INTRODUCTION

There are many forms of lipodystrophy, ranging from generalized or localized to congenital or acquired.1,2 The current most common type is acquired lipodystrophy due to the use of ‘combination antiretroviral therapy’ (CART) in patients infected with HIV. CART reduces the mortality and morbidity of HIV-positive patients. Since the introduction of these drugs in 1996, the quality of life (QoL) of those infected with HIV has improved substantially.3 The therapy is, however, not always straightforward and compliance is of major importance in preventing resistance. The medication schedules are constructed from a base drug/drugs and a supplementary drug.4 The base generally consists of two nucleoside reverse-transcriptase inhibitors (NRTIs), to which traditionally a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) has been added. CART usually consists of at least three active antiretroviral drugs. Side-effects induced by CART range from gastrointestinal complaints, anaemia, peripheral neuropathy to lipodystrophy.5 HIV lipodystrophy syndrome (HIV-LS) is a term used to designate the CART-induced complex of peripheral lipodystrophy, central lipohypertrophy, hyperlipidaemia, insulin resistance and hyperglycaemia.5,6 Lipodystrophy is the loss of subcutaneous fatty tissue, through which morphological abnormalities, such as pits and recesses, arise. Especially facial lipodystrophy (FLA), commonly referred to as ‘facial wasting’, is known to create significant distress in patients.7 The pathogenesis of CART-induced LS is believed to be multifactorial, originating partly from HIV clinical stage and CD4+ lymphocyte cell count, race (white ethnicity), gender and age at start of CART.8,9 However, the main cause of this syndrome is the exposure to thymidine analogue NRTIs.

The early-generation NRTIs, especially thymidine NRTIs (tNRTIs; like stavudine in particular) and to a lesser extent zidovudine and the older PIs have been strongly associated with the development of HIV-LS and FLA in HIV-infected patients (Table 1).6,10,11 Other studies have demonstrated that the use of PIs in combination with NRTIs accelerates the process of fat loss.6,12 Although the exact mechanism by which HIV-LS and FLA are generated has not yet been elucidated, it has been shown that tNRTIs cause mitochondrial toxicity, in part by inhibiting the mtDNA polymerase γ.13 This inhibition results in impaired fatty acid oxidation and intracellular accumulation of triglycerides and lactate, which can also enter the systemic circulation.8 PIs inhibit the maturation of sterol response element binding proteins (SREBPs) which affect intracellular fatty acid, glucose metabolism and adipocyte differentiation.14 PIs are also known to cause down-regulation of peroxisome proliferator-activated receptor gamma (PPARγ), necessary for adipocyte differentiation and fatty acid metabolism.15 Whereas the tNRTIs are believed to be mainly responsible for peripheral lipodystrophy, PIs are more prone to induce central fat hypertrophy and metabolic complications.9 With the new generation of antiretroviral drugs, these side-effects occur much less.6,8,16 Interestingly, the HIV viral protein R accessory protein also inhibits PPARγ.8 This (partly) explains why CART-naïve HIV-infected patients may also exhibit signs of HIV-LS and FLA.5,9

Also, children and adolescents with perinatally acquired HIV infection have been shown to develop abnormal fat distribution when being treated with CART.17,18 In a cohort of 426 HIV-infected children, Alam et al.18 showed that...
57% developed HIV-LS, of which 42% had body fat abnormalities. Their study shows that these abnormalities occur with the same complex range of phenotypes as seen in adults. Even the associated risk factors are similar to those in adults, with CART (especially stavudine) being the main driving force behind HIV-LS and FLA.

Grading of lipoatrophy

James et al.19 were the first to create a grading scheme that expresses the severity of FLA in HIV-infected patients (Figure 1). Grade 1 corresponds to mild and localized FLA in which appearance creates the impression of being virtually normal. Grade 2 is characterized by deeper cheek atrophy, with facial muscles just beginning to become visible. In grade 3, the effects of lipoatrophy are more easily recognized on the face. Here, the atrophic part is even deeper and wider and the muscles have become clearly visible. For patients with grade 4, the atrophy covers an even greater area and extends to the orbital region, resulting in a typical bony, emaciated appearance. Since the facial skin lies directly on the muscles, the lines of the muscles can be clearly seen.

THERAPY

There are several reasons to consider treatment of FLA:

- Patients are often troubled by the physical changes in their appearance. FLA can have a significant negative influence on the self-image and self-esteem of patients.7
- Due to the morphological abnormalities in the face and its stigmatising effect, a proportion of patients worry that their HIV status has now become visible to the outside world.7,20
- Lipoatrophy or the fear of developing it can severely prejudice the compliance of patients or cause them to resist starting CART.7,21

The fat changes (peripheral lipoatrophy and central lipohypertrophy) in HIV-LS have a profoundly negative social and psychological impact on HIV-infected individuals.7 Patients feel disfigured, stigmatized and isolated resulting in low self-esteem, poor body image and depression. It has been shown that adherence to CART schedule is poorer in such patients.7,21,22

Treatment of FLA has been shown to be able to improve body image perception.23–25

In recent years, various treatment methods have been proposed to reduce the facial abnormalities and restore the original face contours. Attempts have been made to punctuate CART in a structured manner or to interchange various antiretroviral components within the CART schedule.6,26,27 A pharmacological approach has also been investigated through the administration of glitazones or the use of a growth hormone-releasing hormone (GHRH), both with uncertain outcomes on FLA.28–30

At present local invasive treatments seem most promising,31–34 though no definitive remedial treatment exists for lipoatrophy.

Systemic treatment options

As previously mentioned, several epidemiological studies and clinical trials have demonstrated that use of thymidine analogue NRTIs (particularly stavudine and to a lesser extent, zidovudine) are strongly associated with the development of FLA.6,10 Complementary to this, other studies have shown that use of PIs in combination with NRTIs can accelerate the process of fat loss.6 Exchanging these drugs for other NNRTIs unfortunately does not lead to significant improvements or a convincing increase in the thickness of subcutaneous adipose tissue.5,36

The process of fat loss will be halted, but not reversed. By changing a thymidine analogue NRTI for another NRTI (abacavir or tenofovir) some increase in subcutaneous fat can be achieved, but the effect remains minimal.5,16

Leptin. Several studies have shown that lipodystrophy syndromes are characterized by a relative deficiency of the adipose-secreted hormone leptin.37,38 This has also been demonstrated

<table>
<thead>
<tr>
<th>Type</th>
<th>Generic name</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>HIV-LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Abacavir</td>
<td>Ziagen</td>
<td>ViiV Healthcare, Brentford, UK</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
<td>Videx</td>
<td>Bristol-Myers Squibb, New York, NY, USA</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>Gilead Sciences, Foster City, CA, USA</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
<td>Epivir</td>
<td>ViiV Healthcare, Brentford, UK</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
<td>Zerit</td>
<td>Bristol-Myers Squibb, New York, NY, USA</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Viread</td>
<td>Gilead Sciences, Foster City, CA, USA</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>ViiV Healthcare, Brentford, UK</td>
<td>+</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Efavirenz</td>
<td>Stocrin</td>
<td>MSD, Brentford, UK</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Etravirine</td>
<td>Intelinece</td>
<td>Janssen, Tilburg, Netherlands</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>Viramune</td>
<td>Boehringer-Ingelheid</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Nipiravir</td>
<td>Eduarant</td>
<td>Janssen</td>
<td>–</td>
</tr>
<tr>
<td>PI</td>
<td>Darunavir</td>
<td>Prezista</td>
<td>Bristol-Myers Squibb</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Telzir</td>
<td>ViiV Healthcare</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>Crixivan</td>
<td>MSD</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Lopinavir</td>
<td>Kaletra</td>
<td>Abbott</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
<td>Virecept</td>
<td>Roche</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>Norvir</td>
<td>Abbott</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Saquinavir</td>
<td>Inivrase</td>
<td>Roche</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Tipranavir</td>
<td>Aptivus</td>
<td>Boehringer-Ingelheim</td>
<td>–</td>
</tr>
</tbody>
</table>

CART = combination antiretroviral therapy; NRTI = nucleoside reverse-transcriptase inhibitor; NNRTI = non-nucleoside reverse-transcriptase inhibitor; PI = protease inhibitor

The association between the use of a specific antiretroviral drug and the development of HIV lipodystrophy syndrome (HIV-LS) is expressed as strong (+), possible (±) and absent (–)
for CART-induced lipoatrophy, as leptin concentrations in HIV-positive patients with lipoatrophy are lower than in HIV-positive patients without lipoatrophy. Numerous trials have shown that treatment with leptin in patient with lipodystrophy substantially improved metabolic outcomes, such as glycaemic variables, liver enzymes and triglycerides. In a pilot crossover study, Lee et al. investigated the use of recombinant methionyl leptin supplements in seven HIV-positive patients with CART-induced leptin deficiency and lipoatrophy. The results after two months showed a marked improvement in insulin resistance and HDL concentrations, as well as a decrease in truncal fat mass. However, an increase in peripheral (facial) fat mass was not observed. Future studies, in patients with more severe metabolic and physical abnormalities, may eventually show a beneficial role of leptin supplementation on peripheral fat mass (i.e. facial fat loss).

Uridine, a pyrimidine nucleoside, has proven to be able to protect adipocytes against the negative effect of thymidine analogues in an in vitro model. This molecule supposedly reverses the toxic effect of NRTIs on mitochondria. Several studies showed analogous in vitro effects of uridine supplementation for the treatment of CART-induced lipoatrophy, which resulted in a significant increase in subcutaneous fat tissue. In a large randomized multicenter trial, McComsey et al. treated 165 HIV-positive patients suffering from lipodystrophy with uridine (or a placebo). They found a modest transient improvement in limb fat after 24 weeks. In another smaller study with 20 patients, treatment with uridine resulted in a significant increase in total limb fat ($P < 0.001$) after three months, in which the proportion of limb fat to total body fat increased from 18% to 25% ($P < 0.05$).

Thiazolidinediones are insulin-sensitizing agents. They are used in the treatment of type 2 diabetes mellitus. Treatment with thiazolidinediones in congenital forms of lipodystrophy (not associated with HIV) was shown to reduce haemoglobin A1c levels ($P < 0.001$), fasting triglyceride levels ($P = 0.019$) and free fatty acid levels ($P = 0.035$). Magnetic resonance imaging showed an increase in subcutaneous adipose tissue but not in visceral fat. Tungsiripat et al. demonstrated that rosiglitazone significantly improves peripheral lipoatrophy in individuals treated with thymidine analogue NRTI (tNRTI)-sparing regimens. At 48 weeks, limb fat increased significantly ($P = 0.02$) more in the rosiglitazone than in the placebo group. In their opinion glitazones could be a promising addition for accelerating fat recovery in individuals who switched to tNTRI-sparing regimens and remain with considerable lipoatrophy. It has been postulated that in patients taking tNTRI regimens, treatment with thiazolidinediones will not lead to improvement of lipoatrophy since tNTRI-associated mitochondrial toxicity and subsequent lower adipose tissue expression of PPARγ (PPARG gene) are detrimental for the effect of thiazolidinediones, being PPARγ agonists. However, a meta-analysis of six placebo-controlled trials of thiazolidinedione treatment for CART-induced lipoatrophy showed that their effectiveness did not vary according to whether or not patients were receiving tNRTIs. This paper, in which the combined data-set of 427 patients were studied, also showed that pioglitazone therapy was more effective that placebo to increase limb fat mass ($P < 0.1$), whereas rosiglitazone was not ($P = 0.48$).

GHRH has also been studied in the treatment of CART-induced lipodystrophy. A recent review of tesamorelin, a synthetic analogue of human GHRH and so far the only treatment indicated for reduction of excess abdominal fat in patients with HIV-LS, suggested that it may be useful for reducing visceral adipose tissue (VAT). This effect on VAT was confirmed in a systematic review of placebo-controlled trials of GNRH treatments for HIV-LS, which showed that GH axis treatments are effective in reducing VAT and increasing lean body mass. However, in both articles the effects on FLA were not described as applies to other published papers.
Local treatment by means of fillers

There are two main indications for using filler materials in the face: for elective or cosmetic reasons and for the treatment of CART-induced FLA.53 Based on their active period, these injectable fillers are classified into three groups (Table 2):52

- **Short-acting, absorbable fillers.** These are broken down by the body and only have an effect for a few months. Examples are hyaluronic acid (HA, non cross-linked) and collagen.
- **Semi-permanent or medium-acting fillers.** These can also be broken down but have a longer effect, generally ranging from six months to three years. Examples are poly-L-lactic acid (PLLA, Sculptra®, Valeant Pharmaceuticals, North America) and calcium hydroxylapatite (CaHA, Radiesse™, Merz Aesthetics, USA);
- **Permanent or long-acting fillers.** These are undegradable or contain permanent components that can remain present in the injected area indefinitely. Examples are liquid silicone oil (i.e. Silskin®, RJ Development Corp., Peabody, MA, USA) and polymethylmethacrylate (Artecoll® and Artefill®, Suneva Medical Inc., USA).

HA is a short-acting filler. It is obtained by bacterial fermentation, thus avoiding potential antigenic contamination and hypersensitivity reactions to animal-derived alternatives.53 Complications or allergic reactions are exceedingly rare.54 HA is gradually broken down by the body. To maintain a good and stable result, injections should be repeated every 4–6 months. Due to the required high frequency of injections and the cost of this filler, classic HA fillers are not the ideal treatment option for FLA in patients infected with HIV. However, in 2004 a large particle HA gel was introduced, consisting of highly cross-linked, high-density HA.55,56 This gel was injected at the dermal-subcutaneous junction or supraperiosteally. It seems to compensate for the subcutaneous fat loss. A treatment generally consists of several (3–6) injection sessions with intervals of at least four weeks. In one of the first large studies on PLLA treatment of FLA, Valantin et al. evaluated PLLA injections in 50 patients by clinical examination, facial ultrasound and photography until week 96.70 They observed an increase in cutaneous thickness, which remained significant until week 96 (P < 0.001). Several studies have shown similar results.59,64,71,72 Long-term effects have also been investigated. In a single-centre study with 30 patients randomized to immediate or delayed PLLA treatment, improvement of VAS-scores for facial appearance were sustained until 18 months in both groups (P < 0.05 and P < 0.001).73 Another study with 65 patients showed that treatment with PLLA resulted in significant improvement in FLA-score lasting up to three years with additional treatment sessions.61 A recently published study by Bassichis et al.72 with 290 treated subjects demonstrated that PLLA is a safe and effective long-term treatment for FLA. Mean improvement in James’ FLA grading scale was 1.4 (P < 0.001) and 89.4% of the patients and 95.5% of physicians rated treatment satisfaction as very good or excellent. A study on retreatment with PLLA after an initial 12-month follow-up demonstrated that the time to first required retreatment varied from 21.4 months in patients with grade 1

### Table 2 Injectable filler materials described in this article and complications reported in the literature

<table>
<thead>
<tr>
<th>Filler type</th>
<th>Term of effect</th>
<th>Transient injection-site reactions</th>
<th>Described complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-linked (or high-density) hyaluronic acid</td>
<td>12–24 months</td>
<td>Redness, swelling, ecchymosis and pain</td>
<td>Induration and nodules</td>
</tr>
<tr>
<td>Poly-L-lactic acid</td>
<td>18–36 months</td>
<td>Redness, swelling, ecchymosis and haematomas and pain</td>
<td>Nodules, inflammation and subcutaneous swelling</td>
</tr>
<tr>
<td>Calcium hydroxyapatite</td>
<td>12–18 months</td>
<td>Redness, swelling, ecchymosis and pain</td>
<td>Non-inflammatory nodules and delayed granulomatous reactions</td>
</tr>
<tr>
<td>Polycrylamide 2.5% gel</td>
<td>Permanent</td>
<td>Redness, swelling, haematomas, pain and pruritus</td>
<td>Induration and nodules, infection, delayed granulomatous reactions and migration</td>
</tr>
<tr>
<td>Polyalkylene 4% gel</td>
<td>Permanent</td>
<td>Redness, swelling, ecchymosis and pain</td>
<td>Induration, infection/inflammation, abscesses, delayed granulomatous reactions and migration</td>
</tr>
<tr>
<td>Polymethylmethacrylate 20% + bovine collagen 3.5%</td>
<td>Permanent</td>
<td>Redness and swelling</td>
<td>Hypersensitivity reactions, nodules, persistent redness, hypertrophic scarring and delayed granulomatous reactions</td>
</tr>
<tr>
<td>Polymethylsiloxane (LIS)</td>
<td>Permanent</td>
<td>Redness, swelling and pain</td>
<td>Induration and nodules, migration, inflammation, hyperpigmentation, delayed granulomatous reactions and ulceration</td>
</tr>
</tbody>
</table>
FLA to 13.0 months in the grade 4 FLA group.\textsuperscript{63} Milder FLA on initial presentation required fewer treatments and resulted in more sustained correction. A recent study described the use of PLLA in combination with natural glycolic acid.\textsuperscript{66} The authors speculated that both materials would act in concert to stimulate collagen production and hydrate the outer layers of the skin. They treated 30 patients with FLA with a two-year follow-up. The dermal skin thickness increases ranged from 0.22 to 0.37 cm. No serious adverse events were reported, patient satisfaction was high and in some cases the effect lasted up to two years.\textsuperscript{66} Complications after treatment with PLLA might include local redness and/or oedema, haematoma that typically disappears within a few days, or nodules and granulomas that can be somewhat more persistent.\textsuperscript{72,74–76} In the VEGA study, adverse events such as injection site tenderness, bleeding and induration occurred in less than 5\% of patients.\textsuperscript{70} In another study 13\% of patients developed papules or nodules at the injection site.\textsuperscript{76} In the study by Bassischis et al.,\textsuperscript{72} treatment-emergent adverse events were also recorded. Adverse events were classified as potentially related to the study product (18.3\%) or the injection procedure (24.5\%). Bruising, papules and nodules were most prevalent. It has been suggested that increasing reconstitution volume for PLLA, as well as increased hydration time combined with larger intervals between treatments may lead to a lower incidence of nodule formation.\textsuperscript{65} The general perspective remains that adverse events of PLLA treatment are mild and tolerable for most patients.\textsuperscript{59,64,71} Recent studies have shown that the use of PLLA for aged-related wrinkles and contour deficiencies also gives satisfying results, lasting up to 25 months.\textsuperscript{77}

\textbf{CaHA} is a semi-permanent filler consisting of a synthetic form of a natural substance found in bones and teeth.\textsuperscript{78} It can be used for treatment of vocal cord insufficiency, dental defects or as filler for soft tissue augmentation. As filler it consists of 30\% CaHA microspheres and 70\% sodium carboxymethyl cellulose gel.\textsuperscript{79} It has an active period of 12–18 months.\textsuperscript{78} The microspheres are radio-opaque, which could be a contraindication for the use of this filler. However, a study performed by Carruthers et al.\textsuperscript{80} showed no apparent interference with radiographic procedures (X-ray and computed tomography) after injections with CaHA. Once injected, the microspheres act as a platform for newly synthesized collagen, and as a result the surrounding gel is slowly replaced by autologous connective tissue.\textsuperscript{79} CaHA must be injected into the subcutaneous fat layer. Literature on the use of this filling agent in the face reveals good, long-term, outcomes.\textsuperscript{28,79,81–84} In a prospective, open-label trial, 100 patients suffering from FLA were treated with CaHA, with touch-up injections at one, six and 18 months.\textsuperscript{78} All patients showed improvement (Global Aesthetic Improvement Scale) at every time point through the first 12 months of follow-up. At 18 months 91\% still showed an improved facial appearance. In another prospective study with 30 patients the average cheek thickness was significantly increased (\(P < 0.001\)) at all measured time points (3, 6 and 12 months).\textsuperscript{81} In a large population of 1000 patients treated with CaHA for various facial aesthetic applications, the treatment effect persisted for at least one year in 80\% of the patients and 88\% of the patients were satisfied with the results.\textsuperscript{81} Thereafter, in that study nodule formation was observed in 1.7\% of cases, mostly when lip-augmentation was performed. Transient adverse events such as ecchymosis, oedema, erythema, pain and pruritus have been reported in varying degrees.\textsuperscript{78,79,81,82} Nodule and granuloma formation have been described, though not often and associated with inadequate technique.\textsuperscript{82} Patient satisfaction is considered to be high and ranging from 87–89\%.\textsuperscript{85–87}

\textbf{Polyacrylamide gel (PAAG)} was introduced as permanent filling agent for soft-tissue augmentation approximately 18 years ago and obtained CE certification as Aquamid\textsuperscript{16} (Contura International, Copenhagen, Denmark) in 2001.\textsuperscript{88} It consists of 2.5\% polyacrylamide gel and 97.5\% water.\textsuperscript{88} PAAG was designed as a permanent implant, such as a breast prosthesis. As a consequence, injection of the agent must take place under strict sterile conditions. The agent should be injected into the subcutaneous fat layer or into the supra-periostal level.\textsuperscript{89} PAAG is indicated for augmentation of congenital and acquired soft tissue defects and deformities, breast and perineal augmentation, post-traumatic (facial) reconstruction, treatment of female stress urinary incontinence, facial and maxillofacial contouring and lip augmentation.\textsuperscript{89,90} Several studies have been performed to evaluate PAAG treatment in CART-induced FLA.\textsuperscript{25,91–94} Mansor et al.\textsuperscript{91} treated 40 patients suffering from FLA with PAAG in 3–6 sessions with 14-day intervals. Follow-up was performed until two years post-treatment. Results were measured by the observed FLA-grade reduction (0 = no FLA, 1 = mild, 2 = moderate, 3 = severe). In 11 patients a 1-grade reduction was achieved, in 20 cases a 2-grade reduction and in three cases a 3-grade reduction. No complications were recorded. In another study 32 individuals with FLA were treated with PAAG with an 18-month follow-up.\textsuperscript{92} Full restoration was achieved in 2.3 sessions and besides non-visible nodules in 13 cases no complications were recorded. Negredo et al.\textsuperscript{93} treated 145 patients with PAAG to correct CART-related FLA. After a four-year follow-up period non-visible nodules and indurations were present in 19.3\% and 6.2\% of patients, respectively. Overall patient satisfaction was 88.9\%. Similar results were obtained in a recent five-year follow-up study with polyacrylamide.\textsuperscript{25} The most widely described complications are infection, granuloma formation and migration of filler material from the injected site.\textsuperscript{88,95,96} Migration and infection were not reported during the follow-up periods of FLA treatments.\textsuperscript{94} These results stand in contrast to reported complications after aesthetic use of PAAG.\textsuperscript{95–100}

\textbf{Polyalkylimide gel (PAIG)} (PAIG, Bio-alcamid\textsuperscript{16}; Polymekon, Italy) is a non-resorbable polymer derived from acrylic acid. It contains 96\% water and 4\% alkylidine-amide groups and was brought on the market as a biocompatible endoprosthesis.\textsuperscript{101} PAIG should be injected subdermally. After injection, the body supposedly forms a thin capsule around the injected material making migration impossible. In addition, the material could easily and completely be removed at all times through an 18-gauge needle.\textsuperscript{102} Indications for treatment with PAIG are congenital and acquired skin malformations/depressions, scar corrections, filling of pectoral excavatum and FLA. Multiple studies have investigated the use of this agent as a soft tissue filling material, with varying results.\textsuperscript{23,103–106} Ramon et al.\textsuperscript{103} reported on the treatment with PAIG of CART-induced FLA in 13 HIV-patients. Their follow-up period ranged from 12 to 24 months and no substantial complications were observed. In a study by our group, 17 patients with FLA were treated with PAIG in a single session.\textsuperscript{107} A mean volume of 14 cm\(^3\) was injected. Complications occurred in four patients, of which three needed no intervention. This study demonstrated a significant reduction of FLA-severity at week 48, correlated with a significant improvement of QoL. Another study
FLA treatment with PMMA. 115 – 117 PMMA has a certain allergic potential because it is suspended in bovine collagen. In Europe PMMA has been on the market since 1994 as Artecoll® and Artefill® for treatment of CART-induced FLA.113,114 It is a biphasic filling agent consisting of 20% PMMA microspheres suspended in a 3.5% bovine collagen solution.115 In Europe PMMA has been treated either with lipofilling (14 patients) or with PAAG (9 patients).135 Fat was harvested from lipohypertrophied areas such as the lower abdomen, mammary region and buffalo hump. No major complications were recorded.

Surgical treatment options

Talmor et al.137 reported on three cases of CART-induced FLA that were surgically treated by inserting Binder Sub-Malar-II-silicone implants. Depending on the extent of the lipoatrophy, one or two prostheses per side (cheek) were implanted. In two cases, additional collagen injections were administered to ameliorate the results. No complications were observed and patients were satisfied with the final aesthetic outcome.

DISCUSSION

Systemic treatment options of CART-induced lipoatrophy have yet to be investigated more thoroughly. Some systemic therapies have resulted in increase in limb fat in clinical trials and therefore seem promising. However, to our knowledge no studies showing restoration of wasted facial subcutaneous adipose tissue after systemic therapies have been published. This could be explained by the fact that FLA has been shown to be less reversible than fat atrophy of the extremities. Furthermore, research has shown that introduction of new generation antiretroviral agents has not been able to reverse facial wasting that has already occurred. Therefore, avoiding thymidine analogue NRTIs, stavudine and zidovudine in particular, appears to remain the sole preventive approach in combatting FLA.6,9,10,12

In recent years, much experience has been gained in local treatment options by using injectable filler materials, varying from injectable fillers only in cases where lipofilling is not possible, which in patients were satisfied with the final aesthetic outcome. For example, one or two prostheses per side (cheek) were implanted. In two cases, additional collagen injections were administered to ameliorate the results. No complications were observed and patients were satisfied with the final aesthetic outcome.
from short-acting to permanent types. Permanent soft tissue fillers can be very cost-effective and the theoretical permanent effect appears patient friendly. However, the term ‘permanent’ does not refer to the permanent result but to the permanent presence of the filling agent with the ensuing permanent risk of complications. FLA, just as the normal ageing of the face should be considered a dynamic and progressive process. Therefore, treatment with permanent fillers will, in time, still require maintenance by touch-up injections. In addition, due to the permanent nature of these filling agents, the risk of complications merits consideration. For instance, PAIG can lead to unpleasant complications when used for the treatment of CART-induced FLA, such as migration, LGIs and abscess formation.107–112 On the other hand, compared with other permanent fillers such as PAAG and LIS, PAIG is somewhat easier to remove.95,101,108,125 PAAG induces fibrosis, which makes removal very challenging.95 Although PMMA has a certain allergic potential the incidence of allergic reactions is estimated at merely 0.1–0.2%.119 The main complications observed after PMMA injections are foreign body granulomas with an estimated incidence around 0.02–0.1%, 122,123 The risk of complications with this agent appears relatively low when compared with the other permanent fillers. LIS is injected in small quantities, and injections must be repeated regularly (every 4–6 months). In addition, fibrosis may be significant and LIS is extremely hard to remove.125,126

Treatment with semi-permanent fillers such as PLLA, CaHA and HDHA currently generates the most promising outcomes.55–59,64,71,78,85 PLLA and CaHA stimulate autologous collagen synthesis.97,99 Long-term results are encouraging, with few complications.61,63,75,85 Recently, lipofilling has also shown promising results, and appears to deserve a place among the semi-permanent fillers as first-line invasive treatment for FLA.135,136 Although surgical implantation of silicone prostheses may provide a visibly good result, the face contours will not feel natural on palpation. Furthermore, the requirement of additional injections with filling agents close to the surgical implants can be unpleasant for patients and increases the risk of prosthesis infection.137

CONCLUSION

When choosing injectable filling materials for the treatment of CART-induced FLA, biodegradable semi-permanent fillers should be considered as the best treatment option. A disadvantage may be that the treatment has to be repeated and is therefore time-consuming, both for the patient and physician. End-results are achieved faster after treatment with CaHA and HDHA. As recent publications show positive results with lipofilling, this method should also be considered as an option. However, for good results substantial technical experience is required. Despite the promising results after treatment with semi-permanent fillers, prevention of lipatrophy by removing thymidine analogue NRTIs from the CART schedule still deserves the highest focus of attention.

Conflict of interest: LvR provides clinical training in the use of the fillers Sculptra™ (Sanofi-aventis Netherlands BV, Gouda, The Netherlands) and Radiesse™ (Merz Aesthetics Benelux, Oosterhout, The Netherlands).

Financial support: None reported.

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(Accepted 19 December 2012)