 diabetes, the best choice of treatment in ART-treated patients with proteinuria associated with hypertension would be an ACE inhibitor or an angiotensin II receptor antagonist. In addition to blood pressure reduction, they have a favourable effect on insulin resistance and renal function. ACE inhibition initiated prior to the onset of severe renal insufficiency may offer long-term renal survival benefits in patients with HIV-associated renal disease[123] but no randomised trials comparing different antihypertensive drugs in HIV-positive patients are published. The Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America[124] recommend that all patients at the onset of HIV diagnosis be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function. If there is no evidence of proteinuria at initial evaluation, patients at high risk for the development of proteinuric renal disease (e.g. African Americans, those with CD4+ cell counts <200 cells/μL or HIV RNA levels >4000 copies/mL, or those with diabetes, hypertension, or hepatitis C virus coinfection) should undergo annual screening. Patients with proteinuria of grade ≥1+ by dipstick analysis or reduced renal function (glomerular filtration rate <60 mL/min per 1.73m^2) [figure 3] should undergo additional evaluation, including quantification of proteinuria, renal ultrasound and potentially renal biopsy.

4. Conclusion

Accumulating evidence suggests an association between ART and increased CHD risk, although prospective studies comparing HIV-positive and HIV-negative patients are needed to allow conclusions about the magnitude of this problem. Important factors relevant for estimating CHD risk should be assessed before initiating ART, such as fasting lipid levels, fasting glucose levels, blood pressure, ECG and information about cigarette smoking, family history, previous diseases and recent medication. Patients with elevated lipid levels, elevated fasting glucose levels or hypertension should be referred to a dietician for advice regarding diet, exercise and smoking cessation. The ART regimen should be tailored according to the guidelines described in this review and additional drug therapy should be considered if the goals are not achieved by lifestyle intervention. However, the most important intervention in HIV-positive patients receiving ART is to support the cigarette smokers in their struggle with smoking cessation.

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References

1. Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. AIDS 2002; 16 (12): 1663-71
2. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 2005 Feb; 34 (1): 121-130. Epub 2004 Nov 23
3. Calabrese LH, Albrecht M, Young J, et al. Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. N Engl J Med 2003; 348 (23): 2323-8
4. UNAIDS. 2004 report on the global AIDS epidemic: 4th global report July 2004 [online]. Available from URL: http://www.unaids.org/bangkok2004/GAR2004_html/GAR2004_00_en.htm [Accessed 2006 July 26]
5. Bozzette SA, Ake CF, Tam HK, et al. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl J Med 2003; 348 (8): 702-10
6. Klein D, Hurley LB, Quesenberry Jr CP, et al. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? J Acquir Immune Defic Syndr 2002; 30 (5): 471-7
7. 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 (21): 1993-2003
8. Coplan PM, Nikas A, Japour A, et al. Incidence of myocardial infarction in randomized clinical trials of protease inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. AIDS Res Hum Retroviruses 2003; 19 (6): 449-55
9. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr 2003; 33 (4): 506-12

10. Mary-Krause M, Cotte L, Simon A, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 2003; 17 (17): 2479-86
11. Barbaro G, Di Lorenzo G, Cirelli A, et al. An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV infection receiving highly active antiretroviral therapy. Clin Ther 2003; 25 (9): 2405-18
12. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 2002; 360 (9347): 1747-8
13. d'Arminio A, Sabin CA, Phillips AN, et al. Cardio- and cerebrovascular events in HIV-infected persons. AIDS 2004; 18 (13): 1811-7
14. Nordoy I, Aukrust P, Muller F, et al. Abnormal levels of circulating adhesion molecules in HIV-1 infection with characteristic alterations in opportunistic infections. Clin Immunol Immunopathol 1996; 81 (1): 16-21
15. Chi D, Henry J, Kelley J, et al. The effects of HIV infection on endothelial function. Endothelium 2000; 7 (4): 223-42
16. Depairon M, Chessex S, Sudre P, et al. Premature atherosclerosis in HIV-infected individuals: focus on protease inhibitor therapy. AIDS 2001; 15 (3): 329-34
17. Maggi P, Lillo A, Perilli F, et al. Colour-Doppler ultrasonography of carotid vessels in patients treated with antiretroviral therapy: a comparative study. AIDS 2004; 18 (7): 1023-8
18. de Saint Martin L, Vandhuick O, Guillo P, et al. Premature atherosclerosis in HIV positive patients and cumulated time of exposure to antiretroviral therapy (SHIVA study). Atherosclerosis 2006; 185 (2): 361-7. Epub 2005 Aug 30
19. Mercie P, Thiebaut R, Aurillac-Lavignolle V, et al. Carotid intima-media thickness is slightly increased over time in HIV-1-infected patients. HIV Med 2005; 6 (6): 380-7
20. Meng Q, Lima JA, Lai H, et al. Coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in black injection drug users infected with human immunodeficiency virus-1 treated with protease inhibitors. Am Heart J 2002; 144 (4): 642-8
21. Talwani R, Falusi OM, Mendes de Leon CF, et al. Electron beam computed tomography for assessment of coronary artery disease in HIV-infected men receiving antiretroviral therapy. J Acquir Immune Defic Syndr 2002; 30 (2): 191-5
22. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24 (11): 987-1003
23. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 2002; 105 (3): 310-5
24. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. Am Heart J 1991; 121 (1 Pt 2): 293-8
25. Bergersen BM, Sandvik L, Bruun JN, et al. Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects. Eur J Clin Microbiol Infect Dis 2004; 23 (8): 625-30
26. Grover SA, Coupal L, Gilmore N, et al. Impact of dyslipidemia associated with Highly Active Antiretroviral Therapy (HAART) on cardiovascular risk and life expectancy. Am J Cardiol 2005; 95 (5): 586-91
27. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients: association with antiretroviral therapy: results from the DAD study. AIDS 2003; 17 (8): 1179-93
28. Empana JP, Ducimetiere P, Arveiler D, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J 2003; 24 (21): 1903-11
29. Thomsen TF, McGee D, Davidsen M, et al. A cross-validation of risk-scores for coronary heart disease mortality based on data from the Glostrup Population Studies and Framingham Heart Study. Int J Epidemiol 2002; 31 (4): 817-22
30. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12 (7): F51-8
31. Foster DW. The lipodystrophies and other rare disorders of adipose tissue. In: Wilson JD, editor. Harrison's principles of internal medicine. 12th ed. International edition. New York: McGraw-Hill Inc., 1991: 1883-7
32. Garg A. Lipodystrophies. Am J Med 2000; 108 (2): 143-52
33. Grunfeld C, Pang M, Doerrler W, et al. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 1992; 74 (5): 1045-52
34. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. JAMA 2003; 289 (22): 2978-82
35. Moriya K, Shintani Y, Fujie H, et al. Serum lipid profile of patients with genotype 1b hepatitis C viral infection in Japan. Hepatol Res 2003; 25 (4): 371-6
36. Polgreen PM, Fultz SL, Justice AC, et al. Association of hypocholesterolaemia with hepatitis C virus infection in HIV-infected people. HIV Med 2004; 5 (3): 144-50
37. Bergersen BM, Schumacher A, Sandvik L, et al. Important differences in components of the metabolic syndrome between HIV-patients with and without highly active antiretroviral therapy and healthy controls. Scand J Infect Dis 2006; 38 (8): 682-9
38. van der Valk, Kastelein JJ, Murphy RL, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 2001; 15 (18): 2407-14
39. Bergersen BM, Tonstad S, Sandvik L, et al. Low prevalence of high-density lipoprotein cholesterol level < 1 mmol/L in non-nucleoside reverse transcriptase inhibitor recipients. Int J STD AIDS 2005; 16 (5): 365-9
40. Fontas E, van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? J Infect Dis 2004; 189 (6): 1056-74
41. Periard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors: the Swiss HIV Cohort Study. Circulation 1999; 100 (7): 700-5
42. Manfredi R, Chiodo F. Disorders of lipid metabolism in patients with HIV disease treated with antiretroviral agents: frequency, relationship with administered drugs, and role of hypolipidaemic therapy with bezafibrate. J Infect 2001; 42 (3): 181-8
43. Bastard JP, Caron M, Vidal H, et al. Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. Lancet 2002; 359 (9311): 1026-31
44. Mynarcik DC, McNurlan MA, Steigbigel RT, et al. Association of severe insulin resistance with both loss of limb fat and elevated serum tumor necrosis factor receptor levels in HIV lipodystrophy. J Acquir Immune Defic Syndr 2000; 25 (4): 312-21
45. Ledru E, Christeff N, Patey O, et al. Alteration of tumor necrosis factor-alpha T-cell homeostasis following potent antiretroviral therapy: contribution to the development of human immunodeficiency virus-associated lipodystrophy syndrome. Blood 2000; 95 (10): 3191-8

46. Limone P, Biglino A, Valle M, et al. Insulin resistance in HIV-infected patients: relationship with pro-inflammatory cytokines released by peripheral leukocytes. J Infect 2003; 47 (1): 52-8
47. Nolan D, Moore C, Castley A, et al. Tumour necrosis factor-alpha gene -238G/A promoter polymorphism associated with a more rapid onset of lipodystrophy. AIDS 2003; 17 (1): 121-3
48. Brinkman K, Smeitink JA, Romijn JA, et al. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet 1999; 354 (9184): 1112-5
49. Balasubramanyam A, Sekhar RV, Jahoor F, et al. Pathophysiology of dyslipidemia and increased cardiovascular risk in HIV lipodystrophy: a model of 'systemic steatosis'. Curr Opin Lipidol 2004; 15 (1): 59-67
50. Mauss S, Stechel J, Willers R, et al. Differentiating hyperlipidaemia associated with antiretroviral therapy. AIDS 2003; 17 (2): 189-94
51. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? Lancet 1997; 350 (9075): 430-6
52. Ghuran A, Nolan J. Recreational drug misuse: issues for the cardiologist. Heart 2000; 83 (6): 627-33
53. International Task Force for the Prevention of Coronary Heart Disease. Coronary heart assessment [online]. Available from URL: http://www.chd-taskforce.com [Accessed 2006 Jun 28]
54. National Cholesterol Education Program. Risk assessment tool for estimating your 10-year risk of having a heart attack [online]. Available from URL: http://hp2010.nhlbihin.net/atpiii/calculator.asp [Accessed 2006 Jun 28]
55. Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 2003; 37 (5): 613-27
56. Grundy SM, Denke MA. Dietary influences on serum lipids and lipoproteins. J Lipid Res 1990; 31 (7): 1149-72
57. Barrios A, Blanco F, Garcia-Benayas T, et al. Effect of dietary intervention on highly active antiretroviral therapy-related dyslipemia. AIDS 2002; 16 (15): 2079-81
58. Moyle GJ, Lloyd M, Reynolds B, et al. Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. AIDS 2001; 15 (12): 1503-8
59. Henry K, Melroe H, Huebesch J, et al. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. Lancet 1998; 352 (9133): 1031-2
60. Jones SP, Doran DA, Leatt PB, et al. Short-term exercise training improves body composition and hyperlipidaemia in HIV-positive individuals with lipodystrophy. AIDS 2001; 15 (15): 2049-51
61. Roubenoff R, Weiss L, McDermott A, et al. A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. AIDS 1999; 13 (11): 1373-5
62. Perret B, Ruidavets JB, Vieu C, et al. Alcohol consumption is associated with enrichment of high-density lipoprotein particles in polyunsaturated lipids and increased cholesterol esterification rate. Alcohol Clin Exp Res 2002; 26 (8): 1134-40
63. Hadigan C, Jeste S, Anderson EJ, et al. Modifiable dietary habits and their relation to metabolic abnormalities in men and women with human immunodeficiency virus infection and fat redistribution. Clin Infect Dis 2001; 33 (5): 710-7
64. Spoerl D, Elzi L, Voggensperger J. A stop smoking program in HIV-1-infected patients: a pilot study [abstract no. PS5/4 2006]. Program and abstracts from the 10th European AIDS Conference; 2005 Nov 17-20; Dublin
65. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. Semin Liver Dis 2003; 23 (2): 173-82
66. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther 2001; 23 (10): 1603-14
67. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. J Acquir Immune Defic Syndr 2002; 31 (3): 257-75
68. Saves M, Raffi F, Capeau J, et al. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. Clin Infect Dis 2002; 34 (10): 1396-405
69. Clumeck N, Goebel F, Rozenbaum W, et al. Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor-based highly active antiretroviral therapy in HIV-1-infected patients with undetectable plasma HIV-1 RNA. AIDS 2001; 15 (12): 1517-26
70. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002; 359 (9308): 727-32
71. Martin AM, Nolan D, Mallal S. HLA-B*5701 typing by sequence-specific amplification: validation and comparison with sequence-based typing. Tissue Antigens 2005; 65 (6): 571-4
72. National Institute of Allergy and Infectious Diseases. Important interim results from a phase III, randomized, double-blind comparison of three protease-inhibitor-sparing regimens for the initial treatment of HIV infection (AACTG Protocol A5095). March 12, 2003 [online]. Available from URL: http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html [Accessed 2006 Jul 26]
73. Moreno S, Domingo P, Labarga P, et al. Dyslipidemia improvement in patients switching from d4T to tenofovir [poster]. 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 Sep 14-17; Chicago, H-355b
74. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA 2004; 292 (2): 191-201
75. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. Clin Infect Dis 2006; 42 (1): 126-31
76. Molina JM, Cox SL. Emtricitabine: a novel nucleoside reverse transcriptase inhibitor. Drugs Today (Barc) 2005; 41 (4): 241-52
77. Levy AR, McCandless L, Harrigan PR, et al. Changes in lipids over twelve months after initiating protease inhibitor therapy among persons treated for HIV/AIDS. Lipids Health Dis 2005; 4 (1): 4
78. Sanne I, Piliero P, Squires K, et al. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. J Acquir Immune Defic Syndr 2003; 32 (1): 18-29
79. Lee GA, Seneviratne T, Noor MA, et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. AIDS 2004; 18 (4): 641-9
80. Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. AIDS 2006; 20 (5): 711-8
81. Noor MA, Parker RA, O'Mara E, et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. AIDS 2004; 18 (16): 2137-44

82. Pearce D, Carpio F Guyer B, et al. The VeLLA Study: a prospective study of tenofovir DF/emtricitabine/atazanavir/ritonavir in naive patients [abstract no. PE7/15]. Abstracts of 10th European AIDS Conference/EACS; 2005 Nov 17-20; Dublin
83. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. Drugs 2005; 65 (12): 1669-77
84. Gathe Jr JC, Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. AIDS 2004; 18 (11): 1529-37
85. Friis-Møller N, Reiss P, El Sadr W, et al. Exposure to PI and NNRTI and risk of myocardial infarction: results from the D: A: D Study [abstract no. 144]. 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)
86. Fisac C, Fumero E, Crespo M, et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. AIDS 2005; 19 (9): 917-25
87. Executive Summary of the Third Report of the 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 (19): 2486-97 [online]. Available from URL: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf [Accessed 2006 Jul 27]
88. Miller J, Brown D, Amin J, et al. A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. AIDS 2002; 16 (16): 2195-200
89. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291 (9): 1071-80
90. Fichtenbaum CJ, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. Clin Pharmacokinet 2002; 41 (14): 1195-211
91. Dube MP, Aberg JA. Safety and efficacy of extended-release niacin for the treatment of dyslipidemia in patiens with HIV infection: a prospective, multicenter study (ACTG 5148) [abstract no. 12]. Program and abstracts of the 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV; 2005 Nov 13-16; Dublin
92. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 2004; 148 (3): 447-55
93. Negredo E, Rey-Joly C, Puig J. Ezetimibe, a selective inhibitor of cholesterol absorption, as a new strategy for treatment of hypercholesterolemia secondary to antiretroviral therapy [abstract no. H-336]. Program and abstracts from the 45th ICAAC; 2005 Dec 16-19; Washington, DC
94. Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. AIDS 2001; 15 (7): F11-8
95. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. AIDS 2002; 16 (6): 859-63
96. Kino T, Chrousos GP. Human immunodeficiency virus type-1 accessory protein Vpr: a causative agent of the AIDS-related insulin resistance/lipodystrophy syndrome? Ann N Y Acad Sci 2004; 1024: 153-67
97. Torriani M, Hadigan C, Jensen ME, et al. Psoas muscle attenuation measurement with computed tomography indicates intramuscular fat accumulation in patients with the HIV-lipodystrophy syndrome. J Appl Physiol 2003; 95 (3): 1005-10
98. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. Clin Infect Dis 2001; 32 (1): 130-9
99. Grinspoon S. Insulin resistance in the HIV-lipodystrophy syndrome. Trends Endocrinol Metab 2001; 12 (9): 413-9
100. Gazzaruso C, Sacchi P, Garzaniti A, et al. Prevalence of metabolic syndrome among HIV patients. Diabetes Care 2002; 25 (7): 1253-4
101. De Larranaga G, Galich A, Puga L, et al. Insulin resistance status is an important determinant of PAI-1 levels in HIV-infected patients, independently of the lipid profile. J Thromb Haemost 2004; 2 (3): 532-4
102. Arioglu E, Duncan-Morin J, Sebring N, et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. Ann Intern Med 2000; 133 (4): 263-74
103. Sutinen J, Hakkinen AM, Westerbacka J, et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy: a randomized double-blind placebo-controlled study. Antivir Ther 2003; 8 (3): 199-207
104. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipoatrophy: randomised, double-blind, placebo-controlled trial. Lancet 2004; 363 (9407): 429-38
105. Hadigan C, Yawetz S, Thomas A, et al. Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. Ann Intern Med 2004; 140 (10): 786-94
106. Slama L, Lanoy E, Valentin MA, et al. Effect of pioglitazone on HIV-1 related lipoatrophy: a randomized double-blind placebo-controlled trial (ANRS 113) with 130 patients [abstract no. 151LB]. Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8; Denver (CO)
107. Mattana J, Siegal FP, Sankaran RT, et al. Absence of age-related increase in systolic blood pressure in ambulatory patients with HIV infection. Am J Med Sci 1999; 317 (4): 232-7
108. Aoun S, Ramos E. Hypertension in the HIV-infected patient. Curr Hypertens Rep 2000; 2 (5): 478-81
109. Cattelan AM, Trevenzoli M, Sasset L, et al. Indinavir and systemic hypertension. AIDS 2001; 15 (6): 805-7
110. Sattler FR, Qian D, Louie S, et al. Elevated blood pressure in subjects with lipodystrophy. AIDS 2001; 15 (15): 2001-10
111. Gazzaruso C, Bruno R, Garzaniti A, et al. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. J Hypertens 2003; 21 (7): 1377-82
112. Palacios R, Santos J, Garcia A, et al. Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients: a prospective study in a cohort of naive patients. HIV Med 2006; 7 (1): 10-5
113. Bergersen BM, Sandvik L, Dunlop O, et al. Prevalence of hypertension in HIV-positive patients on highly active retroviral therapy (HAART) compared with HAART-naive and HIV-negative controls: results from a Norwegian study of 721 patients. Eur J Clin Microbiol Infect Dis 2003; 22 (12): 731-6
114. Seaberg EC, Munoz A, Lu M, et al. HIV infection, HAART and blood pressure: results from the Multicenter AIDS Cohort Study (MACS) [abstract no. P-774]. 10th Conference on Retroviruses and Opportunistic Infections; 2003 Feb 10-14; Boston (MA)
115. Jung O, Bickel M, Ditting T, et al. Hypertension in HIV-1-infected patients and its impact on renal and cardiovascular integrity. Nephrol Dial Transplant 2004; 19 (9): 2250-8
116. Thiebaut R, El Sadr WM, Friis-Moller N, et al. Predictors of hypertension and changes of blood pressure in HIV-infected patients. Antivir Ther 2005; 10 (7): 811-23
117. Cockroft DW, Gault M. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41

118. Levey AS, Green T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. J Am Soc Nephrol 2000; 11: 155A
119. National Kidney Foundation. CLCR calculator [online]. Available from URL: http://www.kidney.org/progfessionals/KDOQI/gfr_calculator.cfm [Accessed 2006 Jul 26]
120. HIV InSite. Database of antiretroviral drug interactions [online]. Available from URL: http://hivinsite.ucsf.edu/InSite?page=ar-00-02 [Accessed 2006 Jul 26]
121. Glesby MJ, Aberg JA, Kendall MA, et al. Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. Clin Pharmacol Ther 2005; 78 (2): 143-53
122. Izzedine H, Launay-Vacher V, Deray G, et al. Nelfinavir and felodipine: a cytochrome P450 3A4-mediated drug interaction. Clin Pharmacol Ther 2004; 75 (4): 362-3
123. Wei A, Burns GC, Williams BA, et al. Long-term renal survival in HIV-associated nephropathy with angiotensin-converting enzyme inhibition. Kidney Int 2003; 64 (4): 1462-71
124. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005; 40 (11): 1559-85

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