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Appendix to the German-Austrian HIV Therapeutic Guidelines

Strategies for Treating Morphological and Metabolic Alterations under Antiretroviral Treatment

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Preliminary Note

Metabolic alterations and defects in fat distribution during antiretroviral therapy are frequently observed. The underlying pathogenic mechanisms and the physical changes occurring are still poorly understood and have been summarized as "HIV associated lipodystrophy". An attempt to define HIV-associated lipodystrophy objectively was provided by a case definition based on a score developed by Carr et al. Under http://www.med.unsw.edu.au/nchecr/ the likelihood of the diagnosis of lipodystrophy can be obtained by entering clinical and laboratory variables from an individual patient under the keyword "Lipodystrophy Case Definition". It must be considered, however, that - being based on a historical model, where lipodystrophy is considered as a single syndrome - this "Lipodystrophy Case Definition" is not able to reflect the individual manifestations of the lipodystrophy complex adequately.

The recommendations made in this review are based on the current clinical knowledge with regard to the origin and therapy of lipodystrophy. They should be regarded as provisional and will change with expanding knowledge. The recommendations for treating dyslipidaemia in particular are oriented closely on the American recommendations of the National Cholesterol Education Program (NCEP III), and may be regarded both by HIV practitioners and patients as excessive and too rigid. The therapeutic goals of the NCEP in the first intervention studies in HIV-positive individuals were only achieved for a small proportion of the HIV patients. In addition, preliminary results suggest a potentially higher risk of adverse events in HIV-patients under statins or fibrates. The clinical efficacy of interventions with lipid lowering drugs has not been validated in HIV-seropositive patients. However, therapeutic decisions so far have been based on data obtained in non-HIV cardiovascular intervention studies. With more and more results becoming available from the HIV patient population a revision of these recommendations will be required.

Changes in Body Shape

Changes in body shape under antiretroviral therapy can be subclassified into two probably pathogenetically distinct, but sometimes simultaneously occurring, syndromes (Table 1). On the one hand a sometimes spontaneously reversible fat accumulation occuring at the trunk (particularly in the abdomen, but also in the neck area), whereby a clinical association exists with protease inhibitor therapy (PIs), and a certain similarity exists with the so-called metabolic syndrome. On the other hand an often irreversible fat loss syndrome is observed that preferentially affects the body periphery (i.e. the extremities and the face). Reverse transcriptase inhibitors (NRTIs) in general and stavudine and to a lesser extent zidovudine in particular are risk factors for the development of this form of fat wasting [1, 2]. According to more recent studies, therapies with non-thymidine-containing NRTIs in combination

Table 1. Clinical and laboratory parameters in HIV-associated lipodystrophy syndrome.

Lipoatrophy
- Face (sunken cheeks, hollow temples, sunken eyes, prominent cygomatic arch)
- Arms and legs (prominent veins)
- Buttocks (loss of form, skin flaps)

Lipohypertrophy
- Abdomen (increase in abdominal girth due to increase in visceral adipose tissue)
- Neck ("buffalo hump")

Associated symptoms
- Breast enlargement (females)
- Hypertriglyceridaemia
- Hypercholesterinaemia
- Insulin resistance, pathological glucose tolerance or first manifestation of a diabetes mellitus
- Elevated C-peptide

with a PI or NNRTI in therapy-naive patients induce lipoatrophy much more rarely, at least over the follow-up period of about 2 years [3, 4, 5].

Adipose Tissue Accumulation

The switching of a PI to a non-nucleoside reverse transcriptase inhibitor (NNRTI) reverses visceral fat accumulation, but does not lead to visible improvements in peripheral fat loss [6-9]. Various studies have shown a protective effect of endurance training as well as a quantitatively varying, but statistical significant reduction of visceral fat from regular physical activity [10-13]. Subcutaneous fat accumulation, especially in the neck region, can only be partially removed by liposuction [14, 15]. Recurrence has been observed in approx. 50 % of patients [15]. Visceral fat, however, is not accessible to liposuction. A clear reduction in visceral fat was achieved with recombinant human growth hormone. This intervention also led to a clear improvement in gastrointestinal complaints amongst patients with marked visceral lipohypertrophy. The most frequently used dose of growth hormone was 6 mg/d, although studies designed to determine the most effective dose are lacking. The average treatment duration was short in most studies 8-12 weeks [16-19]. After cessation of growth hormone treatment, however, a recurrence of the visceral fat accumulation was observed insome cases [16, 17, 20]. Possible adverse events of growth hormone treatment include arthralgia, oedemas and diabetes mellitus or an aggravation of simultaneously occurring lipoatrophy [17, 20, 21]. A recent study has shown that therapeutic success can be maintained over a period of 60 weeks by a lower dose of growth hormone with fewer side effects [22].

Treatment with metformin (2550 mg/ day over 8 weeks) led to approximately 30% reduction in visceral fat in a controlled French pilot study enrolling patients with pathological glucose tolerance [23]. Gastrointestinal side effects, however, led to treatment discontinuation in 2 of the 14 patients treated. The results of this pilot study could only be partly confirmed in a controlled study with a lower metformin dosing (1000 mg/day) [24].

Breast enlargement was observed both in women and men. In men it appears to be related to a genuine gynaecomastia. A testosterone deficit was suggested to be the probable cause. A direct relationship with the classical lipodystrophy syndrome has not been confirmed. In men there are anecdotal reports of therapeutic success with external testosterone preparations [22, 23]. Gynaecomastia can also disappear spontaneously [27].

Lipoatrophy

Treatment is more difficult for the atrophic component of the lipodystrophy syndrome than for fat accumulation.

The first report of a partial regression of lipoatrophy was published by French researchers after stavudine was replaced by zidovudine or abacavir [1]. In the following randomised studies on lipoatrophic patients, switching from a stavudine-containing therapy led to a significant, but clinically small increase in subcutaneous fat [28-31]. Fat loss in the face however is in the majority of cases not changed to a cosmetically relevant degree by changes in the composition of antiretroviral therapy. Clearly, reversal of lipoatrophy is a very long process in which objective changes but clinically minor improvements can be noted beginning after 24 weeks. If the slope of the currently available improvements is linear, a convincing clinical improvement of lipoatrophy would only be evident after years. Caution must also be exercised when replacing antiretroviral agents since this approach may lead to virological failure particularly in the case of archived resistance mutations [32, 33].

The efficacy of intermittent treatment interruptions, designed to reduce cumulative drug toxicity, and thus to avoid the development of lipoatrophy, has not been examined systematically.

Plastic surgery in the form of injections with polylactate-hydrogel or the use of Goretex® implants can lead to cosmetic improvement [34, 35]. The benefit of multiple subcutaneous injections with polylactat-hydrogel (New-Fill®) into the face at sites with marked lipoatrophy was examined in 90 patients in two studies. The success was subjectively judged to be positive by the patients; these appraisals were supported also by ultrasonic measurements of cheek thickness. With polylactate-hydrogel, long-term results over 96 weeks have now been published [35]. In general the volume effect partly recedes upon completion of treatment. Adverse events of this procedure are rare, although it should be carried out by an experienced surgeon in order to minimise the risk of any possible facial distortions. Injections with hyaluronic acid or collagen have the disadvantage of a relatively short effect caused by rapid degradation of the filler substance. Individual case reports have shown that the same applies to the injection of adipose tissue cells (Prof. Bull, Uerdingen, personal communication). Silicon implants or silicon injections are not recommended by most plastic surgeons because of the higher complication rate. Systematic studies for determining the best procedure are lacking up until now.

The use of rosiglitazone (a thiozolidindione) in two prospective, double-blind studies over 24 and 48 weeks revealed no improvement in subcutaneous or visceral fat distribution, but did lead in both studies to an increase in triglycerides and cholesterol [36, 37]. However for another glitazone, pioglitazone, a non-significant increase in subcutaneous adipose tissue was found after 24 weeks in a small uncontrolled pilot study [38].

Dyslipidaemia

Antiretroviral therapy can induce dyslipidaemia, or worsen an existing lipid disorder. The PI component of an antiretroviral combination in particular has been associated with such changes [39]. Increases in very-low density lipoprotein (VLDL) are usually observed, while the often low concentration of high-density lipoproteins (HDL) may be increased by fos-amprenavir or nelfinavir or remain unchanged under treatment with other PIs . Increases in low density lipoprotein (LDL) may also be observed [39]. There is an as-

sociation of lipid changes with the ritonavir dose in ritonavir boosted PIs.

Although it is likely that not all PIs change the lipoprotein composition to the same extent, systematic comparisons between PIs remain to be published. Some studies have indicated a more marked dyslipidaemia under ritonavir or lopinavir treatment boosted by ritonavir in comparison with saquinavir or indinavir. Newer PIs, such as atazanavir, seem to be less likely to induce hyperlipidaemia.

The influence of NRTIs on lipid metabolism has not been fully clarified. Studies have observed a mild hypercholesterolemia and hypertriglyceridaemia under stavudine [40]. Tenofovir in contrast seems to have only a minor effect on lipid metabolism [41].

NNRTIs, i.e. nevirapine and efavirenz, may increase HDL. Under efavirenz an increase in triglyceridaemia and LDL-cholesterol has been observed whereas nevirapine seems to have a less pronounced effect on triglicerides and non-HDL cholesterol (overview in Table 3).

Cardiovascular Risk

The constellation of a high LDL and a low HDL led to concerns that antiretroviral therapy might be a risk factor for myocardial infarction. Additional cardiovascular risk factors such as insulin resistance, visceral fat accumulation or smoking are also prevalent in HIV-seropositive patients. Valid prospective study results, despite the public focus on this topic, can not be obtained in a short period however. While in several cohort studies an increase in cardiovascular events and a possible association with PIs was found [42-46], such an increase was not observed in another large study [47]. To date the small increase in cardiovascular complications did not result in an increase in overall mortality. In addition transient hyperlipidaemia induced by antiretroviral therapy may not result in an increase in lifetime cardiovascular risk in young men without any other cardiovascular risk factor or amongst women before menopause [48]. Furthermore, it is still unclear

Table 2. NCEP recommendations for therapeutic interventions in patients with hypercholesterinaemia.

Risk category	therapeutic goal	LDL cholesterol level [mg/dl] Diet, endurance exercise, nicotine abstinence	medical interventions indicated
CAD, symptomatic atherosclerosis, diabetes mellitus or 10-year' risk >20 %	<100	≥100	≥130[a]
≥2 risk factors, 10 year risk 10-20 %	< 130	≥130	≥130
≥2 risk factors 10 year risk <10 %	< 130	≥130	≥160
0-1 risk factor	< 160	≥160	≥190[b]

Note: The reduction in LDL is the primary goal. The reduction of "non-HDL cholesterol" is a secondary goal when triglyceride levels are >200 mg/dl. The target values for the non-HDL cholesterol are 30 mg/dl higher than those for the LDL cholesterol.
[a] for LDL values of 100-129 mg/dl the medication-based therapy is optional
[b] for LDL values of 160-189 mg/dl the medication-based therapy is optional

Table 3. Description of the qualitative effect of antiretroviral substances on lipids.

Class	Medicine	TG/VLDL	LDL	HDL
PI	RTV	↑↑↑	↑	↔
	LPV/r	↑↑	↑	↔
	SQV/r/	↑/↔	↑	↑/↔?
	IDV	↔	↑	↔
	FPV/r	↑	↑	↑↑
	NFV	↔?	↑	↑↑
	ATV	↔	↔	↑?
NNRTI	EFV	↑	↑	↑↑
	NVP	↔	↑	↑↑↑
NRTI	D4T	↑?	↑	↔
	other NRTI	↔	↔	↔

RTV = Ritonavir, LPV = Lopinavir, SQV = Saquinavir, IDV = Indinavir, FPV = Fosamprenavir, NFV = Nelfinavir, ATV = Atazanavir, EFV = Efavirenz, NVP = Nevirapine, d4T = Stavudine, TG = Triglyceride, VLDL = Very low density lipoprotein - cholesterol, LDL = Low density lipoprotein - cholesterol, HDL = high density lipoprotein - cholesterol

whether the large VLDL particles frequently observed in HIV patients may be different than the smaller VLDL particles observed in patients with familial hypercholesterolemia and thus less atherogenic [49]. Therapeutic interventions for lowering lipids may not be necessary in such a situation. It is still under debate if an isolated increase in triglycerides [50] leads to an independent increase in cardiovascular risk since currently only a low atherogenic potential is attributed to triglycerides. The classical cardiovascular risk factors such as age, smoking, hypertension and diabetes mellitus should be considered together with the dyslipidemia for treatment decisions. They should be the focus of lifestyle changes.

Evaluation of HIV-seropositive Patients with Dyslipidaemia

Evidence based recommendations for interventions in HIV-seropositive patients with dyslipidemia do not exist. Clinical studies that have confirmed a reduction of cardiovascular complications in HIV-seropositive patients due to lipid lowering interventions are lacking. The expert panel of the Adult AIDS Clinical Trials Group has therefore mainly followed the recommendations of the American National Cholesterol Education Program (NCEP) for Lipid Diseases in the general population [51]. Even though the assumption of similar long-term consequences of dyslipidaemia in HIV-seropositive and seronegative patients may be justified, the relatively short duration of dyslipidemia due to antiretroviral therapy may lead to an overestimation of the cardiovascular risk if the available risk calculators (e. g. Framingham, PROCAM) are used. The therapy of HIV-seropositive patients with statins may induce immunosuppression, however clinical outcome data showing an increased morbidity in statin treated HIV-seropositive patients are not available [52, 53].

For each patient, before and 3-6 months after introduction or switch of antiretroviral therapy, a lipid profile should be obtained. The laboratory analysis must be fasted, and should at least include cholesterol, HDL and triglycerides and if possible also LDL. At the same time cardiovascular risk factors should be recorded, in particular smoking, blood pressure, cardiovascular familial risk (cardiovascular events in a first degree male relative < 55 years, cardiovascular event in a first degree female relative < 65 years) and age (>45 years for men, >55 years for women). In a substantial number of patients HDL may be low. From these risk factors, the cardiovascular 10-year risk can be calculated based on the findings of the Framingham Heart Study or the PROCAM study (http://hin.nhlbi.nih.gov/atpiii/calculator.asp or www.CHD-taskforce.com). Based on the calculated risk plus the presence or absence of coronary artery disease or diabetes mellitus type 2 (the latter is now considered as a coronary artery disease equivalent) target LDL values (Table 2) and the corresponding lipid lowering intervention are recommended (Fig. 1).

Therapy of Dyslipidaemia

Diet and Physical Exercise

The first line treatment of hypercholesterolemia consists of lifestyle changes [54]. Physical endurance training in combination with a modification of diet was reported to reduce cholesterol 11-18 % and triglycerides by about 25% in HIV-seropositive patients [11, 12, 55,

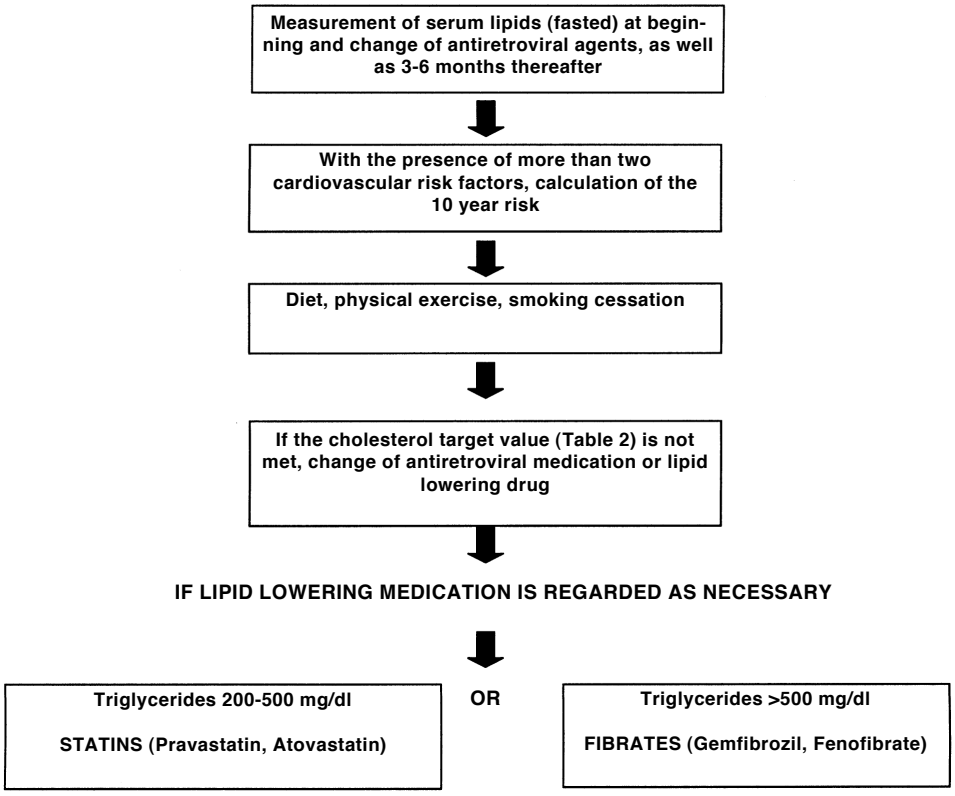

Fig. 1. Exploration and treatment of hypercholesterinaemia under HIV-therapy.

56], and can also improve insulin resistance. Even if these interventions frequently only have a moderate effect (particularly on hypercholesterolemia), they are still considered the basis for a subsequent intervention with a lipid lowering drug [48, 57].

Lipid Lowering Medication

Although for anecdotal cases a clinical association between PI-induced hypertriglyceridaemia and pancreatitis can not be excluded, other risk factors e. g. other drugs were mostly also present in these cases [58]. A severe hypertriglyceridaemia may represent a treatment indication for fibrate therapy.

The efficacy of different classes of lipid lowering agents in HIV-seronegative individuals is listed in Table 4.

Table 4. Effects of lipid lowering agents in HIV-seronegative individuals.

	Statins	Nicotinic acid	Fibrates
LDL-cholesterol	-24 to -50 %	Up to -30 %	-10 to -33 %
HDL-cholesterol	+6 to +12%	Up to +30%	+4 to +21%
Triglycerides	-13 to -29 %	-30 to -40 %	-30 to -65 %

Unfortunately only pilot studies with low patient numbers and a short therapy duration have been performed in HIV-seropositive patients with lipid lowering therapy [59-61]. Statins, i.e. pravastatin, fluvastatin or low dose atovarstatin, are the first choice for treating high LDL-cholesterol levels or a combined hyperlipidemia consisting of high non-HDL cholesterol levels and triglycerides between 200-500 mg/dl [51]. For pharmacologic therapy of marked hypertriglyceridaemia, fibrates are recommended, e. g. gemfibrozil 600 mg twice daily, fenofibrate 200 mg daily [62, 63]. Alternatively omega-3 oils (fish oil) can be used which have been shown to reduce hypertriglyceridemia by 30% with no effect on cholesterol.

Statins in patients with PI treatment can reduce total cholesterol by approx. 20-30%, while fibrates decrease triglycerides up to 50 % [64]. The combination of a fibrate with a statin has a synergistic effect on dyslipidemia and PI-treated HIV-seropositive patients were more likely to achieve target levels for both cholesterol and triglycerides [59, 60]. A combination of a statin with a fibrate should be given however only in exceptional cases and with close monitoring since the incidence of rhabdomyolysis appears to be higher compared to monotherapy [65, 66]. Concomittant treatment with macrolides or conazoles further increases the risk [66, 67].

Statin use can result in hepatotoxic adverse events [68]. Interactions with the cytochrome isoenzymes P450 3A4, 2C8 and 2C9 are reported. A first pharmacokinetic study looked at the interaction of the combination of ritonavir and saquinavir on the serum levels of various statins and revealed an increase in the AUC value of 32-fold for simvastatin, 4.5 fold for atovarstatin and a reduction for pravastatin by around 20% [69]. According to these findings pravastatin and fluvastatin are currently considered as the safest substances. Data with regard to other antiretroviral agents and combinations are lacking. Likewise, data on the effects of statins and fibrates on the pharmacokinetics of antiretrovirals have been sparse until now. In a small study, pravastatin showed no influence on the pharmacokinetics of several PIs [70].

Niacin is not recommended as a first line therapy in HIV-infected patients and in particular with lipoatrophy since it can cause or worsen insulin resistance [71].

For ezetimib, which in combination with statins can lead to a marked reduction in LDL cholesterol, no controlled data has been published HIV-seropositive patients until now.

Modification of Antiretroviral Therapy

The replacement of PI by a reverse transcriptase inhibitor was the first approach in modifying antiretroviral therapy. Several studies have shown, that replacing a PI with nevirapine or abacavir results in a reduction of cholesterol and triglyceride levels [6, 8, 72, 73]. Under unboosted saquinavir, amprenavir and atazanavir, a low or absent risk of a hyperlipidaemia is apparent [74-77]. However, boosting these substances with ritonavir leads to an increase of triglycerides and in some studies also of cholesterol. For efavirenz, results from switch studies are unambiguous [78]. In general an increase in HDL is observed, but this is accompanied by no or little change in LDL-cholesterol and triglycerides. Amongst the NRTIs, stavudine in particular has been associated with metabolic alterations. In a controlled study, patients under stavudine showed higher cholesterol and triglyceride levels than patients treated with tenofovir [41]. Decreases of triglycerides and to a lesser extent of cholesterol have also been reported when stavudine is replaced by other nucleoside analogues [4, 79].

Systematic data on the effect of treatment interuptions are lacking, although a reduction of hyperlipidaemia induced by antiretroviral therapy usually occurs upon cessation of the antiretroviral therapy. It is not considered justifiable, however, to interrupt a vital antiretroviral therapy in order to lower lipids, since the HIV-associated mortality in such a situation clearly exceeds the expected reduction in cardiovascular mortality.

Glucose Metabolism

Pathogenesis

Pathological glucose tolerance was observed particularly under therapy with specific PIs (indinavir, boosted lopinavir) [80, 81]. The induction of insulin resistance can be attributed at least partially to a specific effect of the agent such a glucose transporter 4 inhibition [75]. Nelfinavir for example, unlike indinavir, does not seem to impair insulin sensitivity and is equivalent also to efavirenz in this respect [82, 83]. Atazanavir apparently has also none or little influ-

ence on insulin sensitivity [75]. Apart from direct pharmacologic effects, lipodystrophy and dyslipidaemia may induce insulin resistance by metabolic alterations.

Diet, Insulin, Sulphonylureas

The treatment of diabetes mellitus in HIV patients is based on the recommendations for HIV-seronegative patients with this condition [84]. Apart from diet, insulin should also be applied according to current recommendations and the regimen should be based on the skills and needs of the patient. The use of oral sulphonylureas to treat HIV-positives has not been systematically studied. Because of the hepatic metabolism of these agents, interactions at the level of cytochrome P450 2D6 in case of concomittant treatment with PIs or NNRTIs can be expected.

Modification of an Antiretroviral Therapy

A replacement of PIs with nevirapine or abacavir has led to an improvement in insulin resistance [85]. Whether a change to atazanavir also leads to an improvement in insulin resistance has not yet been clinically proven.

Metformin

Currently the use of metformin, a biguanide, is recommended for obese non-insulin-dependent diabetics. In HIV-seropositive patients metformin improved insulin sensitivity [86]. A further improvement in insulin resistance can be achieved by combining metformin with endurance training [13, 87]. Lactic acidosis is a rare but serious adverse event of metformin. However at present there is no evidence for an increased risk of lactic acidosis in association with metformin in HIV-seropositive patients [86, 88].

Glitazone

The thiozolidindiones ("insulin-sensitizers", glitazones) represent a relatively new class of antidiabetic medication. An improvement of insulin sensitivity was reported for troglitazone in a pilot study for HIV-seropositive patients [89]. However troglitazone was withdrawn from the market, because of hepatotoxicity. To date the clinical benefit of the approved substances rosiglitazone and pioglitazone in combination with oral sulphonylureas for the management of diabetes remains to be proven. Studies in HIV-seropositive patients showed a moderate improvement of insulin sensitivity with rosiglitazone which is however associated with an increase in cholesterol and triglycerides [36, 37].

Lactic Acidosis and Hyperlacatemia

Lactic acidosis is a life-threatening complication of HIV-therapy and based on the mitochondrial toxicity of certain NRTIs. Although lactic acidosis was first observed in the era of zidovudine monotherapy; it is now mostly asossiated with stavudine and didanosine [90]. An additional (synergistic or additive) increase in risk may exist when stavudine is combined with didanosine [28, 91, 92]. Numerous drug interactions may contribute to mitochondrial toxicity and should be taken into account (Table 5). In lactic acidosis, the most important intervention is the immediate cessation of antiretroviral therapy in general and of the nucleoside analogues in particular. In the case of an asymptomatic hyperlactaemia with repeated lactate measurements > 5 mmol/l, or a symptomatic hyperlactaemia (lactate 2-5 mmol/l), didanosine, stavudine and zalzitabine should be replaced by a weaker inhibitor of gamma-polymerase (e.g. tenofovir, lamivudin), if possible [93].

Table 5. Substances that should be avoided with lactate acidosis.

allopurinol, tenofovir	Increase in didanosine levels
ribavirin	Phosphorylation of didanosine
hydroxyurea	Increase in didanosine toxicity
aminoglycosides, chloramphenicol, tetracycline	Inhibitors of mitochondrial translation
statins	Inhibitors of the synthesis of CoQ10
chinolones	mtDNA depletion
adefovir, cidofovir	Nucleotide inhibitors of gamma -polymerase
acetylsalicylate, valproate	Inhibitors of mitochondrial lipid import
alcohol	causes mtDNA depletion
atovaquone(?), leflunomide	DHODH inhibitor

In vitro studies and individual case reports suggest a potential benefit of therapeutic or prophylactic uridine substitution [94]. The rationale behind this is, that respiratory chain dysfunction as a result of mitochondrial toxicity leads to an intracellular uridine deficit [95]. There is also evidence that when mitochondrial toxicity occurs, tissues are not damaged by an ATP deficit, but that instead they perish because of a uridine deficit [96]. All metabolic defects in vitro resulting from the mtDNA depletion (lactate acidosis, reduced cell growth, cell death as well as fat storage disorders) were prevented by uridine substitution in hepatocytes and adipocytes while vitamin cocktails and l-carnitine showed no protective effect [97, 98]. Uridine substitution is well tolerated in humans after oral or intravenous dosing [99]. The results of clinical studies are expected in 2005.

For lactic acidosis, a therapy with vitamin cocktails (riboflavin, thiamine, nicotinamide, vitamin C and E, pyridoxine), l-carnitine and coenzyme Q is recommended [93]. Even when taking all measures it can last several weeks before the lactate values normalise. After normalisation of lactate levels a reexposure seems

possible. However didanosine, stavudine and zalzitabine should be avoided wherever possible.

Final Remarks

Metabolic alterations are a well recognized consequence of ART, even if their pathophysiology is still not fully understood. In the treatment of lipodystrophy like in other therapeutic areas of HIV some approaches are not evidence based and have to be considered experimental. For these treatment strategies a validation as part of a clinical trial or a cohort studies is warranted. Costs, inconvenience and possible side effects of an intervention to improve disorders associated with the lipodystrophy syndrome should always be weighed against its potential benefit.

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