Drugs and Cardiotoxicity in HIV and AIDS

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ABSTRACT: **The advent of potent antiretroviral drugs in recent years has had an impressive impact on mortality and disease progression in HIV-infected patients, so that issues related to long-term effects of drugs are of growing importance. Hyperlipidemia, hyperglycemia, and lipodystrophy are increasingly described adverse effects of highly active antiretroviral therapy (HAART), in particular when protease inhibitors are used. Hyperlipidemia is strikingly associated with the use of most available protease inhibitors, with an estimated prevalence of up to 50%. Because of the short observation period and the small number of cardiovascular events, epidemiological evidence for an increased risk of coronary heart disease in HIV-infected patients treated with HAART is not adequate at present; however, it is likely that shortly more data will accumulate to quantify this risk. Before starting HAART and during treatment it is reasonable to evaluate all patients for traditional coronary risk factors, including lipid profile. Among the drugs that are currently used in HIV$^+$ patients, antibacterials, antifungals, psychotropic drugs and anti-histamines have been associated with QT prolongation or torsade de pointe, a life-threatening ventricular arrhythmia. Among the risk factors that may precipitate an asymptomatic electrocardiographic abnormality into a dangerous arrhythmia is the concomitant use of drugs that share the CYP3A metabolic pathway. Since most protease inhibitors are potent inhibitors of CYP3A, clinicians should be aware of this potentially dangerous effect of HAART. Anthracyclines are potent cytotoxic antibiotics that have been widely used for the treatment of HIV-related neoplasms. Their cardiotoxicity is well known, ranging from benign and reversible arrhythmias to progressive severe cardiomyopathy. The increased survival and quality of life of HIV$^+$ patients emphasize the importance of a high awareness of adverse drug-related cardiac effects.**

KEYWORDS: **cardiotoxicity; antiretrovirals; HAART; dyslipidemia; cardiomyopathy**

Cardiac involvement in HIV disease is estimated to be approximately 6–7%.[1] A proportion of cardiac morbidity may be ascribed to the toxic effect of drugs used for the treatment of HIV$^+$ patients. The pharmacological treatment of AIDS and HIV-related diseases includes the use of antiretroviral and other anti-infective or anti-neoplastic drugs. Moreover, patients with HIV infection are at higher risk for conditions such as psychiatric diseases or allergic diseases that require additional drug treatments. Until recently the prognosis for people with the acquired immunodeficiency

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syndrome (AIDS) was so poor that concerns about long-term effects of drug treatment were relatively minor. The advent of potent antiretroviral drugs in recent years has had an impressive effect on mortality, disease progression, and incidence of HIV-related disorders.[2,3] Indeed, in an increasing proportion of patients HIV disease should be considered a chronic condition and issues related to long-term drug are of growing importance.[4] Some of the drugs that are presently prescribed have been used for years or decades and are well known, whereas some of the most frequently prescribed antiretrovirals are of recent origin and their long-term toxicities have not yet been assessed. Cardiotoxicity related to the use of anthracyclines, amphotericin B, zidovudine, macrolides, and interferon have been extensively described,[5–9] although the molecular mechanisms of all their effects have not been thoroughly assessed. A most important field of research is the possible increase of cardiovascular risk in patients treated with protease inhibitors. Some drugs commonly prescribed in HIV^+ patients have a direct effect on the myocyte, others cause electrophysiologic impairment, others are possibly involved in vascular alterations. The present review focuses on the cardiotoxicity of the drugs used for HIV disease.

ANTIRETROVIRAL THERAPY

The clinical management of HIV^+ patients is based on antiretroviral therapy, which has been demonstrated to provide clinical benefit in all patients with advanced disease and immunosuppression.[10] Although there is indeed a theoretical benefit in treating also asymptomatic individuals, the decision on when to start an aggressive treatment, with significant side effects and drug interactions, must take into account many factors, including patient adherence to treatment[11] and quality of life.[4] Until 1996, before the use of triple combination treatments, the effect of antiretroviral therapy on disease progression and overall survival was not very impressive. Nowadays, the improved survival, the availability of a number of antiretroviral agents, and the possibility of complex individualized combination regimens underscores the need for long-term treatment programs.

There are three classes of drugs that are presently used for people with HIV infection (see TABLE 1): the nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine (AZT), didanosine (DDI), zalcitabine (DDC), stavudine (D4T),

TABLE 1. Antiretroviral drugs

Nucleoside transcriptase inhibitors (NRTIs)	Non-nucleoside transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
Zidovudine (AZT)	Nevirapine	Saquinavir
Didanosine (DDI)	Delavirdine	Ritonavir
Zalcitabine (DDC)	Efavirenz	Indinavir
Stavudine (D4T)		Nelfinavir
Lamivudine (3TC)		Amprenavir
Abacavir		Lopinavir

lamivudine (3TC), and abacavir; the non-nucleoside reverse transcriptase inhibitors (NNRTI) including nevirapine and efavirenz; and the protease inhibitors (PIs), including ritonavir, saquinavir, indinavir, nelfinavir, amprenavir, and lopinavir. The standard of treatment is a PI or a NNRTI in combination with 2 NRTIs. Recent data indicate that the use of reduced doses of 2 PIs in combination with 2 NRTIs can achieve the same virological and immunological benefits of standard regimens with improved pharmacocynetic properties and possibly better patient adherence.[10]

Cardiomyopathy

Zidovudine (AZT) was the first antiretroviral drug to be widely used[12] and it is presently prescribed in combination regimens. AZT is also widely used in pregnant mothers and newborns after the demonstration of a dramatic decrease of perinatally transmitted HIV infection.[13] Soon after the widespread use of AZT, one report was published on the role of the drug in inducing dilated cardiomyopathy in a small number of adult patients. In this report the discontinuation of treatment resulted in an improved left ventricular function.[7] In a prospective study performed in Italy on an adult population, among patients receiving AZT the incidence of cardiomyopathy was greater in those with a higher degree of immunosuppression.[14,15] In a retrospective study, treatment of HIV^+ children with zidovudine has been associated with a greater risk of developing cardiomyopathy.[16] More recently, in two large prospective studies, infants born to HIV^+ mothers, exposed to AZT *in utero* and perinatally, were followed up from birth to as long as five years of age and no clinically relevant cardiotoxicity was observed.[17,18] Side-effects of NRTIs more frequently encountered than cardiotoxicity include myopathy, bone-marrow and hepatic toxicity, and neuropathy. The mechanism of all these adverse events is a toxic effect on mitochondria. The damage of cardiac mitochondrial ultrastructures and inhibition of mitochondrial DNA replication has been observed in animal models.[19] AZT acts as a competitive and non-competitive inhibitor of mitochondrial DNA polymerase.[19,20] The inhibitory action of NRTIs on DNA polymerase-γ, the only DNA polymerase involved in mitochondrial DNA replication, does interfere *in vitro* with mitochondrial replication and function.[21] Mitochondrial damage has been also indicated as a putative etiology for lipodystrophy, a debilitating adverse effect of potent combination antiretroviral therapy. Molecular mechanisms of cardiotoxicity other than mitochondrial damage have been hypothesized. In an animal model, the short term cardiotoxicity of DDC was not the direct consequence of mitochondrial DNA-related damage, but of reactive oxygen species (ROS)-mediated signaling through poly- and mono-ADP-ribosylation reactions and depression of heat shock protein (HSP)70 levels.[22]

The clinical relevance of combined regimens of NRTIs has not yet extensively been studied with regard to mitochondrial toxicity. Prospective clinical and *in vitro* studies are warranted, since the use of NRTIs combination regimens is likely to increase over time.

Dyslipidemia and Cardiovascular Risk

Hyperlipidemia, hyperglicemia, and lipodystrophy are increasingly described adverse effects of potent antiretroviral combination therapy, in particular when PIs are used.[23] According to Carr[24] the metabolic and somatic alterations in PI-treated

subjects could be ascribed to the homology of the catalytic region of HIV protease, the molecular target of PIs, to regions of two human proteins that regulate lipid metabolism: cytoplasmic retinoic-acid binding protein 1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP). The hypothesis is that PIs inhibit CRABP-1-modified and CYP3A-mediated synthesis of *cis*-9-retinoic acid and peroxisome proliferator-activated receptor type-γ (PPAR-γ) heterodimer. This results in an increased apoptosis of adipocytes and in a reduced differentiation from preadipocytes to adipocytes, with the final effect of a reduced triglyceride storage and increased lipid release. PI binding to LRP would impair hepatic chylomicron uptake and endothelial triglyceride clearance, resulting in hyperlipidemia and insulin resistance.

Patients treated with NRTIs who have never used PIs can also experience hyperlipidemia and lipodystrophy, suggesting alternative or additional pathogenetic mechanisms,[20] related to the inhibition of mitochondrial DNA polymerase-γ. Indeed, it has been hypothesized that the mitochondrial toxicity of NRTIs is similar to the mitochondrial dysfunction observed in multiple symmetrical lipomatosis (MSL) or Madelung's disease.[25] Also NNRTIs can have adverse effects on lipid levels, although more limited data are presently available.[26]

Hyperlipidemia is strikingly associated with the use of most available PIs, with an estimated prevalence of up to 50%.[27–29] Data from large published series indicate that there is a wide variation in the degree of hyperlipidemia, with an average increase of total cholesterol and triglyceride levels of 28% and 96%, respectively, compared with pre-treatment levels.[23,29–32] The level of increase seems to be proportional to the duration of therapy[30] and to the type of drug.[31]

In a prospective study the administration of ritonavir, indinavir, nelfinavir or ritonavir/saquinavir, nelfinavir/saquinavir to HIV^+ subjects was associated with a significant compound-specific increase in plasma levels of both cholesterol and triglycerides. The mean duration of treatment was 470 ± 22 days; the proportion of subjects with total cholesterol level greater than 6.2 mmol/L (cardiovascular risk threshold according to National Cholesterol Education Program) rose from 7% to 44% in the ritonavir group, from 5% to 33% in the nelfinavir group and from 12% to 35% in the indinavir group. Moreover, a 48% increase in plasma levels of lipoprotein(a) was detected in treated subjects with pre-treatment values greater than 20 mg/dL.[31] In another study that involved 292 patients, hypercholesterolemia seemed to be reversible after PI discontinuation, whereas the levels of lipoprotein, insulin and plasminogen activator inhibitor 1 were constantly increased after 12 month follow-up.[33]

Although abnormalities of lipid metabolism in HIV^+ patients have been described in the pre-HAART era, recent reports of myocardial infarctions in young patients receiving PIs has focused interest in examining the associations between HIV infection, antiretroviral therapy, and coronary artery disease. Cardiovascular events closely associated with PI therapy were anecdotally described.[34–37] Now that the prolonged survival of HIV^+ patients is well established, the risk of premature cardiovascular events caused by coronary artery disease in HAART-treated patients is likely to become a key issue in the near future. In a study from the French Hospital Data Base on HIV it was found that patients treated with PIs had a 2.79-fold increased risk of myocardial infarction when compared with untreated patients.[38]

The study however was limited by the small number of events. An American retrospective case-control study examined 15 HIV^+ individuals with a recent cardiovascular event and compared them with matched controls. In this study HAART did not appear to be a risk factor in a multivariate analysis.[39] Also, the issue of surrogate markers of subclinical atherosclerosis has been addressed. A study was performed on a cohort of French HIV^+ patients to measure the intima-media thickness and assess indirectly the cardiovascular risk. In this population no independent link between intima-media thickness, lipodystrophy and HAART was observed.[40,41]

Many prospective trials are presently addressing this important aspect of HAART, but until now quantitative data on the risk of premature atherosclerosis and risk of coronary events in PI-treated subjects are lacking or uncertain. The rapid development of atherosclerosis has not yet been demonstrated in PI-treated individuals, owing to the relatively short observation period since the widespread use of HAART. This possibility is worrisome, since rapidly forming plaques can be unstable and more easily prone to rupture with consequent acute coronary event. More consistent data will be available by merging large cohorts and analyzing prospectively the cardiovascular risk related to drug-induced metabolic alterations. However, the observation that drug-induced changes in lipid levels has resulted in an increased cardiovascular risk in other diseases[42–44] is a reason for concern in HIV^+ patients, as clinical experience with HAART continues to grow. In some HIV^+ groups, such as i.v. drug users, heavy cigarette smoking is highly prevalent, adding a well-known risk factor for ischemic heart disease. Moreover, the role of non-traditional risk factors for coronary artery disease that may possibly be more prevalent in HIV^+ populations; for example the use of cocaine and anabolic steroids, must be taken into account.

Preliminary guidelines for the evaluation and management of dyslipidemia in HIV^+ patients receiving HAART have recently been published.[45] Key points of these recommendations are the routine screening of HIV^+ patients for coronary risk factors, a comprehensive analysis of the fasting lipid profile before starting antiretroviral therapy and the treatment of selected cases. In case of hypercholesterolemia, except for those patients with extreme elevations in cholesterol (greater than 400 mg/dL) a first attempt of treatment should include dietary interventions and reduction or abolishment of correctable risk factors for coronary disease, such as cigarette smoking, physical inactivity, diabetes mellitus, and hypertension. Eventually, the 3-hydroxy-3-methylglutaryil coenzyme A reductase inhibitors or statins can be prescribed. Since many of these compounds are cytochrome P 450 substrates, the concomitant use with PIs could retard their metabolism, with an increase of toxicity. The safest drugs in this respect have proved to be pravastatin[46] and atorvastatin.[27] Hypertriglyceridemia should also be treated initially with non-pharmacological therapies, such as diet, exercise, smoking cessation. Marked increases in triglyceride serum levels are a risk factor not only for coronary disease, but also for pancreatitis and should be treated with lipid-lowering agents. Fibrates are the most effective drugs used for the treatment of hypertriglyceridemia and have been proposed as possible first-line drugs for patients with both hypercholesterolemia and hypertriglyceridemia.[45] Genfibrozil has been used successfully in dyslipidemic HIV^+ patients receiving PIs.[27]

Another frequent side-effect of PI therapy is hyperinsulinemia, an independent risk factor for coronary artery disease.[47] Among PI-treated patients a prevalence of 25–62% of insulin resistance was reported.[23,29]

At present, the optimal time for initiation of HAART takes into account the clinical stage of disease, baseline viral load, and $CD4^+$ counts. For asymptomatic persons with relatively high $CD4^+$ counts and low or undetectable viral load it is important to balance the possible long-term adverse events, the decreasing adherence to treatment over time, and the emergence of viral resistance. There are patients with a high atherosclerotic co-morbidity or risk, a high $CD4^+$ cell count, and a low plasma viral load; for such patients it is possible that the risk/benefit ratio of treating with HAART will be demonstrated to be not beneficial.[48]

DRUGS USED FOR HIV-RELATED DISORDERS

In the HAART era, the use of drugs for HIV-related opportunistic infections and neoplasms has significantly decreased, owing to the declining incidence of these conditions.[2] Nonetheless, there are circumstances in which HAART regimens fail, as a consequence of acquired drug resistance, poor patient adherence or treatment discontinuation for side-effects, especially in advanced stage patients. In such conditions, the incidence of HIV-related disorders may rise, leading to the use of drugs commonly administered in the pre-HAART era.

Drugs used for HIV-related diseases may have adverse cardiac effects including cardiomyopathy (as was extensively studied for anthracyclines), changes of the action potential of the myocardium leading to prolongation of the electrocardiographic QT-interval (as observed with many antimicrobials), and various other cardiac effects as described with the use of immunomodulators (see TABLE 2).

Cardiomyopathy is a disorder of cardiac muscle that produces systolic and less frequently diastolic dysfunction. The 1995 WHO/ISFC Report classifies cardiomyopathies as dilated, hypertrophic, restrictive and arrhythmogenic right ventricular cardiomyopathy.[49] The anthracyclines, anticancer drugs widely used for the treatment

TABLE 2. Drugs with potential cardiotoxicity used for HIV^+ persons

Drugs	Use in HIV^+ Persons	Potential Cardiotoxicity
NRTIs	HIV disease	Cardiomyopathy?
NNRTIs	HIV disease	Increased C.V. risk?
PIs	HIV disease	Increased C.V. risk?
Anti-infective drugs	Opportunistic infections	Prolonged QT interval
Psychotropic drugs	Psychotic disorders, depression	Prolonged QT interval
Antihistamines	Allergic reactions	Prolonged QT interval
Anthracyclines	HIV-related neoplasms	Cardiomyopathy
Interferon	KS, HIV/HCV coinfection	CHD, cardiomyopathy
Interleukin-2	HIV disease	CHD, cardiomyopathy

TABLE 3. Anti-infective drugs with QT-prolonging potential used for HIV$^+$ persons

Anti-infective Drugs	Use in HIV$^+$ Persons
Erythromycin	Bacillary angiomatosis
Clarithromycin	Mycobacterial diseases
TMP/SMX	PCP treatment and prophylaxis
Pentamidine	PCP treatment and prophylaxis
Fluoroquinolones	Mycobacterial diseases, other bacterial infections
Amphotericin B	Disseminated fungal infections
Azole antifungals	Mucosal and disseminated fungal infections

of HIV-related neoplasms, may be toxic to the myocardium and produce a specific cardiomyopathy characterized by mild dilation and impaired contraction of the left ventricle or, less commonly, of both ventricles. The pathologic features of anthracycline cardiomyopathy are unique, showing myocyte vacuolization progressing to cell drop out.

The prolongation of the electrocardiographic QT interval indicates an increased risk for the development of life-threatening arrhythmias, in particular of torsade de pointe, a polymorphous ventricular arrhythmia, that may cause syncope and degenerate into ventricular fibrillation.[50] Although the clinical relevance of asymptomatic QT interval prolongation is yet to be established, it should be considered a useful

TABLE 4. Other drugs with QT-prolonging potential used for HIV$^+$ persons

Antidepressants	
	Amitryptiline
	Doxepine
	Desipramine
	Imipramine
	Clomipramine
Antipsychotics	
	Thioridazine
	Chlorpromazine
	Pimozide
	Sertindole
	Haloperidol
Antihistamines	
	Astemizole
	Terfenadine

surrogate marker of cardiotoxicity of both cardiac and non-cardiac drugs. An important issue is the identification of co-factors that, together with the prescription of potentially cardiotoxic drugs, may precipitate a malignant arrhythmia. These factors are hepatic or renal impairment, electrolyte imbalance (especially hypokalemia and hypomagnesemia), and the concomitant use of diverse drugs with QT-prolonging potential. Among the drugs that are currently used in HIV^+ patients, antibacterials, antifungals, psychotropic drugs, and anti-histamines have been associated with QT prolongation or torsade de pointe (see TABLES 3 and 4). In most cases the effect is dose-dependent and/or associated with co-factors or concomitant treatment with CYP3A4 isoenzyme inhibitors.[51] The common mechanism with which so many chemically unrelated compounds prolong the QT interval is thought to be the blockade of myocardial ion channels, particularly the rapidly activating delayed repolarizing potassium current (I_{Kr}).[51,52] For most drugs QT prolongation and torsades de pointe should be considered a rare side-effect. In fact, most case-reports refer to concomitant use of drugs that share a QT-prolonging potential.

Anti-Infective Drugs

Macrolide antibiotics have a QT interval-prolonging potential. Erythromycin was the most extensively studied drug in this respect and its effects on electrocardiogram are well established, especially with i.v. administration.[51] As has been shown for antiarrhythmic drugs, a female predominance of erythromycin-associated arrhythmias was found.[53] Erythromycin has had wide applications in anti-infective therapy, but it has limited specific indications in HIV^+ patients. Clarithromycin, which is chemically closely related to erythromycin has wider applications in AIDS patients and it is currently recommended for the treatment of mycobacterial diseases. Its potential for electrocardiographic alterations and cardiac arrhythmias is not as high as erythromycin, but cases have been reported of QT prolongation and torsades de pointes.[54,55] Case reports of QT prolongation have been published both with clarithromycin used in combination and alone.[56,57]

Isolated cases of QT prolongation and torsades de pointes associated with the use of *trimethoprim/sulfametoxazole* in HIV-uninfected patients have been reported.[58,59] However, this must be considered an extremely rare event, since in the pre-HAART era trimethoprim/sulfamethoxazole has been extensively used at very high dosages in AIDS patients with *Pneumocystis carinii* pneumonia and among the frequent and severe side-effects, electrocardiographic abnormalities were not reported.

The use of *fluoroquinolones* has also been associated with QT prolongation, mostly with sparfloxacin.[60–63] Since the use of this class of antimicrobials is very extensive worldwide, the QT prolongation potential, especially when they are used in combination, should be carefully assessed.[64,65] Fluoroquinolones have wide indications in both HIV-related and unrelated infections. *Amphotericin B and azole antifungals*—ketoconazole, fluconazole, itraconazole—all have a QT prolongation potential.[66–69] The use of antifungal agents is most common in HIV^+ patients. *Candida* spp. infections range from mild oral thrush to life-threatening multi-organ involvement. Aspergillosis, as in non-HIV^+ patients, usually causes malignant lung or sinus abscesses. Amphotericin B, the most potent and most toxic of the commonly used antifungals, can also cause hypokalemia, precipitating the long-QT syndrome

and arrhythmias.[70] Amphotericin B was also reported to cause bradycardia.[71] The more recent liposomal formulations of amphotericin B have improved the overall tolerability of the drug, but the potential for electrolyte unbalance and QT prolongation remains.[72,73] QT prolongations associated with the use of azole antifungals were believed to occur by inhibition of the hepatic metabolism of other QT-prolonging drugs;[70–77] however, a direct effect was also observed.[78]

Pentamidine is a second-line drug structurally similar to procainamide used for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia. Pentamidine in several anecdotal reports and prospective studies was considered responsible for QT-prolongation and ventricular arrythmias.[79–83] The adverse cardiac electrophysiologic effects of pentamidine in fact occur in only a small proportion of patients and are enhanced by hypomagnesemia and hypokalemia.[84,85] When using other drugs with QT-prolongation potential it must be remembered that appreciable tissue levels of pentamidine may be present months after the discontinuation of the drug.[86]

Ganciclovir and foscarnet are first-line drugs for the treatment of cytomegalovirus (CMV) infections. In AIDS patients retinal or life-threatening disseminated CMV infections are common, although the prevalence has dropped with the advent of successful antiretroviral therapy. Anecdotal reports of cardiotoxicity with the use of ganciclovir and foscarnet were published. Two patients developed ventricular tachycardia during intravenous infusion of ganciclovir[87] and one patient developed reversible cardiomyopathy when treated with foscarnet.[88] The mechanism of cardiotoxicity of the drugs was not apparent. CMV can itself affect the myocardium, suggesting that in the cases described there was a possible concomitant effect of the drugs and the virus.

Antihistamines

Antihistamines may have potential indications in HIV^+ patients, since allergic reactions are much more frequent than in the general population.[89] Two non-sedating anti-histamines, astemizole and terfenadine, have a well known effect on QT interval, and torsades de pointe and sudden death have also been reported.[51,90–93] The newer non-sedating anti-histamines (ebastine, loratadine, cetirizine, acrivastatina, fexofenadine, and mizolastatine) seem to be safer,[93,94] but some of them do have an effect on I_{Kr} and their cardiotoxic potential needs to be assessed further. The cardiotoxicity of antihistamines is dose-dependent and usually influenced by the concomitant use of other drugs with a QT prolongation effect or inhibition of cytochrome P450.

Psychotropic Drugs

Psychotropic drugs have a potential cardiotoxicity related to their QT-prolonging effect. The tricyclic anti-depressants amitriptyline, doxepine, desipramine, imipramine and clomipramine have all been associated with QT prolongation, and sudden death was reported with desipramine, clomipramine and imipramine.[95,96] Antipsychotic agents in the butyrophenones and phenotiazine classes appear to be significantly cardiotoxic[97] both at therapeutic and supra-therapeutic doses. Case reports or treatment of healthy volunteers pointed out the cardiotoxicity of thioridazine,[98] chlorpromazine, haloperidol,[99–101] pimozide[102] and sertindole.[103] In

numerous studies psychiatric morbidity in HIV^+ patients ranges widely according to definitions, study populations, and study design. There is however general agreement that psychiatric disorders, ranging from mild anxiety to major depression and psychosis, are far more prevalent than in the general population.[104–108] In a study that examined HIV^+ persons in a large outpatient clinic, 53% of the women and 70% of the men met Structural Clinical Interview for DSM-III-R criteria for psychiatric disorders.[109] The increased survival of HIV^+ patients with the need to cope with complex therapeutic regimens, adverse effects, and alterations of body image due to lipodystrophy could also potentially increase the long-term psychiatric morbidity. Since psychotropic drugs are routinely used in HIV^+ patients, there is the need for careful monitoring of potentially dangerous side-effects, including cardiac toxicity.

Drugs Used for HIV-related Neoplasms

The effects of anthracyclines on myocardial structure and function have been extensively studied.[110–113] Anthracyclines are potent cytotoxic antibiotics that have been widely used also in patients with AIDS-related neoplasms, but their use is limited by cardiotoxicity. A variety of cardiac effects have been described, ranging from benign and reversible arrhythmias to progressive severe cardiomyopathy. The most common cardiac toxicity is a cardiomyopathy that can lead to congestive heart failure. Endomyocardial biopsy is the most sensitive and specific test for the diagnosis of cardiomyopathy, but its routine use is limited by its invasiveness. Serial echocardiographic evaluation of left ventricular ejection fraction has also proved to be a valuable tool to guide therapy and promptly identify a cardiomyopathy. A 10% reduction of the ejection fraction from baseline or a value below 50% is an indication to discontinue therapy. A baseline ejection fraction less than 30% is generally considered a contraindication to starting a treatment with anthracyclines. A relevant issue is the progression of anthracycline-induced cardiomyopathy to chronic heart failure, after the cure of the tumor. A significant proportion (23–38%) of patients successfully treated with antracyclines have a persistent decrease of the ejection fraction. Of these, approximately 5% will eventually develop chronic heart failure. The overall increased survival of HIV^+ persons, including those with HIV-related malignancies will perhaps cause increased concern over this issue. Anthracycline toxicity is believed to be related to the generation of highly reactive oxygen species which cause direct damage to cardiac myocyte membranes.[114] The heart tissue is able to generate free radicals from anthracyclines at multiple cellular sites, including mitochondria, cytosol and sarcoplasmic reticulum.[115] Doxorubicin impairs glutathione peroxidase activity, a key mechanism of peroxidase removal, and cardiac tissue has low levels of catalase, the principal enzyme for the removal of hydrogen peroxide. In spite of this mechanism, free radical scavenger drugs have not proved effective in the prevention of anthracycline-related toxicity, suggesting an alternative mechanism. In fact, it was demonstrated that doxorubicin has a high binding activity to iron and that an iron-doxorubicin complex was the potent catalyzer of many free oxygen species. Consistent with these findings, iron chelators have proven effective in the prevention of anthracycline cardiac toxicity.[116] The myocardial degenerative process is dose-dependent and related to the high peak plasma level reached after the bolus dose of the drug and by the cumulative dose, with a significant increase of risk above the dose of 550 mg/m^2. However, there is significant individual variability in

this dose-dependent toxic effect. Risk factors for increased toxicity include prior chest radiation, age over 70, pre-existing heart disease, and female gender. A less common cardiac effect of anthracyclines is an acute toxicity that is unrelated to cumulative dose and that can be observed hours or days after the administration of the drugs. This acute syndrome presents as supraventricular or ventricular arrhythmias, heart block, and acute congestive heart failure. Asymptomatic electrocardiographic abnormalities including ST-T changes, decreased QRS voltage, prolongation of QT-interval occur in up to 30% of cases. These changes usually regress within weeks and do not prompt the discontinuation of treatment. Patients that develop an early cardiotoxicity after anthracycline therapy are more likely to progress towards late congestive heart failure.[113] In recent years there have been efforts to prevent the cardiotoxicity of anthracyclines while preserving their anticancer effects by the administration of continuous infusions, lower doses at more frequent intervals,[117] the use of agents that selectively block the cardiotoxicity,[118] and the use of liposomial formulations.[119,120]

Anthracyclines are used for the treatment of a wide range of hematological and solid malignancies. In AIDS patients the risk of Kaposi's sarcoma (KS) and B-cell non-Hodgkin's lymphoma is greatly increased.[121] The clinical presentation of KS is highly variable, ranging from slow-growing and isolated cutaneous lesions to disseminated muco-cutaneous and visceral involvement. For less aggressive or localized KS, treatment options can be intralesional chemotherapy, radiation or systemic interferon. Many patients with immune reconstitution consequent to successful antiretroviral therapy have experienced remission of KS lesions.[122] For disseminated or rapidly progressing KS, systemic chemotherapy is indicated and can be life-saving. At present two liposomal-formulated anthracyclines, liposomal daunorubicin and liposomal doxorubicin, have largely replaced the formerly used combination regimen ABV (i.e. adriamycin-bleomycin-vincristine) for the treatment of disseminated KS.[123] Liposomal anthracyclines appear to have an efficacy comparable to ABV, while being better tolerated.[124] In AIDS patients treated with pegylated liposomal doxorubicin compared with historical controls, a reduced cardiotoxicity was demonstrated by cardiac biopsy.[125]

In approximately 3% of AIDS patients a non-Hodgkin's lymphoma occurs. The treatment of AIDS-related lymphomas is generally based on cycles of combined chemotherapeutic agents. Among others, m-BACOD, CHOP, CDE, ACVB have been proposed, all containing anthracyclines. Mitoxantrone is a completely synthetic analog of the anthracyclines that has been proposed in combination regimens for the first-line or second-line treatment of AIDS-related lymphomas.[126,127] Mitoxantrone does cause cardiotoxicity, but less than the anthracyclines.[128] When treating AIDS patients with lymphoma, clinicians must be aware of the risk of cardiotoxicity related to anthracyclines, especially if the patients are receiving other cardiotoxic drugs or have underlying conditions that cause myocardial dysfunction.

Immunomodulators

Interferon

Interferons (IFNs) are human cytokines that have been used in therapy since the late 1950s. In the early years of the HIV epidemic treatment with α- and β-interferon

was proposed for its antiviral effect. After disappointing results, this approach was abandoned. At present, recombinant human α-interferon is approved for the treatment of early stage Kaposi's sarcoma (KS) in patients with CD4 cell counts more than 200/mm^3. In the HAART era KS still remains the most commonly diagnosed malignancy in HIV$^+$ persons. α-Interferon is also approved for the treatment of chronic hepatitis C in HIV$^-$ as well as in HIV$^+$ patients. Common side effects of interferon include an early flu-like syndrome, fatigue, behavioral changes, autoimmune disorders, neutropenia.[129] While tachycardia and hypo- or hypertension have frequently been reported, there have also been occasional reports of other interferon-induced cardiovascular manifestations. Supraventricular arrhythmias are frequently reported after the first dose of IFN and may be related to the flu-like reaction. In a review of 44 cases of cancer patients from 15 reports in the literature the most common cardiac adverse events were arrhythmia, ischemic heart disease, and dilated cardiomyopathy.[130] In many of these patients there were underlying cardiovascular risks, including the use of anticancer drugs known to be cardiotoxic. The various manifestations of IFN cardiac toxicity suggest different mechanisms. The pathogenesis of interferon-related cardiomyopathy is not clear. In the 3 HIV$^+$ patients of the review it was suggested that cardiomyopathy resulted from a combined effect of interferon and HIV.[131] The common flu-like syndrome itself, with fever, chills and increased oxygen consumption may precipitate acute cardiovascular events, including arryhthmias and acute coronary events. No relationship has been demonstrated between IFN toxicity and dose or duration of treatment. Taken together, the data on IFN cardiotoxicity seem to indicate that many cases of arrhythmia and coronary artery disease are related to drug-induced peripheral vasodilation and increased cardiac work load. Accordingly, IFN should not be administered in patients with unstable ischemic disorders.

Interleukin-2

Interleukin-2 (IL-2) is an immunoregulatory cytokine that induces production of other lymphokines, including interleukin-6 and γ-interferon. Moreover, IL-2 enhances the cytolitic activity of NK cells and induces the differentiation of T-cell precursors transforming them into LAK cells, which have an anti-neoplastic activity. One of the first immunologic defects described in HIV$^+$ patients was impaired IL-2 production, with consequently reduced NK activity. Recombinant IL-2 has been used for the treatment of HIV$^+$ patients in all stages of disease, with or without malignancies, although its widespread use has been limited by significant side-effects and high cost. Recently, a pooled analysis of controlled trials of IL-2 therapy in HIV disease showed significant immunological and virological benefits in treated patients.[132] Phase II/III trials are ongoing to evaluate the effects of combination treatment with IL-2 and HAART. IL-2 has a potential cardiotoxicity, that is believed to be dose dependent.[133] In 199 consecutive patients with metastatic melanoma or renal cell carcinoma, arrhythmias occurred in 6% of the courses, hypotension in 53%, and elevated creatine kinase levels with elevated MB isoenzymes in 2.5%.[134] Acute myocardial infarction, cardiomyopathy, and asymptomatic electrocardiographic changes were also reported.[133] The possible pathogenetic mechanism could be the production of secondary-message molecules such as nitric oxide and myocardial stunning.[135] Owing to the potential benefit of combination treatment with IL-2 and HAART, a

variety of treatment schedules are being evaluated in HIV^+ patients to minimize IL-2 toxicity.[136]

ANTIRETROVIRAL THERAPY AND DRUG INTERACTIONS

Many antiretroviral agents share metabolic pathways with a great number of drugs commonly prescribed for HIV^+ persons. Some of the consequent drug interactions are clinically relevant and suggest the need for a close monitoring of potential side-effects. The most important drug interactions are between PIs and drugs that are substrates for the cytochrome P450 3A (CYP3A). The cytochrome P450 mixed function oxidases are a family of enzymes that account for most oxidative transformations of exogenous and endogenous biological compounds.[137] The isoforms of human CYP3A include 3A3, 3A4, 3A5, and 3A7. CYP3A4 is the predominant form of CYP3A in adult humans and it is one of the most important enzymes, since it biotransforms approximately 60% of oxidized drugs.[138] Cytochrome P450 activity is conditioned by age,[139] sex,[140] and liver disease.[141] In HIV^+ individuals, the variability in activity of CYP3A4 may be even greater than in uninfected persons.[142] The effect of these variables must be taken into account when prescribing drugs and combinations of drugs that are metabolized by the CYP3A4. Many drugs from a wide range of therapeutic groups are substrates for CYP3A4. A significant rise in plasma levels of various drugs, with consequent increase of dose-related toxicity, has been observed when they were co-administered with PIs, especially with ritonavir, the most potent CYP3A inhibitor of the class. Relevant interactions have been described between PIs and antimycobacterials, antifungals, macrolide and quinolone antibacterials, antihistamines, psychotropic drugs, anti-arrhythmics, cisapride (a gastrointestinal prokinetic), statins, anti-epileptics, and anti-neoplastic alkaloids. Some of these interactions can yield potentially cardiotoxic effects. As was previously noted, many medications that are CYP3A4 substrates may produce an electrocardiographic QT prolongation and torsades de pointe. An increased risk of arrythmias is present when all PIs are co-administered with bepridil, and this combination must be avoided. Potentially dangerous interactions that require close monitoring or dose adjustment can occur between PIs and amiodarone, disopyramide, flecainide, lignocaine, mexiletine, propafenone, and quinidine. Co-administration of PIs with astemizole, terfenadine or cisapride is contraindicated, owing to the risk of life-threatening arrhythmias. Many antipsychotic, antidepressant and anticonvulsant drugs interact with PIs. Some of these interactions are clinically relevant and contraindicate concomitant use or require dose adjustment. In everyday practice, clinicians should be aware of the potential severity of the cardiac side-effects caused by drug interactions between PIs and CYP3A substrates.

CONCLUSIONS

Drug-induced cardiotoxicity has been described in HIV^+ patients in the early years of the epidemic. Initially, however, this issue did not raise widespread concern, because the progression of HIV infection was much faster than drug-induced heart

diseases. In addition, acute cardiotoxicity was relatively infrequent, when compared to other major drug toxicities. A new scenario was created by the advent of potent anti-retroviral therapies, with significant immune reconstitution, dramatically increased survival of patients, and the recognition of new adverse effects of HAART. In this new situation it is likely that an increase of drug-related cardiac adverse effects will be observed. Probably the major issue is the possibility of HAART-induced accelerated atherosclerosis with increased risk of coronary events. Dyslipidemia and insulin resistance caused by PIs is well established and large epidemiological studies are ongoing to quantify cardiovascular risk of patients treated with HAART. Other important information will derive from studies addressing the issues of abnormalities of endothelium and coagulation in HIV^+ patients. It will be also necessary to understand if in HAART-treated patients there are additional co-factors, other than the traditional ones, that influence lipid and glucose metabolism. It is likely that all these data will have an impact on the development of future guidelines for the treatment of HIV^+ persons, especially on the timing of treatment initiation. Until definitive data are available, it is reasonable to evaluate all HIV^+ patients also for traditional coronary disease risk factors, including lipid metabolism. First line treatment of dyslipidemia should include dietary interventions and reduction or abolishment of correctable risk factors for coronary disease. Pharmacological treatment of dyslipidemia should be proposed only if significant drug interactions between lipid-lowering agents and antiretroviral drugs can be excluded.

Many drugs used in HIV disease have a QT interval prolonging potential. The identification and widespread knowledge of risk factors that may precipitate this asymptomatic electrocardiographic abnormality into a life-threatening arrhythmia is an important issue. Among these factors is the concomitant use of drugs that share the CYP3A metabolic pathway. Since most PIs are potent inhibitors of CYP3A, clinicians involved in the treatment of HIV patients should be particularly aware of these potentially dangerous effects of HAART.

The increased survival and quality of life of HIV patients emphasizes the importance of a high awareness of drug-related cardiac adverse effects, since the success of HAART may be frustrated by the risks related to unrecognized toxicity.

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