Prevention and treatment of lipodystrophy in Quebec in 2005

Memorandum submitted to the Ministère de la Santé et des Services sociaux du Québec

by the Comité LIPO-ACTION !
June 10, 2005

English translation of the French original
Translation approved by the Comité LIPO-ACTION !

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Summary

LIPO-ACTION!, a community group composed of people living with HIV (PHAs), who also have the lipodystrophy syndrome, plus their families and friends, presents this memorandum to the Ministre de la Santé et des Services sociaux du Québec.

The memorandum is composed of six parts:

1. An introduction describing the historical context of the situation in Quebec of people living with HIV (PHAs) and experiencing lipodystrophy. The origin of this memorandum is also explained;

2, The definition and description of the morphologic changes caused by lipodystrophy, taken from recent publications by the Quebec Health Ministry;

3, The three requests from Quebec PHAs who are also living with morphological changes related to lipodystrophy:

   a, the creation of a systematic program for the prevention and diagnosis of morphologic changes related to lipodystrophy;
   b, access to reparative interventions for the effects of facial lipoatrophy (access to New-Fill and Bio-Alcamid);
   c, access to appropriate reparative interventions for the effects of lipoaccumulation (for example, the “buffalo hump”);

4, A summary of the recent international research on the prevention and repair of morphological changes related to lipoatrophy and lipoaccumulation, including sections on:
   - the aetiology of these syndromes;
   - recent HIV treatment guidelines concerning these issues from France, the United Kingdom and the United States of America;
   - the prevalence of the lipodystrophy syndrome: lipoatrophy and lipoaccumulation;
   - the impact on the quality of life of those PHAs in Quebec living with morphologic changes related to lipodystrophy (research presented at CAHR in 2005);
   - recognised approaches for treating lipoatrophy based on recent research;

- recognised approaches for treating lipoaccumulation (example: “buffalo hump”) based on recent research;

5, Our point of view on the benefits for Quebec society of introducing a prevention and reparative program for the damages related to lipodystrophy; this observation is, in part, based on the results of the Quebec quality of life study addressing the situation of PHAs with morphologic changes caused by lipodystrophy;

6, Appendices containing complimentary information, including:

- extracts from the HIV treatment guidelines presently used in France, the United Kingdom and the United States of America;
- the contents of the Quebec research on the quality of life of Quebec PHAs affected by morphologic changes related to lipodystrophy.

1. Introduction: A brief history of HIV and lipodystrophy in Quebec

The dark ages

HIV first appeared at the beginning of the 1980s; it was a time of great trauma on both the human and medical levels. At the time, nobody knew what was really happening. A new disease, virulent and fatal, had just appeared. Faced with this scourge, the medical community was shaken and powerless. No one had an answer. For patients and their loved ones, it seemed hopeless.

The period of distress

After years of devastation and sustained efforts in research, HIV and its mechanisms of development and transmission started to be better known. However, the disease was progressing, bringing in its wake human tragedy. HIV was hitting hard and without discrimination, a veritable hecatomb.

Some hope

Thanks to superhuman efforts by researchers and the voluntary participation of many patients, years of medical research finally bore its first fruit: AZT was finally discovered and administered to patients. Nevertheless, the virus remained active and patients continued to suffer and die . . .

A first victory

In 1996, triple therapy was introduced. For the first time since HIV's appearance, PHAs could at last be treated appropriately and with unquestionable success. Indeed, the treatments were saving lives and the number of deaths dropped by 80%. This was an historical step in the fight against HIV. Victory was declared.

Disenchantment

Unexpectedly, some patients on ARV therapy started to metamorphose. At the end of the 1990s, large bellies commonly referred to as "Crix bellies" (referring to the effect of Crixivan, the main cause of the abdominal swelling) appeared. A few years later, yet another HIV-related stigma appeared: lipodystrophy. Indeed, a growing number of HIV-positive people on ARV therapy were ending up with deformed bodies: thin legs, raised veins, inexistent buttocks, "buffalo humps." Our faces became extremely emaciated, many to the point where we no longer recognised ourselves. It is this "new face of AIDS" that first worried us and then overwhelmed us, as it leads to stigmatisation and discrimination. Over time, little by little, we became "mutants," displaying HIV on our faces.

A Difficult Awareness

The heath care system and the community organisations took time to react to this new phenomenon. It is clear that the lipodystrophy syndrome is complex and that it is a delicate subject. Physicians feared the discontinuation of treatments, while

the silence became unbearable for the patients. We really wanted to know what was happening. What seemed anecdotal became a widespread phenomenon that affected an ever-increasing number of HIV-positive men, women, and children.

The HIV-positive patients' response: Breaking the silence
LIPO-ACTION! (*Le comité LIPO-ACTION !)* was founded in Montreal on October 16, 2003, following a public meeting called to find solutions to the devastating impact of lipodystrophy for HIV-positive persons who use ARV therapy. This movement brings together patients who have the lipodystrophy syndrome, their friends, their spouses . . . all of whom are affected by this distress.

Support from the HIV-infected community in Quebec
At the end of November 2004, the first Quebec PHA Forum voted officially to support LIPO-ACTION!'s actions and the demands expressed in this memorandum. Since then, great efforts have been made to get both the health care system and the clinicians more interested in this condition in order to obtain adequate follow-up and care.

The Quebec Minister of Health's request for an in-depth, rational study
Following World AIDS Day on December 2, 2004, Quebec's Health Minister, Mr. Philippe Couillard, stated in the National Assembly that this issue required a "rational" and "in-depth analysis" prior to his considering reimbursing the costs of necessary reparative treatments due to the impact of lipodystrophy on HIV-infected persons on ARV therapy. (Source: *Le Journal de Montréal*, December 2, 2004, p.33*, La Presse,* December 2, 2004, p. A-17.)

LIPO-ACTION! therefore decided to submit an in-depth study on the subject of lipodystrophy that will meet the criteria of rationality of scientific research and of equity with respect to repairing the consequences of both the disease and antiretroviral treatments.

Hope for social solidarity for the prevention and reconstruction of lipodystrophy
We remain hopeful about regaining our human dignity. Today, in 2005, we are still at the same point: affected in our physical integrity, wounded by life, and, in some cases, ostracised. Nonetheless, we are confident that the Quebec government will recognise the urgency of dealing with the disastrous impact of lipodystrophy on HIV-positive patients. In order to facilitate the adequate management of the persons concerned, and considering the recognition of the contribution of HIV-positive persons to our society, we are demanding concrete measures for the prevention and treatment of lipodystrophy. It is for this reason

that we are now submitting our request, in the name of all HIV-infected persons in Quebec.

The members of the Comité LIPO-ACTION ! sub-committee that worked on "*Prevention and treatment of lipodystrophy in Quebec in 2005*"

Suzanne Desbiens
Claire Desjardins
Michael Hendricks
Marc Leclerc
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Laurette Lévy
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José Sousa

2. Definition and description of the lipodystrophy syndrome

For the purpose of this request, we will address specifically the issues related to morphological changes associated with lipodystrophy (lipoaccumulation, lipoatrophy, and the “mixed syndrome”). Although the definition of lipodystrophy can often include “metabolic complications” (diabetes, cholesterol, etc.), we will deal only with those aspects that are the most stigmatizing for patients, that is, the characteristic physical changes that allow an HIV-infected person to be identified by simple observation and that have a devastating impact on that person’s life.

2.1 The lipodystrophy syndrome

Lipodystrophy is a complex syndrome affecting HIV-infected people who take antiretroviral therapy. This condition has serious consequences for the patient’s health, physical integrity, and quality of life. It is characterised by various metabolic disorders and by visible and measurable body deformations.

“Lipodystrophy groups together several symptoms that are characterised by an abnormal distribution of fat mass on the body. Three distinct entities have been described: lipoatrophy, lipoaccumulation, or mixed manifestations, which include both lipoatrophy and lipoaccumulation (sometimes called the mixed syndrome).”

« *Le Syndrome de la lipodystrophie : guide pour les professionnels de la santé* » *(“The lipodystrophy syndrome: A guide for health professionals”)*, Santé et services sociaux, Gouvernement du Québec, written by the Comité consultatif sur la prise en charge des personnes vivant avec le VIH, under the direction of Dr. Jean-Guy Baril, 2005.

2.2 Visible and measurable symptoms of lipodystrophy

Lipoatrophy (fat loss)

- in the face: appearance of having lost (a great deal of) weight or having (very) hollow cheeks and temples;
- on legs and arms: veins become (much) more visible;
- on the buttocks: the seated position can become uncomfortable (due to pain).

Lipoaccumulation (fat deposits)

- in the abdomen (visceral, non-subcutaneous fat) and breasts of both men and women: the principal effect of fat accumulation in the abdominal area is a larger waistline, which can alter a person's physical appearance (causing discomfort and dramatically changing the body posture). In severe cases, the internal organs can also be compressed, leading to difficulties with normal functions, like breathing and eating;
- in the neck area: the "buffalo hump" is the term used to designate fat accumulation in the back, between the shoulders. (...) In some patients, fat can also accumulate under the chin (in serious cases this can eventually lead to difficulty with normal functions like breathing and eating);
- under the skin: small lumps of fat, called lipomas, are sometimes seen. Usually, these lumps do not cause symptoms. (When visible, they are unattractive.) They can occasionally be painful.

Mixed syndrome (fat loss and accumulation)

- Some people can have both fat loss and fat accumulation in different areas of the body.

« *La lipodystrophie: informations pour les personnes vivant avec le VIH* » *("Lipodistrophy: Information for HIV-Infected Persons")*, Santé et services sociaux, Gouvernement du Québec, written by the Comité consultatif sur la prise en charge clinique des personnes vivant avec le VIH, under the direction of Dr. Jean-Guy Baril, 2004.

3. Requests from HIV-infected persons (PHAs) in Quebec concerning lipodystrophy

In Quebec, since 1996, HIV-infected persons (PHAs) have witnessed the efficacy of antiretroviral (ARV) treatments in fighting HIV. This led, among other things, to improving health and to prolonging life expectancy considerably. One thing is certain, there is no longer any doubt as to the necessity for ARV treatments. However, these few years of treatment have left some stigmatising traces on a large number of PHAs who learned, at their expense, that undesirable effects of treatment can have a devastating impact over time. In fact, the unexpected consequences of lipodystrophy are now a great source of distress for PHAs, especially for those who have experienced physical, moral, or social damage. In the past, very few studies addressed these issues, but, recently, considerable research has confirmed this sad reality. In Part 4.4, we discuss these issues, and, more specifically, a 2004 Quebec study documenting the lived reality of Quebec HIV-positive men and women with lipodystrophy. Its findings provide the elements necessary for understanding the serious consequences of this syndrome, and demonstrate the relevance of our request for concrete and effective solutions for this worrisome condition.

In light of the willingness expressed by Mr. Philippe Couillard, the Quebec Health Minister, in the National Assembly on World AIDS Day 2004, we wish to submit to Québec's Health and Social Services Ministry an "*in-depth and rational analysis"* concerning the prevention and treatment of lipodystrophy in Quebec. Following a census of recently published scientific literature and of reports from international conferences in 2004 and 2005, LIPO-ACTION! prepared the present request on behalf of PHAs in Quebec.

After the first Quebec PHA Forum in November 2004 and after regular consultations with community organizations, LIPO-ACTION!, in collaboration with many HIV-infected people across Quebec, has been able to identify three essential and urgent needs concerning the morphological changes related to ARV therapy and HIV:

1. The creation of a systematic prevention and diagnostic program for lipoatrophy and lipoaccumulation;

2. Access to reparative procedures for certain morphological manifestations of lipoaccumulation (particularly the "buffalo hump") associated with antiretroviral therapy;

3. Access to reparative procedures for facial lipoatrophy associated with antiretroviral therapy.

3.1 The creation of a systematic program for the prevention and diagnosis of lipoatrophy and lipoaccumulation

3.1.1 Prevention

The following is an extract from the Continuing Education Program by Clinical Care Options HIV, "*Metabolic Complications and Lipodystrophy, coverage of the 12th Conference on Retroviruses (CROI)",* published on April 1st, 2005, where three renowned authorities on HIV clinical practice address the prevention of lipoatrophy, according to the studies presented at CROI this year:

Dr William G. Powderley, MD, Professor of Medicine and Therapeutics, University College Dublin, Ireland:
"*All in all, the piece of data that will have the greatest impact on my clinical practice is the finding that fat loss continues to progress if you remain on a thymidine analogue. I think all patients should be made aware of that fact. Even if we cannot achieve obvious measurable changes immediately, we may be able to prevent further fat loss, and switching (treatments) is the only effective medical intervention we have at present."*

"*Sufficient data have now been reported to support that primary prevention of lipoatrophy is possible by avoidance of thymidine analogue NRTIs."*

Dr Peter Reiss, Associate Professor of Medicine, Deputy Director, National AIDS Therapy Evaluation Center, University of Amsterdam:
"Primarily, what all of these studies are telling us is that we now have regimes that may prevent lipoatrophy, and, overall, I think that prevention is clearly better than cure."

Dr Donald Kotler, MD, Professor of Medicine, Columbia College of Physicians and Surgeons, New York:
"We should not only be considering the cardiovascular risk involved with fat changes but also our patients' concerns regarding their physical appearance."

"There are basically three approaches to managing lipoatrophy: avoid, switch or treat. I think we would all agree that avoidance is best, switching is second best, and treatment (e.g. using insulin-sensitizing agents) is still a murky issue."

In Parts 4.2, 4.5 and 4.6, we have presented the results of the research on the means known to date to prevent lipoatrophy and lipoaccumulation. Even if the aetiology of the syndrome has not yet been identified, the associated cause of lipoatrophy is known. The simplest and most direct way to avoid this problem, for the majority of patients, is to switch antiretrovirals at the appearance of the

syndrome (that is, to switch from thymidine analogues, like d4T or AZT, to other nucleosides or to a nucleotide). For lipoaccumulation, neither the aetiology nor the associated cause has been as well determined. Consequently, a more individual, case-by-case approach is required.

The members of LIPO-ACTION! request that the Health Ministry establish an education program for clinicians treating HIV, so that they no longer act as they did in the past and that they are provided with all the pertinent information on morphological changes caused by lipodystrophy in PHAs in order to prevent the syndrome before it gets out of control and the patients find themselves with advanced cases.

3.1.2 Diagnosis

Over the past years, many people living with severe body deformations related to lipodystrophy have reported that their physicians refused to take their stigmatising condition seriously even when they are incapacitating as well as physically and morally painful. Our doctors told us that it was impossible to diagnose morphological changes even when they were faced with our hollow faces displaying our HIV status, our skeleton-like limbs, and our Quasimodo-like "buffalo humps". We were told that the techniques available to assess fat loss or fat gain, the markers of lipodystrophy, are used only in the context of research. Yet these techniques are available to any dietician and in most Quebec hospitals.

Therefore, we request that clinical care standards for all PHAs in Quebec include access to the diagnosis procedures for lipodystrophy to assess the body changes caused by lipoatrophy and lipoaccumulation:

- Anthropometric measurements, such as measuring cutaneous folds, analysis by electronic bio-impedance, etc.;
- Radiological techniques, like DEXA scan (dual-energy X-ray absorptiometry), ECG, tomodensitometry and magnetic resonance imaging (MRI).

3.2 Access to reparative surgical procedures for facial lipoatrophy caused by antiretroviral (ARV) therapy.

For PHAs affected by lipoatrophy, we request:

a. The inclusion of reparative techniques for lipoatrophy in the general nomenclature of professional acts in order to allow coverage by the Quebec

Healthcare Insurance Plan (RAMQ), along with reimbursement of such an act so that all patients who need it will have access;

b. The inclusion of two injectable filling products: Sculptra (New-Fill) and Bio-Alcamid on the list of products and drugs covered by the RAMQ, upon their approval in Canada;

c. The issuing of directives on HIV care standards, including indications for monitoring the development of lipoatrophy, informing physicians of the cause of this condition in order to plan for a change of medications to stop its progression. For instance, the withdrawal of thymidine analogues from the therapeutic regime and their replacement with less toxic ARVs (replacing d4T or AZT with ABC or TDF), when possible;

d. The transfer of TDF (Viread, tenofovir) from the "list of exceptions" to the regular list of antiretroviral drugs in order to provide the choice of an antiretroviral regime that prevents facial lipoatrophy. This represents a solid therapeutic advantage for the patient.

3.3 Access to reparative surgery for certain morphological manifestations of lipoaccumulation (particularly, the "buffalo hump") caused by ARV therapy

For PHAs affected by lipoaccumulation, we request:

a. The inclusion of reparative techniques for the "buffalo hump" in the general nomenclature of professional acts in order to allow coverage by the Quebec Healthcare Insurance Plan (RAMQ), along with reimbursement for such an act so that all patients who need it will have access;

b. The issuing of directives on HIV care standards, including indications for monitoring the development of lipoaccumulation and the use of well-known solutions. For instance, in the presence of central lipoaccumulation (fat deposit in the abdominal cavity) in a patient taking indinavir (Crixivan), change the protease inhibitor for another, less toxic medication;

c. Financial support from the Quebec government to encourage an expanded access research program for Theratechnologies' leading-edge peptide TH9057. (Theratechnologies is a Montreal-based company.) This would allow access for the greatest number of patients possible, should they want to participate.

4. Summary of the research on the prevention of, and reparative techniques for, morphological changes due to lipoatrophy and lipoaccumulation

4.1 Aetiology of morphological changes due to lipodystrophy

The lipodystrophy syndrome causes abnormal fat distribution. There are two principal phenomena: lipoatrophy (subcutaneous fat loss affecting the face, limbs, and buttocks) and lipoaccumulation (fat deposits on the abdomen, back, neck, breasts, and the development of lipomas). Over time, it causes visible and measurable morphological changes that threaten the physical integrity, health, and quality of life of the affected persons.

The direct association of these physical abnormalities to ARV therapy is now widely accepted. In some studies, more than 50% of the patients on ARV therapy are affected by lipodystrophy, either by a gain or a loss of fat or both (the mixed syndrome). Both phenomena are often found in the same individual but they are modulated by different antiretroviral agents. Lipodystrophy is especially aggravated in older patients and in those taking ARV for a longer period of time. HIV virus, heredity, and environmental factors also play a role in the appearance of the syndrome. The term generally used for this phenomenon is “lipodystrophy,” but the causes are still poorly understood and are apparently different for each phenomenon.

While researchers are still debating the cause of these two conditions, there is a strong consensus emerging among patients and some clinicians about lipodystrophy. We observe a growing number of HIV-positive persons affected by lipodystrophy who present increasingly severe conditions that gravely impact their health, physical integrity, and quality of life. For clinicians, while ARV therapy succeeds in controlling HIV infection, the appearance of lipodystrophy in patients is frustrating and menacing because it can eventually lead to therapeutic failure. Indeed, many distressed patients have taken the risk of discontinuing ARV therapy at the first sign of the syndrome. For patients affected by lipodystrophy, it is a source of serious worry, despair, and depression.

Since 2000, many scientific studies have been published on approaches to preventing both forms of lipodystrophy. One of the first, published in the *Journal of Acquired Immune Deficiency Syndromes,* presented the pathogenesis of lipodystrophy. This research already determined a significant association between lipoaccumulation and the use of protease inhibitors and between lipoatrophy and the use of thymidine analogues like AZT and d4t.

See: Bogner *et al*, "*Stavudine Versus Zidovudine and the Development of Lipodystrophy*," Journal of Acquired Immune Deficiency Syndromes, vol. 27, no. 3, July 2001.

Scientific research on the associations between ARV therapies and both forms of lipodystrophy is progressing rapidly; however, up until now, it has not explained the mechanisms that can cause lipodystrophy in some patients and not in others. On the other hand, the way to prevent lipoatrophy is now more evident.

Recently, the members of Lipo-ACTION! read with great interest an interview with Dr. David Nolan, a world-renowned clinician and researcher, who identified the different adipose-tissue pathologies associated with AVR therapies and mitochondrial toxicity.

"*One is the potential impact of nucleoside thymidine analog like d4t (Zerit, Stavudine) and AZT (Zidovudine) on subcutaneous (under the skin) fat wasting. Studies in which patients were switched from these drugs to abacavir (Ziagen) or tenofovir (Viread) have produced encouraging results in reversing lipoatrophy, even if at a slow rate."*
See: Vergel, N. "*Face to face with lipoatrophy, an interview with David Nolan*", *GMHC Treatment Issues*, Newsletter of Current Issues in HIV/AIDS, March / April 2005, vol. 18, no. 3/4.

(See this text in Appendix 6.6)

International congresses on HIV therapies and specialised scientific journals have presented a large number of switch studies as an approach to preventing or stabilising lipoatrophy caused by thymidine analogues. Here are a few:

A brief chronology of scientific switch studies

2002
Carr, A, Workman C, Smith DE, "*Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial (the **MITOX** study),"* Journal of the American Medical Association, 2002; 288: 207-215

2003
John, M, McKinnon, EJ, James, IR *et al*, "*Randomized, controlled, 48-week study of switching stavudine and/or protease inhibitors to combivir/abacavir to prevent or reverse lipoatrophy in HIV-infected patients,*" Journal of Acquired Immune Deficiency Syndrome, 2003 May 1;33 (1).

2004
McComsey, GA, Ward, DJ, Hessenthaler, SM *et al*, "*Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the **TARHEEL** study,*" Clinical Infectious Diseases, 2004 Jan 15;38(2).

Shlay, JC, Visnegarwal F, Bartsch G, *et al*, "*Body composition and metabolic changes in antiretrovial-naive patients randomized to didanosine and stavudine (ddI + d4t) vs abacavir and lamivudine (ABC +*

3TC)," Program and abstracts from the XV International Conference on AIDS, July, 2004, abs. ThOrB1360

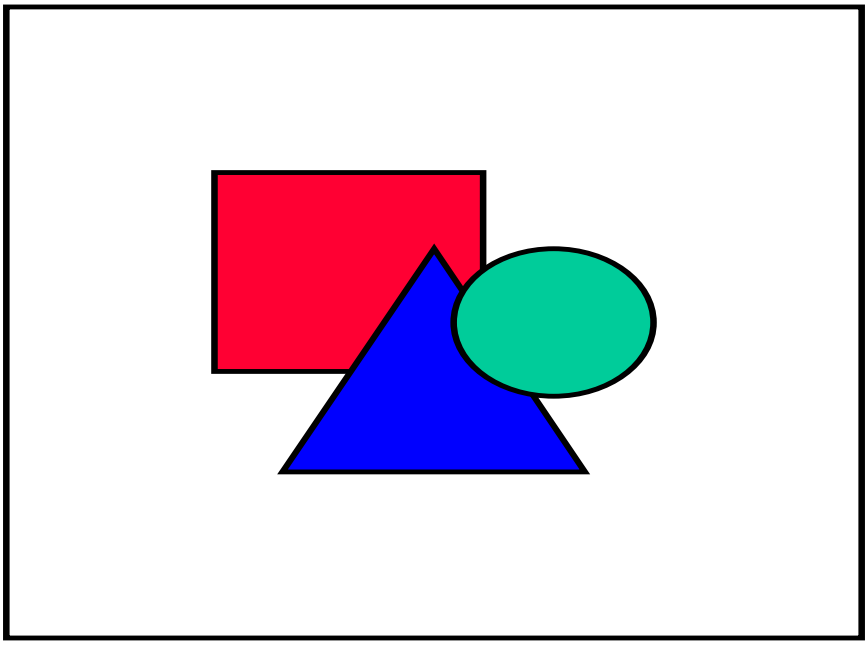
2005
McComsey, GA, Paulsen, D, Lonergan,J, *et al*, "*Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine,*" AIDS, vol. 19(1), January 3, 2005.

Moyle, G, Sabin, C, Cartledge, J *et al*, "*A 48-week, randomized, open-label comparative study of tenofovir DF vs abacavir as substitutes for a thymidine analog in persons with lipoatrophy and sustained virological suppression on HAART,*" Program and abstracts from the 12th Conference on retroviral risk and opportunistic injections (CROI), February 22-25, 2005, Abstract 44LB.

"*Switching to a thymidine analogue-sparing or a nucleoside-sparing regime improves lipoatrophy: 24-week results of a prospective, randomized clinical trial: AFCTG A5110,*" Program and abstracts from the 12th Conference on retrovirus and opportunistic infections (CROI), February 22-25, 2005, Abstract 45.

"*Switch to protease inhibitor-containing/nucleoside reverse transcriptase inhibitor-sparing regimen increases appendicular fat and serum lipid levels without affecting glucose metabolism or bone mineral density: the results of a prospective randomized trial, ACTG 5125S.*" Program and resume from the 12th Conference on retrovirus and opportunistic infections (CROI), February 22-25, 2005, Abstract 40.

None of these studies established beyond a doubt the usefulness of switching from one protease inhibitor to another in order to stop lipoaccumulation; however, in clinic, visceral fat gain has been observed when using Crixivan (indinavir). The switch from a thymidine analogue (d4t) to another nucleoside inhibitor or nucleotide (like abacavir or tenofovir) seems to be associated with a modest peripheral fat gain. Most important is the discontinuation of d4t which stops the progression of the lipoatrophy syndrome. Below is a graph from the **MITOX**



extension study where d4t or AZT was replaced by abacavir:

Martin, A *et al* (for the Mitochondrial Toxicity (MITOX) Study Group), "*Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir, the MITOX Extension Study*", AIDS, 18(7): 1029-1036, April 30, 2004.

4.2 International guidelines on the use of certain therapies associated with lipodystrophy

NOTE: As in the original memorandum in French, guidelines are not translated and are presented in the original language.

Based on scientific presentations on lipodystrophy and the recommendations for switching ARV therapies in order to reverse the progression of the syndrome or to prevent it altogether, France, the United States, and the United Kingdom revised their HIV treatment guidelines.

In France:
"Prise en charge thérapeutique des personnes infectées par le VIH: recommandations du groupe d'experts (Therapeutic Management of HIV-infected Persons: Recommendations of a Group of Experts)" (Direction: Professor J-F Delfraissy), Report (June) 2004.

Chapitre 9: Complications des traitements antirétroviraux, Anomalies de répartition des graisses, Prise en charge des patients, Lipo-atrophie, page 134:

"*Lipo-atrophie. Elle est plus volontiers associée aux inhibiteurs nucléosidiques (dérivés de la thymidine) et en particulier à la d4t. Seule la substitution de la d4t par l'abacavir a permis d'observer, dans une étude comparative (étude MITOX), une amélioration significative des lipodystrophies périphériques évaluées par DEXA, mais sans bénéfice réel perçu par les patients après deux ans de suivi. Une autre étude comparant le ténofovir à la d4t, associé à 3TC et éfavirenz chez des patients naïfs a montré une fréquence inférieure de survenue d'une lipodystrophie évaluée cliniquement (1 p. 100 versus 12 pp. 100 à 48 semaines), et un gain significatif de masse adipeuse évaluée par DEXA au niveau des membres dans le bras ténofovir (+3 kg versus + 0,5).*

De la même manière, la comparaison de la FTC à la d4t a montré une augmentation significative du poids, du BMI ainsi qu'une stabilité du rapport taille sur hanche dans le bras FTC alors qu'il était augmenté significativement dans le bras d4t.

Ces données justifient de tenter de substituer la d4t au profit de l'abacavir et peut-être du ténofovir ou de la FTC en cas de lipo-atrophie, si l'efficacité virologique ne s'en trouve pas compromise."
(See Appendix 6.2)

In the United States
"*Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents*" (by a Panel on Clinical Practices under the leadership of John G. Bartlett and H. Clifford Lane), April 7, 2005:

Table 16c. Adverse Effects Compromising Quality of Life and/or With Potential Impact on Medication Adherence

Adverse effects: Fat maldistribution
Causative ARVs: PIs, d4t
Onset: gradual - months after initiation of therapy
Symptoms:

- Lipoatrophy - peripheral fat loss manifested as facial thinning, thinning of extremities and buttocks (d4t)
- Increase in abdominal girth, breast size, and dosocervical fat pad (buffalo hump)

Estimated frequency: High - exact frequency uncertain; increase with duration on offending agents
Management:

- Switching to other agents may slow or halt progression, however may not reverse effects
- Injectable poly-L-lactic acid for treatment of facial lipoatrophy

(See Appendix 6.3)

In the United Kingdom
Section 12 of the new guidelines for the United Kingdom, *HIV Treatment Guidelines Update 2005* (May 2005), contains pertinent information on lipodystrophy:

Lipodystrophy (12.1)
"Lipodystrophy (LPD) has a two-fold clinical significance. There are the stigmata of body shape changes, which may not cause physical morbidity, but can be psychologically and socially debilitating. This may lead patients to delay initiation of therapy, to stop therapy, or may promote poor adherence. Also, there are the metabolic changes, which do not usually affect the patient in the short-term, but add to the long-term risk of morbidity and mortality."

Aetiology (12.1.1)
"Understanding the aetiology of LPD is important but remains speculative. Evidence from cross-sectional surveys point to an interaction between HIV disease and/or immune recovery and antiretroviral medication, with PIs and nucleoside analogues being implicated. Evidence to date suggests these

hypotheses to be, at best, incomplete. . . . The highest cumulative prevalence of morphological abnormalities in these studies appear to be in persons receiving both PIs and nucleoside analogues together, relative to dual or triple nucleoside or nucleoside plus non-nucleoside regimes. As D4T appears to have the highest relative risk of lipoatrophy, particularly in combination with DDI, its use should generally be restricted to individuals not suitable for alternative agents such as ABC, DDI and ZDV. The co-administration of D4T and DDI should be especially avoided. Although AZT compares favourably with D4T in terms of the extent of fat atrophy, nonetheless it is also closely associated with lipoatrophy. Hence, until the situation becomes clearer, the increased likelihood of lipoatrophy mitigates against the choice of AZT as initial therapy (either alone or in Combivir). Furthermore, for those already on AZT, consideration should be given to the issue of lipoatrophy, and whether a switch might be indicated. Clearly for many patients the current efficacy and tolerability of their AZT containing combination will weigh towards its continued use. There will be patients, however, for whom the possibility of lipoatrophy causes sufficient anxiety such that they will elect to switch after the issues are discussed with them."

Management of Lipodystrophy (12.1.3)

"A structured approach needs to be adopted by those looking after patients with HIV . . . It is important that all patients are made aware of the potential manifestations of lipodystrophy, especially in terms of body shape changes."

"Individuals switching therapy must consider that they may risk their long-term HIV management in exchange for an uncertain outcome with regard to their lipodystrophy. Specifically benefits in terms of clinically evident lipoatrophy have not been consistently observed in trials and, anecdotally, do not appear evident with even prolonged (greater than 6 months) treatment interruption. The majority of switch studies that have reported data have focused on switching away from PIs. As mentioned, whilst metabolic benefits are achieved by switching away from PIs to NNRTIs or ABC in many patients, morphological benefits are more limited or absent. Switching away from D4T and possibly ZDV to ABC, tenofovir or a PI NNRTI regimen is associated with some gain in fat detectable by DEXA scanning over 24-48 weeks. It is not known if this recovery of fat is complete and durable. Improvements in metabolic parameters with this switch are not impressive.

"*Switching away from PI-based regimens may be most beneficial with regards to metabolic parameters but is not effective at managing peripheral lipoatrophy. Switching away from thymidine analogues, especially d4T but probably also AZT, to ABC or tenofovir appears the only successful approach in this regard."*
(See Appendix 6.4)

4.3 Prevalence of morphological changes related to lipodystrophy for patients on ARV therapy

N.B.: It should be remembered that there are always some PHAs who do not appear to be affected by lipoatrophy or lipoaccumulation. Andrew Carr's research in Australia indicates, at least for lipoatrophy, that there is a possibility of genetic factors involved in the aetiology.

Because of the lack of consensus among researchers on the exact definitions of the two forms of lipodystrophy responsible for morphological changes, it is difficult to accurately estimate the number of ARV-treated patients who developed lipoatrophy or lipoaccumulation, or both. In the Bogner *et al* study cited previously, the prevalence of lipodystrophy is 48.7 %, with 33.9 % showing signs of lipoatrophy and 28.7 % presenting with lipoaccumulation (and thus 13.9% with the "mixed" syndrome). In specialised publications, 50 % is often mentioned as being representative of the affected population. The observable symptoms of lipoaccumulation and mixed syndrome seem to be more dominant in women than in men. Conversely, lipoatrophy is more prevalent in the male population.

A rare study on HIV-positive children shows a 26% prevalence of lipodystrophy (124 out of 477). In the group affected by lipodystrophy, the proportion for each manifestation of the syndrome is very similar to the prevalence in adults: 37 % (n = 46) showed a combination of lipoaccumulation and lipoatrophy ("mixed" syndrome), 29 % (n = 36), lipoatrophy and 34 % (n = 42), lipoaccumulation.

European Paediatric Lipodystrophy Group, "*Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe*," AIDS 18: 1443-1451, 2004

The recommendations from the French group of experts describe the following prevalence:

". . . les principales études transversales révèlent une prévalence variant de 30 à 62 p. 100 pour la présence d'au moins une manifestation de lipodystrophie, de 22 à 38 p. 100 pour la prévalence d'au moins un signe de lipo-atrophie et de 18 à 45 p. 100 pour la prévalence de l'hypertrophie tronculaire. Cette dernière serait plus importante chez les femmes." (Appendix 6.2, page 132)

Regarding prevalence, the British guidelines emphasise that:
"*The estimated prevalence of HIV-associated LPD depends both on the extent of investigation & examination, and also the patient population concerned,*

particularly in relation to age and antiretroviral use. This is reflected by reported prevalences between 11 and 83% in cross-sectional studies."
(See section 12.1 in Appendix 6.4)

In light of these sources and for the purpose of this memorandum, we therefore suggest an estimated prevalence of lipodystrophy at 50% for the HIV-infected population on ARV therapy in Quebec (thus approximately 3,500 affected persons). But it should be noted that the prevalence of discrete lipoatrophy or of lipoaccumulation alone is more like 20%-40% for each condition. Obviously, certain persons have symptoms of both conditions (the mixed syndrome).

4.4 Impact of lipoatrophy and lipoaccumulation on the quality of life of HIV-positive persons on ARV therapy

Since the mortality rate for HIV infection dropped by 80 % following the introduction of ARV therapies, HIV-infection is now considered a “chronic disease”. However, for HIV-infected people undergoing treatment and for those who work with these patients, quality of life is now a major issue in deciding when to initiate ARV therapy and in maintaining compliance. That said, too little research has been done on measuring the quality of life of treated HIV-infected patients. In a Spanish study published in ***Clinical Infectious Diseases*** in April 2004, the authors wrote:

"*Few instruments specifically measure QoL (quality of life) in HIV-1 infected patients, and none are specific for lipodystrophy (LD) in such patients. HAART can produce side effects that may impair QoL and threaten compliance; in spite of this, less than 3% of drug trial publications incorporate measurement of QoL as an outcome variable. Instruments that assess body image should be developed to measure QoL in HIV-1 infected patients, and more attention should be paid to specific dimensions of QoL in the management of HIV-infected patients."*

Jordi, Blanch *et al*, "*Factors Associated with Severe Impact of Lipodystrophy on the Quality of Life of Patients Infected with HIV-1*", ***Clinical Infectious Diseases***, April 2004; 38:1469-1475.

This inability to clearly identify the needs of HIV-infected patients using ARVs and to describe the impact of the various forms of lipodystrophy continues even today. A large part of this problem lies in the absence of a clear definition of lipodystrophy and of the means to objectively describe its physical impact, even though body changes are visible and can be measured. It is, however, possible to assess the level of human distress experienced by HIV-infected patients with lipodystrophy. Indeed, some recent research has addressed this issue.

In the April 1, 2005, issue of the ***Journal of Acquired Immune Deficiency Syndrome***, the authors of a French study on the use of New-Fill wrote:

"*Issues such as self-esteem, sexuality, daily performance, and social life might be interesting to address in future studies. . . . There is a critical need for an accurate definition and assessment of lipoatrophy, using validated objective tools. Until then, the patient self-perception of lipoatrophy may represent one of the most appropriate criteria."*
Lafaurie, Matthiu. *et al*, "*Treatment of Facial Lipoatrophy With Intradermal Injections of Polylactic Acid in HIV-Infected Patients,*" AIDS, April 1 , 2005.

During the summer of 2003, the Info-Traitements Sector at CPAVIH (Comité des personnes atteintes du VIH du Québec) was inundated with requests for help

from PHAs confronting lipodystrophy. The level of their distress was such that Info-Traitements initiated a study to better understand the psychosocial impact of this condition. It should be specified that no study measuring the impact of lipodystrophy was available at that time.

Yves Jalbert, the researcher chosen by Info-Traitements, created a 75-question survey based on the main concerns identified by HIV-infected patients during pre-interviews. Thereafter, 186 HIV-infected patients experiencing lipodystrophy associated with ARV responded. The study was presented at the 14th Canadian Annual Conference on AIDS/HIV Research (CAHR) in Vancouver, in May 2005.
(**Poster**) Jalbert, Y., "*Lipodystrophy: The New Look of AIDS ?",* CAHR, May 2005, Poster 406 P
(**Abstract**) Jalbert, Y, "*Lipodystrophy: The New Look of AIDS* ?", *Canadian Journal of Infectious Diseases and Medical Microbiology*, vol. 16, Supplement A, 2005, page 89A.
(See Appendix 6.1 for the content of this research)

The Spanish study (Jordi, Blanch *et al*, ***Clinical Infectious Diseases***, April 2004; 38:1469-1475), published after the Quebec study had started, gives us some noteworthy indications. However, the Quebec study (Jalbert, 2005) provides a much more pertinent global picture. Both studies produced similar results for comparable cohorts:

Study:	**Spanish (Jordi *et al*, 2004)**	**Quebec (Jalbert, 2005)**
Participants:	84	186
The cause of lipodystrophy, according to the patient:		
ARV alone	46%	31.2%
ARV + other host factors (nutrition, anxiety, age):	23%	44.1%
ARV + HIV infection:	18%	20.4%
HIV alone	6%	n/a
Host factors:	7%	n/a
Body location of morphological changes:		
Study:	**Spanish (Jordi *et al*, 2004)**	**Quebec (Jalbert, 2005)**
Face:	58%	83%
Breasts:	20%	32%
Arms:	50%	60%
Legs:	79%	80%
Buttocks:	73%	82%
Abdomen:	60%	68%
Buffalo hump presence:	6%	24%

N.B.: In both studies, all participants reported morphological changes due to ARV therapies. We do not know the duration of the ARV therapies for the Spanish study, but the demographic information shows that the participants had been treated for more than 1 year. In the Quebec study (Jalbert, 2005), 70.4% took ARV agents for more than 7 years, and 47.3% started their therapy before 1996.

The Impact of lipodystrophy on quality of life

In order to assess the impact of lipodystrophy, the researchers in the Spanish study (Jordi *et al*, 2004) adapted an existing questionnaire to measure the impact of dermatological problems on quality of life (Dermatology Life Quality Index), whereas the questionnaire in the Quebec study (Jalbert, 2005) was based on questions initiated by HIV-infected patients. Overall, the findings for both studies are comparable:

The Spanish study (Jordi *et al*, 2004) tells us that body changes:

- had an impact on dressing habits for 65% of the participants;
- produced a feeling of shame in 49% of the participants.

This research also reported that participants had problems at work, in their daily activities, in sports and social activities. People experiencing facial lipoatrophy tried, more than the others, to solve this problem, and this seems to indicate that this condition is extremely important for the affected patients.

The Quebec study (Jalbert, 2005) included a larger sample of respondents and the questionnaire, specifically designed to pinpoint the impact of lipodystrophy, provides more precise results, although there are similar themes in the Spanish study (Jordi *et al*, 2004), for example:

- 65% of the participants (women more than men) reported a significant impact on their dressing habits in the Spanish study (Jordi *et al*, 2004)

whilst in the Quebec study (Jalbert, 2005):

- 57.6% had more difficulties to dress "normally" (women more than men)

49% of the participants expressed a feeling of shame in the Spanish study (Jordi *et al*, 2004), but in the Quebec study (Jalbert, 2005):

- 84.9% said that lipodystrophy affects their self-esteem
- 75.3% said their HIV status is more apparent
- 70.4% were uncomfortable undressing in front of others
- 67.7% felt that others look at them differently
- 55.9% did not want to be photographed
- 37.1% avoided looking at themselves in the mirror
- 33.9% said that people avoid them

N.B.: The issue of shame was not directly targeted in the Quebec study (Jalbert, 2005), but one respondent did write on the questionnaire: "*Personally, while answering your question, I realise how people can suffer and isolate themselves out of fear that others guess or know their diagnostic. Even in 2004, we proceed surrounded by shame and fear of rejection. It's incredible!*"

On the subject of job-related issues, the Quebec study (Jalbert, 2005) reported that:

- 22.6% said that lipodystrophy has affected their relationship with their colleagues at work or with their customers
- 11.8% quit their job
- 5.9% said they had lost their job
- 3.8% said they had quit school
- 80.1% of the respondents were 36-55 years old (age of active life: normal period of contribution to the social and economic life in our society), but only 30.6% are part of the work force and 37.6% have an annual income of $10,000 or less.

With respect to the problems related to sports activities, the Quebec study (Jalbert, 2005) reported that:

- 42.5% said that they no longer do physical activity
- 22.6% avoided going to the gym
- 21.5% said they had stopped all physical activity

Regarding the problems related to social activities, the Quebec study (Jalbert, 2005) reported that:

- 52.2% were not comfortable in public
- 31.7% said they go out of their homes less often
- 30.1% said that lipodystrophy has affected their relationship with their friends (12.4% stopped seeing their friends)
- 21.5% said that their condition has affected their family relationships (9.7% stopped seeing their family)
- 17.7% said that their condition had affected their relationship with their spouse (5.9% said their spouse had left them, while 7.0% had ended their relationship with their spouse)

With respect to the need for reparative surgery, the Quebec study (Jalbert, 2005) reported that:

- 40.1% said they need reparative surgery
- 17.5% got reparative surgery

With regard to the clinical effects, the Quebec study (Jalbert, 2005) reported that:

- 43.3% said they needed to change their medication (28.0% asked their physician to change their medication; 18.3% got their doctor's approval to change)
- 15% stopped their medication (11.8% with their doctor's advice and 3.2% without)
- 12.9% said that lipodystrophy has affected their relationship with their attending physician (5.4% changed doctor)

Concerning the psychological effects, the Quebec study (Jalbert, 2005) reported that:

- 66.7% said they are depressed
- 28.5% said they have suicidal thoughts
- 20.4% are being followed by a psychologist

The Quebec study (Jalbert, 2005) is not only a quantitative research study; it permitted the gathering of eloquent and revealing comments from participants on delicate issues related to quality of life:

The reality of the impact of morphological changes:
"Abandoned *contact lenses, face deformed, impossible to beautify, disinterested in appearance of clothes, subsequent to facial destruction*"

The psychological impact of lipodystrophy:
"*My doctor doubled my dose of antidepressants and I am still depressed.*"

The impact of this condition on human relationships:
"*I changed my circle of friends.*"

The beneficial effect of reconstructive procedures:
"*I received New-Fill injections and the impact is not just aesthetic and physical, but first of all psychological.*"

The Quebec study on the impact of lipodystrophy (Jalbert, 2005) ends with the following conclusions:

"The results of this study suggest that HIV+ people (mostly gay men) with ARV-related lipodystrophy suffer greatly psychologically, economically, sexually and socially. In addition, the more a person is advanced in his/her number of years of ARV treatment for HIV, the more he/she experiences the negative impacts of lipodystrophy. Lipodystrophy, and especially facial lipoatrophy, seems to increase stigmatization for HIV+ people and they respond by being more isolated and depressed. Many gay HIV+ respondents who mentioned receiving New-Fill or

plastic surgery said that not only their physical appearance improved but also their self-esteem and psychological well-being. Some gay HIV+ respondents on ARV reported on their questionnaire that facial or plastic surgery to correct lipodystrophy was not a possibility because they did not have the financial resources. That type of surgery is not covered by the Quebec medical insurance plan. Another problem experienced by some HIV+ respondents was pain caused by lipodystrophy and that problem must be explored further in a future study.

4.5 Approaches to treating lipoatrophy: stop, stabilise, repair

4.5.1 Introduction

Following the 12th Conference on Retroviruses and Opportunistic Infections (CROI) held on February 22-25, 2005, HIV+ patients on ARV therapies have two potential solutions to compensate for the anatomical structural losses caused by lipoatrophy:

1. change the therapy that led to the morphological abnormalities;
2. find a reparative procedure that is appropriate for their condition.

Two significative studies presented at CROI confirm the already published research on changing therapy ("switch studies"). They can be useful in guiding HIV-infected patients in making an informed decision with their doctor. Both studies show that the change from a thymidine analogue to another molecule, like tenofovir or abacavir, halts the progression of lipoatrophy and that a certain quantity of subcutaneous fat comes back progressively, although it is not always apparent in the face.

4.5.2 Approach to stabilising lipoatrophy

The "RAVE" study presents the 48 weeks results of a change from d4t or AZT to TDF (tenofovir) or ABC (abacavir). In both cases, the progression of atrophy was stopped and there was a partial return of subcutaneous fat after 48 weeks. (Overall, TDF was better tolerated then ABC.)

Moyle, G, *et al*, "*A 48-week, Randomized, Open-label Comparative Study of Tenofovir DF vs Abacavir as Substitutes for a Thymidine Analog in Persons with Lipoatrophy and Sustained Virological Suppression on HAART*", Program and abstracts of the 12th CROI, Abstract 44LB

Another study compared patients who reduced their daily dosage of d4t from 40 mg BID to 30 mg BID with patients who had changed from d4t to TDF. After six months, the peripheral fat increased slightly in those who were taking TDF (more so than in those with a reduced dosage of d4t).

Milinkovic, A, *et al*, "*A randomized open study comparing the impact of reducing stavudine dose versus switching to tenofovir on mitochondrial function, metabolic parameters, and subcutaneous fat in HIV-infected patients receiving antiretroviral therapy containing stavudine*", Program and abstracts of the 12th CROI, Abstract 857.

Both studies show that a change from d4t (stavudine) to TDF (tenofovir) improves the condition but the results are not as clear for the switch from AZT to TDF (although some studies show similar results).

Considering the benefits for the patients, the clinician should recognize that even if the change of therapy does not significantly increase peripheral fat, fat loss stops in patients suffering with lipoatrophy caused specifically by thymidine analogues.

Two years after the original MITOX study, the patients who had changed from AZT or d4t to ABC had regained approximately 1/3 of the peripheral fat they had lost during the years of therapy with a thymidine analogue. (In this study, the HIV-infected patients had, on average, 6 years of antiretroviral therapy that included AZT or d4t. It is estimated that they lost 50% of the fat from their arms and legs.)

The results of the MITOX study presented in 2003 show that the reappearance of adipose tissue was apparent to both doctors and patients. But there is a plateau which is hit after 1 year of improvement in the adipose tissues following the change of therapy, leaving these patients with the telltale signs of lipoatrophy.

Smith,D, Martin, A, Carr, A, "*Continued recovery of subcutaneous fat wasting after switch from thymidine analogues to abacavir,*" Program and abstracts of the 2nd IAS Conference on HIV Pathogenesis and Treatment, July 13-16, 2003, Paris, France, Abstract LB18.

The so-called “long-term” (2-year) results of the MITOX study were published in *AIDS*, in April 2004, confirming the persistent of these symptoms. The authors observed that: "*In patients with moderate-to-severe lipodystrophy, significant improvements in subcutaneous fat continued over 104 weeks after switching from a thymidine analogue to ABC****. Nevertheless, the lipodystrophy syndrome was still evident, indicating additional strategies need evaluating***."

Martin, A *et al* (for the Mitochondrial Toxicity (MITOX) Study Group), "*Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir, the MITOX Extension Study*, " AIDS, 18(7): 1029-1036, April 30, 2004.

4.5.3 The failure of pharmacological agents in reversing the fat loss process

While some researchers confirmed the origin of the fat loss associated with certain ARV therapies, many studies were undertaken to identify a pharmacological agent that could stimulate subcutaneous fat regeneration, either while continuing to use the same therapy with a thymidine analogue, or changing the therapeutic regime. To test this theory, rosiglitazone was chosen but the results of these studies were disappointing.

Finally, regardless of whether patients changed therapy, the subcutaneous fat did not come back, leaving the PHA with the same problems related to the loss of physical integrity, to a downgraded quality of life and a worsened state of health.

Mallon, P, Carr, A, *et al*, "*The Effect of Rosiglitazone on PPARg Expression in Human Adipose Tissue Is Limited by Continued Exposure to Thymidine NRTI,*" Program and abstracts of the 12th CROI.

4.5.4 Reparative procedures: filling agents

Once the progression of subcutaneous fat loss (lipoatrophy) is stopped through a by an appropriate change in therapy, the patient should be able to ask the doctor to proceed with the repair of the stigmatising body changes that remain.

The various approaches used for facial reconstruction

For facial lipoatrophy, there are various potential approaches for surgical reconstruction using filling agents. Clinical research has already begun with at least 4 products or approaches. Each can produce satisfactory results for the patient and the researchers.

Just to name the most often-mentioned products, there is poly-L-lactic acid (PLA, Sculptra or New-Fill), the most studied product, but there is also polyalkylimide (Bio-Alcamid) and polymethylmethacrylate (PMMA, Artecoll). Some studies were also published on fat auto-transfer (micro-lipoinjection). All these approaches have led to significant improvements for most patients.

After an analysis of the research and a long period of reflection, we suggest two products for treating facial lipoatrophy in Quebec: New-Fill and Bio-Alcamid. This choice is motivated by the following arguments:

1. The two pharmaceutical companies who are the exclusive distributors of New-Fill (Dermik Laboratories) and Bio-Alcamid (Pur Medical Corporation) are actively seeking to have their products accepted by Health Canada. These two products are expected to be approved in the fall of 2005, and they will soon be available in Canada;

2. These two injectable filling products have different qualities:
   - New-Fill (Sculptra**)** is biodegradable and, even if not “permanent,” it is very useful in reconstructing facial lipoatrophy in stages 1-3. Furthermore, the result of New-Fill therapy is progressive, so the change is more discrete for patients who are obliged to keep their condition confidential for work purposes, for example. However, New-Fill is not very appropriate for filling large hollows, as in stage 4 facial lipoatrophy;

- Bio-Alcamid, not biodegradable, said to be “permanent”, is very well-adapted to filling large hollows, as in stages 3 and 4 facial lipoatrophy.

N.B.: See Appendix 6.5 for a definition of stages 1 to 4 of facial lipoatrophy.

In the following sections we present the available information on both of these products.

New-Fill (PLA, Sculptra)

Regarding filling products, the French guidelines (Delfraissy) mention that:

« *De nombreux produits de comblement bioégradables ou non existent. Le principe est d'obtenir l'épaississement progressif du derme par injections intradermiques du produit qui provoquent une néocollagénose. Il est nécessaire, avec les produits biodégradables, de réaliser des injections itératives, à intervalles réguliers et variables de trois mois à un an ou plus en fonction des produits utilisés… Ces produits obéissent à la réglementation sur les dispositifs médicaux relevant d'un marquage CE (certification européenne, soit un équivalent d'AMM)…*

Cette technique de comblement a l'avantage de la simplicité, autorisant la réalisation du geste au cabinet d'un praticien expérimenté. Les injections peuvent être faites sans anesthésie ou avec une anesthésie locale. En revanche, les produits n'ont pas d'indication réglementaire. Il nécessitent des injections itératives pour les produits résorbables et la tolérance à long terme est incertaine pour les produits non résorbables.

Seul le New-Fill des laboratoires Dermik a obtenu récemment une extension de marquage CE dans le traitement des lipodystrophies faciales dues aux traitements antirétroviraux. Le nombre limité de médecins pratiquant cette technique explique en partie les délais trop longs des rendez-vous. » (see Appendix 6.2, Therapeutic management of HIV-infected patients, August 2004, page 136).

N.B.: In France, since February 2005, Social Security reimburses the cost of New-Fill, as well as the clinical fees related to its injection.

Concerning filling products, the United Kingdom guidelines (updated in May 2005, see Appendix 6.4), says that:

“*In the UK, most experience has been gained with polylactic acid (Sculptra, New-Fill) which is offered by several larger HIV centres. PLA is immunologically inert causing only limited inflammatory response. It stimulates dermal fibroblasts to*

produce collagen leading to thicker skin, which persists despite resorption of PLA. Sunken facial areas are built up with multiple small-volume injections spaced fortnightly. There is an immediate mechanical improvement relating to volume of injection but this disappears and is followed by more durable tissue replacement. Following a course of 3-4 injections, the majority of patients have a satisfactory result with thickening of the buccal and temporal tissues, which may continue for several months following the final injection. The number of treatments required to obtain a successful correction is largely related to the severity of fat loss. Patients with severe wasting can require 6 or more rounds of injections to achieve reasonable results. There are few data on the long-term use of New-Fill or specifically on its use in women or dark-skinned men. However after 18-24 months, approximately half of the patients need a further injection. Side effects include mild to moderate pain, post-inflammatory nodules, and occasional bruising. Massage of the injected tissues in the first few days is vital to prevent palpable tissue nodules. Other biodegradable products such as hyaluronic acid and collagen produce similar effects but are less durable and repeated injections are often needed after 3-6 months. The low relative cost of this procedure, the recognition that is a reparative procedure to reverse treatment related toxicity and the high impact on quality of life has led to PA being provided by some health trusts. However, availability and funding for polylactic acid remain major issues for many other patients and physicians."
(See Section 12.1.5 of these guidelines)

The only product currently approved in Europe and in the United States for the filling of facial fat loss associated with ARV therapy (lipoatrophy) is PLA (Sculptra or New-Fill). The studies with New-Fill started at the end of the 1990s and the first publication appeared in 2000.
See: Amard, P. *et al*, "*The effects of poly-L-lactic acid as therapy for lipoatrophy of the face*", Antiviral Therapy, 2000;5 (Suppl):79.

The French VEGA study was then published in AIDS in 2003.
See: Valantin, M.A. et al, "*Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of an open-label study (VEGA)",* AIDS. 2003; 17(17):2471-2477.

The VEGA study concluded that:

"*In the absence of an aetiological treatment (i.e., treating the underlying cause) and since other treatment approaches, such as modification of the patient's antiretroviral regimen or use of insulin-sensitizing agents or growth hormone have failed to show clinically significant changes in facial lipoatrophy, the use of biodegradable materials to improve physical appearance represents significant progress in therapeutic management of HIV-related lipoatrophy. Furthermore this data provided a basis for health insurances to consider the reimbursement of such therapy in patients with severe lipoatrophy."*

In summary, this study demonstrated the benefits of PLA injections to correct facial lipoatrophy in HIV-infected patients -- an important finding due to the absence of any currently available strategy to manage this complication. The efficacy, safety profile, and the simplicity of the injection schedule associated with the use of PLA make this filling material a potentially attractive treatment that may help alleviate the psychological and social consequences of facial lipoathrophy in affected HIV-infected patients."

These studies were followed in 2004 by a British research study that confirmed the positive impact of the procedure (Moyle, G *et al*, "*A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection*," HIV Medicine, 2004;5:82-87).

In March 2004, the FDA (Food and Drug Administration) in the United States considered a request for the approval of New-Fill for the repair of the markers of facial lipoatrophy resulting from fat loss associated with ARV therapies. Temporary approval was issued on August 3, 2004, under the condition that the manufacturer complete a 2-to-5-year post-marketing (Phase IV) research study on the possible differences in results obtained when the product is administered to patients from minority groups: women, Black persons, etc.

The introduction of New-Fill (now sold in the United States under the name "Sculptra") as the generally accepted filling product was announced with the publication of a study in the *Journal of the American Academy of Dermatology*.
Voir: Burgess, C. M. and Quiroga, R. M., "*Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy,*" *Journal of the American Academy of Dermatology*; Vol. 52, no. 2, February 2005.

In this study, 61 patients, all males affected by different degrees of ARV-related lipoatrophy, were treated with Sculptra (New-Fill) over a 5-month period. The therapy was generally well tolerated, with an average of 3 sessions per patient. This study is unique as it offers a visual and subjective classification system for the assessment of symptoms of lipoatrophy in stages 1 to 4. (See Appendix 6.5 for the definition of the various stages.) The system permits the assessment of the amount of product necessary and, eventually, the comparison of results. In the findings, the authors observed that:

"*At the 6-month follow-up evaluation, 100% of patients and both physicians agreed to "Excellent" responses, and a complete achievement of healthy appearance. Seventy-nine per cent of patients achieved this result in less than 4 sessions and 21% of patients requested 4 or more additional treatment sessions.*

Following 3 treatment sessions, significant improvement and dermal thickening were retained in 37 patients for a duration of 6 months; in 10 patients for a duration of 1 year; in 9 patients for a duration of 18 months; in 5 patients for a duration of 2 years or more. Thirteen patients requested touch up sessions at an average of 1 year; however, on evaluation of the physicians, there was no change from the 90% to 100% dermal enhancement improvement grade."

Another similar French study was published in the *Journal of Acquired Immune Deficiency Syndromes*, on April 1st, 2005:

Ninety-four patients (all men) were treated with New-Fill, followed with a self-assessment based on the visual analogue scale (VAS).

NB: The evaluation scale: patients responded to one question on their satisfaction concerning the look of their faces following therapy. The scale is 0 = total dissatisfaction to 10 = total satisfaction.

According to the researchers:
"*PLA offers advantages over the other facial implants as it is hypoallergenic, biodegradable, and bioresorbable and cannot therefore trigger inflammatory reactions*."

"*The main efficacy endpoint of our study was the patient self-perception of his facial lipoatrophy as assessed by a VAS score using a scale specifically designed for our study. Using this subjective criterion, 82% of the patients perceived an improvement of their facial lipoatrophy at the end of treatment as compared to baseline, and this proportion was sustained to up to 76% at the last assessment visit during follow-up (up to 12 months). <u>According to our psychologist, this benefit was associated with increased self-confidence in most patients, who were able to resume normal social life</u>. The severity of the lipoatrophy as judged at baseline by the physician was not associated with a worse outcome. Only a low baseline patient VAS score was associated with a better outcome . . . in the success of the procedure."* "*Self-assessed patients median VAS score for facial lipoatrophy significantly increased from 3.4/10 at baseline to 6.8/10 at the end of the treatment procedure*."
See: Lafaurie, M, Dolivo, M, *et al*, "*Treatment of Facial Lipoatrophy With Intradermal Injections of Polylactic Acid in HIV-Infected Patients*", Journal of Acquired Immune Deficiency Syndromes, April 2005.

Bio-Alcamid

Bio-Alcamid (polyalkylimide) is an injectable gel implant that, once in place, becomes a supple endoprosthesis. Based on the results obtained in many patients, it appears to be an excellent facial lipoatrophy corrector without significant side effects. This synthetic polymer gel (biopolymer) is made of 97% apyretogenic water (that does not cause fever) and 3% polyalkylimide

substances. Compared to PLA (Sculptra, New-Fill), which generally requires 3 to 6 injections, Bio-Alcamid requires only one injection and one or two touch-ups, if needed. Consequently, fewer injections are required, and a large amount of product can be implanted at once. Contrary to New-Fill, it is not reabsorbed by the system. It is reputed to be a so-called “permanent” product but it can be removed, if necessary.

Following the introduction of New-Fill as a facial corrective procedure, many stage 4 (sometimes stage 3) facial lipoatrophy patients looked for a more appropriate solution to their condition. Bio-Alcamid proved to be the best choice in these cases and at a similar cost. In the study published in 2000 in the *Italian Journal of Anatomy and Embriology*, Bio-Alcamid was used in 2,000 patients presenting various conditions. Only 12 patients experienced post-surgical complications (staphylococcus infection) and only 3 were due to the implant. Following this study, the use of antibiotics was instituted, allowing the rate of infection to be reduced to nearly zero. The study also demonstrated that Bio-Alcamid can be easily removed. The researchers observed that "*Bio-Alcamid can be defined as a sort of endoprostesis, perfectly suitable for soft tissue augmentation and for the correction of different tissue deficiencies, with a long-term safety and efficacy*".

Formigli, L Zecchi, S *et al*, "*Bio-Alcamid: A novelty for reconstructive and cosmetic surgery,*" Italian Journal of Anatomy and Embriology, vol. 107, no. 3, 209-14, July-September 2002.

In the most recent study on facial lipoatrophy and Bio-Alcamid, with 73 patients (40 women and 33 men between the ages of 16 and 48), 90% required a second treatment to complete the reconstruction. The evaluation of the results included the following parameters: the patient’s level of satisfaction (modest, fair, average, good, excellent), the practitioner’s level of satisfaction, the possibility of short-or long-term complications, the potential need to remove the implant. The results of the reconstruction were considered as excellent by patients and physicians. No harmful side effects were identified (i.e. the migration of the implant, granuloma build-up, allergic reactions, or non-tolerability).

Protopapa, C, Sito, G *et al*, "*Bio-Alcamid in drug induced lipodystrophy*", Journal of Cosmetic Laser Therapy, 2003, vol. 5, no. 3-4, pages 226-30.

In another study on facial lipoatrophy with 53 PHAs, the clinical results were considered permanent and highly satisfactory by patients and researchers. The investigators found that total correction was achieved after 2 or 3 treatments, which were well tolerated by all patients. Unexpectedly, the researchers observed a CD4 increase of 63 and an average viral load reduction from 29,200 to 12,730. This surprising improvement was attributed to a reduction in stress and an improvement in the patients’ quality of life.

Casavantes, LC, and Izabul, JM, "*Stability, Tolerance and Safety of Bio-Alcamid (Polyalkyimide) Gel an injectible endroprosthesis for the correction of major soft tissue deficits*", Dermatologia, Cosmetica, Medica y Quirurgica, 2004, vol. 2, no. 2.

A Canadian study

In May 2005, a Canadian pilot study was presented in Vancouver, during the CAHR conference (the 14th Canadian Annual Conference on AIDS and HIV Research). This first phase of the research involved 5 HIV-infected persons with stage 2-4 facial lipoatrophy. Doctor Loufty's summary showed that the use of Bio-Alcamid led to a noticeable improvement from the point of view of all three physicians and the five patients. They also noticed an improvement in the quality of life based on three questionnaires. At this stage of her research, Dr Loufty found that the injection of Bio-Alcamid was safe with a minimum side effect profile. The patients will be followed for another two years and 30 HIV+ persons will be added to the study.

Loufty, MR *et al*, "*Pilot study of the safety, clinical efficacy and impact on quality of life of using Bio-Alcamid for reconstructive treatment of antiretroviral-induced facial lipoatrophy in HIV-positive individuals,*, CAHR, May 2005, Poster

The latest recommendations from the British Guidelines (May 2005)

On the issue of implants used to correct the damage caused by facial lipoatrophy associated with ARV treatment, in section 12.1.5 of "HIV Treatment Guidelines Update 2005," the British HIV Association mentions that:

"Corrective procedures for HAART-associated lipoatrophy
Despite switching away from thymidine drugs when possible, restoration of fat in patients with HAART-associated lipoatrophy (LA) is likely to be incomplete and, if severe, often clinically undetectable. There is currently no treatment to reverse fat loss or to generate new fat cells to grow after significant loss caused by HIV treatment. ***Rates of new onset lipoatrophy are now lower because physicians proactively choose newer drugs that are less likely to cause fat loss and follow guidelines that urge avoidance rather than treatment****.* ***Nevertheless this leaves a significant minority of patients with a significantly reduced quality of life, often leading to complicated social problems and withdrawal.*** *Consequently, a range of bio-absorbable and permanent injectable skin fillers and fat/dermal transplants that are used to correct lost tissue mass have been assessed. Bioabsorbable products include hyaluronic acid, collagen and polyactic acid (New-Fill), with polymethylacrylate, silicon and polyalkylamide (Bio-Alcamid) being examples of permanent fillers. Bioabsorbable products have only been evaluated in facial LA. Each filler/implant*

*has its limitations and very limited scientific data exists to support their use**. However, polylactic acid has been approved in most industrialised nations in recognition of the importance of this complication and the striking benefits of treatment**. This is despite the absence of large comparative trials with long-term follow-up. Whichever technique is used, the training of operators is crucial to safety and success. For permanent fillers and implants, the procedure should only be performed by an accredited plastic surgeon or dermatologist.*"

Following a discussion of the benefits and limitations of the use of PLA (New-Fill) and other products known as “bioabsorbable”, the guidelines present arguments in favour of the use of implants to mitigate the effects of facial lipoatrophy, and a guide for choosing between New-Fill and Bio-Alcamid, based on the patient’s condition and needs:

"*Polyalkylamide (Bio-Alcamid) is a permanent filler which has been demonstrated to correct HAART-associated LA without significant side-effects. Its major advantages are that fewer injections are required, higher volumes can be used, non-facial lipoatrophy can be potentially corrected, and it may be able to be removed in the case of over-filling. Insufficient scientific information exists on Bio-Alacamid to base any guidance on. However, as first occurred with PLA, many patients are accessing private clinics for treatment and patient satisfaction is high. Costs to achieve successful results in severe cases are comparable to or less than using PLA. As severe lipoatrophy is likely to be life-long, a permanent solution for these patients would provide long-term cost and quality of life advantages."*

*"There is general concern with permanent fillers that if lipoatrophy continues to worsen the edges of the filler may become visible and if fat mass increases (after switching nucleosides) the permanent filler may over-correct the original defect and become obvious. Non-surgical removal may also not be straightforward. These concerns are greatest for those with mild to moderate fat loss. In the majority of cases of mild facial LA associated with a thymidine-containing combination, a switch to a non-thymidine HAART should be tried before recourse to using any facial filler. Where moderate facial LA exists or in milder disease when ZDV or D4T cannot be switched, PLA is recommended as the facial filler of choice. For patients with severe LA, it is unlikely that PLA will correct the defect durably or completely and Bio-Alcamid may be preferable. **Long-term safety data are important, but this should not be used as an obstacle to treatment for patients requiring treatment now**. A comparative study between these two agents is needed.*"
See Appendix 6.4

Conclusion

Reparative procedures for surgical reconstruction of the aftermath of lipoatrophy due to antiretroviral therapy are known and used regularly. In France, the public health system has recognised its importance for the health of PHAs, and treatment is now reimbursed. In the United States, New-Fill is already available for facial lipoatrophy treatment. In Great Britain, corrective therapies are offered and the 2005 Guidelines present a guide to help in choosing the most appropriate product and establishing a decision-making context for their use.

In Quebec, our Health system should not hesitate to recognise the importance of restoring the physical integrity of HIV-positive patients on ARV therapy, in order to guarantee the maintenance of their overall health and their quality of life.

For PHAs affected by lipoatrophy, we request:

a. The inclusion of reparative techniques for lipoatrophy in the general nomenclature of professional acts in order to allow coverage by the Quebec Healthcare Insurance Plan (RAMQ), along with reimbursement of such an act so that all patients who need it will have access;

b. The inclusion of two injectable filling products: Sculptra (New-Fill) and Bio-Alcamid on the list of products and drugs covered by the RAMQ, upon their approval in Canada;

c. The issuing of directives on HIV care standards, including indications for monitoring the development of lipoatrophy, informing physicians of the cause of this condition in order to plan for a change of medications to stop its progression. For instance, the withdrawal of thymidine analogues from the therapeutic regime and their replacement with less toxic ARVs (replacing d4T or AZT with ABC or TDF), when possible;

d. The transfer of TDF (Viread, tenofovir) from the “list of exceptions” to the regular list of antiretroviral drugs in order to provide the choice of an antiretroviral regime that prevents facial lipoatrophy. This represents a solid therapeutic advantage for the patient.

4.6 Approaches to the treatment of lipoaccumulation: attempting to stop lipoaccumulation and reparative techniques

The prevalence of morphological changes in PHAs using ARV therapy varies, based on the study, the cohort, and the patient's therapeutic experience. Estimates vary between 11% and 83%. However, the rate is lower for lipoaccumulation than for lipoatrophy. Furthermore, lipoaccumulation is more common in women than in men, so a much smaller number of people are affected.

Fat accumulation appears with or without the presence of fat loss (lipoatrophy) and is located mainly in the abdomen (around the intestines), the breasts, the spine ("buffalo hump"), or the throat ("goitre"), or as lipomas at different places on the body. All studies on fat accumulation have observed that this syndrome is more common in women than in men.

A recent study suggests the following clinical definition of the "buffalo hump": "the presence of fat accumulation distributed or located on the dorsocervical spine." In this study, the researchers found a prevalence of "buffalo hump" of 2% to 13%.

Mallon, P.W. *et al*, "*Buffalo Hump Seen in HIV-Associated Lipodystrophy is Associated with Hyperinsulinemia But Not Dyslipidemia,*" Journal of Acquired Immune Deficiency Syndromes: vol. 38(2), February 1st, 2005.

In a research letter published in *AIDS*, the authors suggest a prevalence of 2.3% in naive patients after a median 86 weeks of therapy and 3% in whole patient community.
Gervasoni, C *et al*, "*Long-term efficacy of the surgical treatment of buffalo hump in patients continuing antiretroviral therapy,*" AIDS, vol. 18(3), pp. 574-576, February 20, 2004

The aetiology of lipoaccumulation has not yet been defined, but there is a consensus with respect to this syndrome's being associated with the use of protease inhibitors combined with nucleoside analogues.

Therapeutic corrective procedures to treat the "buffalo hump" are currently limited to changing therapy, a change in diet, exercise, and reparative surgery.

Changing therapy ("switch")

According to French guidelines, « *cette hypertrophie ainsi que l'adipomastie étant plutôt attribuée aux IP, il est possible de les substituer en particulier par la névirapine ou l'abacavir lorsque cela est possible.* » (Delfraissy *and al*, Appendix 6.2, page 134).

The problem with the “preventive” approach is that, as yet, no study has succeeded in identifying which PIs are the cause of lipoaccumulation (except for indinavir, Crixivan). Consequently, for clinicians, it remains a puzzle and, for patients, a progressively disastrous condition.

N.B.: A research letter published in *AIDS* (2004, 18, 949-957) reported on the regression of the “buffalo hump” in two patients initiating therapy with atazanavir, but this anecdotal phenomenon is still unique in the literature.

For other alternatives related to lifestyle changes (nutrition, exercise), concrete results are difficult to assess, because, in general, the existing fat accumulation doesn’t disappear. Consequently, even if the patient has a healthy diet and exercises, the Quasimodo-style buffalo hump remains.

The other alternative is reparative surgery. Very few studies have been published and the information available is rather anecdotal. Usually, liposuction or “buffalo hump” excision is recommended when the patient complains of pain or respiratory complications. According to French guidelines:
:
« *L'accumulation graisseuse peut faire l'objet d'un remodelage par une technique de lipo-aspiration. Lorsque l'accumulation graisseuse est importante, le traitement est identique à celui de la chirurgie plastique classique de l'obésité (plastie mammaire de réduction, plastie abdominale, lipo-aspiration, dermolipectomie). Il est indispensable d'avertir le patient que le risque de récidive est a priori plus important que dans la population générale* » (Delfraissy et al, Appendix 6.2, page 134).

There is an Italian study comparing two surgical approaches. 18 patients with a “buffalo hump” causing mobility restrictions and abnormal posture, lower back pain and psychological distress, benefited from the procedures. 15 patients had a lipoaspiration lipectomy and 3, a surgical dermolipectomy. After a 19-month follow-up, only one patient had a recurring hump (following liposuction).

Gervasoni, C *et al*, "*Long-term efficacy of the surgical treatment of buffalo hump in patients continuing antiretroviral therapy*", AIDS, vol. 18(3), pp. 574-576, February 20, 2004

N.B.: Other trials indicate a 5% to 50% recurrence rate; there seems to be more recurrence with liposuction.

Pharmaceutical research on lipoaccumulation

In a research project on a peptide that stimulates the production of human growth hormone, a Montreal pharmaceutical company, Theratechnologies, produced an

effective molecule called TH9057. In the Phase II clinical trial for dosage of this peptide, with 61 PHAs affected by abdominal lipoaccumulation, a form of accumulation that cannot be treated with excision or liposuction, the results were very promising. Following a 4-month treatment with TH9057, the participants had, on average, lost at least one kilogram of fat and showed a 16% reduction in abdominal fat volume. A Phase III trial with a larger cohort is planned for the near future.

Grinspoon, S *et al*, "*Effects of a growth hormone releasing factor (GRF) analogue in HIV patients with abdominal fat accumulation: a randomized placebo-controlled trial*", Program and Abstracts of the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, October, 2004, Abstract 2.

Reduction of the "buffalo hump" by ultrasound-assisted lipodissolution

Researchers in Albany, NY, verified the safety and efficacy of ultrasound-assisted lipodissolution for the reduction of the "buffalo hump" associated with ARV therapy. This new technique is considered to be more effective and safer than traditional liposuction, as it can be done on the fibrous tissues typical of the "buffalo hump" and on other parts of the body that cannot be treated with traditional procedures. This technique could possibly be useful for the removal of the "goitre," a mass of fat under the chin. However, the rate of fat recurrence in the patients studied was approximately 50%.

Piliero, P.J. *et al*, "*Use of Ultrasonography-Assisted Liposuction for the Treatment of HIV-Associated Enlargement of the Dorsocervical Fat Pad*", *Clinical Infectious Diseases*, 2003; 37,1374-1377.

The situation in Quebec in 2005

Right after the introduction of the protease inhibitor Crixivan (indinavir) in ARV medical practice in Quebec, a significant change in body morphology was observed in HIV-positive patients who were taking this molecule: the appearance of the "Crix belly" was, in fact, the first appearance of fat accumulation in the abdomen. The "buffalo hump," "goitre," and lipomas on various parts of the body began to appear later.

In Montreal, very few surgeons accept to operate to remove "buffalo humps." We remark that the honorarium for this medical act is really minimal, considering the work it represents. Consequently, surgeons are obliged to offer their services as a charitable gesture. In our opinion, this can discourage many of them.

"I learned that the RAMQ reimburses the surgeon 180$ for a liposuction. For a plastic surgeon, this procedure ("buffalo hump" removal) represents the equivalent of 1,800$ of work: what doctor will perform an 1,800$ procedure for a 180$ reimbursement? The gap between the real cost of the "buffalo hump" procedure and the amount reimbursed by the RAMQ is such that the RAMQ

seems to cover something that will never be done and no doctor in the health system wants to perform the procedure as a volunteer. Consider yourself lucky if you ever find a surgeon who wants to work with HIV-positive patients, be they male or female!"

See: Desbiens, S. « *M-T, militante de l'ombre* », an article published by CRISS in *De Tête et de Cœur*, a special issue on lipodystrophy and women health, Winter 2005, Vol. 10, no. 1, p.11.

There are still a few surgeons who are ready to excise the "buffalo hump". However, presently, this procedure is not included in the Quebec compendium of medical acts. Moreover, various types of surgeries for painful lipomas are included and reimbursement is possible but at a rate that is nominal for a surgeon. It is, for these reasons, extremely difficult for us to find a surgeon willing to perform these procedures. Based on our information, there is only one such surgeon in Montreal. This is absolutely unacceptable.

According to our sources, the use of ultrasound-assisted liposuction, despite being mentioned in the literature as an effective surgical procedure, is still unknown in Quebec. Some patients had access to traditional liposuction in a private office and paid the full price for it: $2,000 or even more, because liposuction is considered as aesthetic surgery and, consequently, it is not covered by the RAMQ.

In fact, one patient attests to the current situation:

". . . in March 2004, tired of enduring these debilitating masses of fat, and while still applying through the public system to surgeons and RAMQ bureaucrats, I decided, once more, to pay for all the reparative charges myself. This time, I spent 3,200$ for "buffalo hump" removal and for visceral fat reduction. 7,200$ later: I fought, with my own money and practically alone, the side effects of my treatments. I thank the doctors who accepted to help me and who continue to help other HIV-infected persons. To the physical pain of the medical procedures, add the moral pain of realising that access to reparative techniques for the effects of lipodystrophy (largely side effects of ARV therapy) is non-existent in Quebec. All this leaves me with a feeling of profound sadness."

See: Desbiens, S. « *M-T, militante de l'ombre* », an article published by CRISS in *De Tête et de Cœur*, a special issue on lipodystrophy and women health, Winter 2005, Vol. 10, no. 1, p.15.

Conclusion

At present, certain encouraging results have been obtained and is possible to use some reparative and therapeutic interventions for the surgical reconstruction of, fat accumulation. Research is ongoing in the United States, in Europe and even

in Quebec. But it seems that our public health system does not yet recognise the importance of these procedures for the physical and mental health of HIV+ patients affected by lipoaccumulation.

For us, this worrisome syndrome represents a serious attack on a person's physical integrity, as well as an unsightly and handicapping deformation of the anatomy. For the health care system, it seems that this situation is underestimated because the request for access to reparative procedures is wrongfully perceived as a request for aesthetic surgery. In fact, for us, the patients, the essential issue is one of physical and mental health.

For PHAs affected by lipoaccumulation, we request:

a. The inclusion of reparative techniques for the "buffalo hump" in the general nomenclature of professional acts in order to allow coverage by the Quebec Healthcare Insurance Plan (RAMQ), along with reimbursement for such an act so that all patients who need it will have access;

b. The issuing of directives on HIV care standards, including indications for monitoring the development of lipoaccumulation and the use of well-known solutions. For instance, in the presence of central lipoaccumulation (fat deposit in the abdominal cavity) in a patient taking indinavir (Crixivan), change the protease inhibitor for another, less toxic medication;

c. Financial support from the Quebec government to encourage an expanded access research program for Theratechnologies' leading-edge peptide TH9057. (Theratechnologies is a Montreal-based company.) This would allow access for the greatest number of patients possible, should they want to participate.

5. The current status quo: a risk of escalation in healthcare costs

In Quebec, it is estimated that approximately 3500 HIV+ persons are affected by lipodystrophy. We believe it would be beneficial to offer concrete solutions to overcome this worrisome condition for the patients, their friends and family, and their caregivers. The people affected by this handicap need accessible and appropriate care.

At the initial appearance of the lipodystrophy syndrome, the Health and Social Services system took considerable time to recognise that it existed. Yet a growing cohort of people living with HIV and treated with antiretroviral agents were going through perceivable morphological changes. Up until now, few concrete measures have been taken to effectively prevent lipodystrophy and delay its progression. Also, in our public health system, no reparative technique is yet accessible to PHAs to adequately repair the damages caused by lipoatrophy. Access to reparative techniques for lipoaccumulation (“buffalo hump”, lipoma) are still difficult to obtain. We believe there is a high risk of an escalation of costs for the government if nothing is done. And we believe that now is the time to act.

If we do nothing to fight lipodystrophy in Quebec, there will be an enormous human and financial cost. Many PHAs on antiretroviral therapy have already lost their jobs due to the marked deterioration of their physical appearance . . . others are no longer able to cope with the fact that their HIV status is now being displayed on their faces. What to do when the deformation of the body continues without stopping? The more lipodystrophy symptoms appear, the more the quality of life of PHAs is threatened. Stigmatization and discrimination cost the citizens of Quebec a great deal.

The Quebec study on quality of life (Jalbert 2005, see Appendix 6.1) revealed that, among the 186 PHA respondents affected by lipodytrophy, 80.1% were 36 to 55 years old, the normal age for an active life in our society, but only 30.6% were still part of the workforce and 37.6% had an annual income of $10,000 or less. Some individuals no longer had a social life, 20.4% were followed by a psychologist, 52.2% said they were uncomfortable in public, 21.5% had stopped all physical activity, and 28.5% said they had had suicidal thoughts. Considering their condition, many PHAs with lipodystrophy need to take antidepressants. It is obvious that the social costs of lipodystrophy are enormous.

In fact, we have inherited a seriously worrisome situation. Today, a growing number of PHAs on ARV therapy are in a severe lipodystrophic condition without access to procedures that are available in other Western countries. According to the above-mentioned study, when characteristic body deformations become apparent, 15% of Quebec PHAs with lipodystrophy discontinue their therapy, with

or without their doctor's advice. These facts are witness to the tremendous distress and the devastating impact of this syndrome. They also represent an enormous risk to the PHAs' health. In fact, an improvised therapy interruption can lead to a series of events that are potentially dangerous to patients and expensive for the health system, e.g. hospitalizations, etc.

We think it would be advantageous to prevent the situation from deteriorating further. Because of the apparent signs of lipodystrophy, can we, as a community, really go on depriving ourselves from the contribution of many competent HIV+ people who are still able to work or play an active role in our society? Could we not choose to act as soon as possible, to assess the various options available and analyze the tangible benefits of universal access to reparative therapies based on needs identified by the treating professionals and their patients?

Finally, we believe that, with preventive measures and by covering the repair of damages caused by lipodystrophy, the government of Quebec could permit many HIV+ persons to keep their jobs and permit others to return to work or at least to a more active life. Furthermore, patients would be less fearful of initiating antiretroviral therapy or of being compliant. Altogether, this would certainly represent substantial savings. However, for us, the patients there is no price for recovering our human dignity and the right to be an integral part of Quebec society.

APPENDICES

Appendix 6.1

"*Lipodystrophy: the New Look of AIDS"* by Yves Jalbert, Ph.D.

2003 study initiated by the Comité des personnes atteintes du VIH du Québec, presented at the 14th Canadian Annual Conference on HIV and AIDS Research (CAHR) in Vancouver, in May 2005 (Poster 406P)

Abstract published: *Canadian Journal of Infectious Diseases and Medical Microbiology,* vol. 16, Supplement A, 2005, page 89A

APPENDICES

Appendix 6.2

Extract from

"Prise en charge thérapeutique des personnes infectées par le HIV, Rapport 2004"
("Therapeutic Management of HIV-Infected Persons – 2004 Report"),
Recommendations from a group of experts, under the leadership of Pr Jean-François Delfraissy, Health and Social Protection Ministry, French Republic

(en français)

APPENDICES

Appendix 6.3

Extract from

"Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, April 7, 2005"

Developed by a panel on clinical practices, under the direction of John G. Bartlett and H. Clifford Lane, convened by the Department of Health and Human Services (DHHS), Republic of the United States of America, April 7, 2005

APPENDICES

Appendix 6.4

Extract from

"HIV Treatment Guidelines Update 2005"

by The British HIV Association, United Kingdom (May 2005)

APPENDICES

Appendix 6.5

Definition of the various stages of facial lipoatrophy (stages 1 to 4),
from Burgess, CM and Quiroga, RM, "*Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy," Journal of the American Academy of Dermatology*, February 2005, part 1, vol. 52, no. 2

APPENDICES

Appendix 6.6

"***Face to face with lipoatrophy, an Interview with David Nolan***," by Nelson Vergel, *GMHC Treatment Issues: Newsletter of Current Issues in HIV/AIDS*, March / April 2005, vol.18, no.3/4