Department of Veterans Affairs Veterans Health Administration Washington, DC 20420 **VHA DIRECTIVE 2008-003**

January 22, 2008

TREATMENT OF ANTIRETROVIRAL-INDUCED FACIAL LIPOATROPHY IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)-INFECTED PATIENTS

1. PURPOSE: This Veterans Health Administration (VHA) Directive clarifies policy regarding treatment of antiretroviral-induced facial lipoatrophy (AIFL) in veterans with human immunodeficiency virus (HIV) infection by subcutaneous injection of permanent or biodegradable filler material.

2. BACKGROUND

- a. HIV-infected patients, particularly those receiving highly active anti-retroviral therapy (HAART) regimens, are at risk for development of abnormalities of lipid metabolism. HIV-associated lipodystrophies include low density lipoprotein hypercholesterolemia and hypertriglyceridemia, which increase the risk of coronary artery and cerebrovascular disease. HIV-infected patients may also develop morphologic alterations in fat distribution, such as abdominal visceral, dorsocervical, breast, and subcutaneous accumulation of fat, or regional fat loss (lipoatrophy) in the extremities, buttocks, and face. This Directive specifically addresses the issue of facial lipoatrophy.
- b. Facial lipoatrophy is a common complication of treatment of HIV infection, affecting over 50 percent of HIV-infected individuals receiving antiretroviral therapy, particularly stavudine, the nucleoside reverse transcriptase inhibitor, although other nucleoside reverse transcriptase inhibitors and HIV-1 protease inhibitors have also been implicated (see subpar. 5b). Discontinuation of HIV medications often does not result in any significant reversal of the underlying morphologic change. Any resolution of AIFL after discontinuation of these drugs is very slow (measured in years) and often incomplete.
- c. AIFL can have a devastating impact on psychological well-being and lead to social isolation and stigmatization because of the apparent facial abnormality and the recognized association of AIFL with treatment for HIV infection (see subpar. 5a). Mental health complications of AIFL include: depression, low self-esteem, isolation, and career barriers because of reluctance to seek employment. In addition, AIFL may cause patients to decrease their level of adherence to prescribed antiretroviral treatment regimens, compromising their HIV infection therapy. Treatment for AIFL has been shown to significantly benefit patients by addressing the underlying cause of such psychological disorders.
- d. The mainstay of AIFL treatment is reconstructive surgery and involves subcutaneous injection of permanent or biodegradable filler material to restore normal facial contours. Department of Veterans Affairs (VA) policy currently prohibits performance of plastic surgery for cosmetic reasons alone. However, AIFL is a complication of therapy of HIV infection frequently leading to serious psychological results; as such, its treatment would not be

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considered purely cosmetic. Therefore, veterans with AIFL may undergo treatment for this disorder at VHA facilities or be referred by VHA on a cost basis to outside facilities for AIFL treatment if such treatment would improve the patient's mental health.

- e. There are currently two therapies approved by the Food and Drug Administration (FDA) for treatment of AIFL: SculptraTM (see subpars. 5e and 5g) and Radiesse® (see subpars. 5d and 5f). *NOTE:* Att. A contains a comparison of their relative characteristics, based in part on information from FDA-approved package inserts and published literature.
- **3. POLICY:** It is VHA policy that eligible veterans with AIFL may undergo treatment for this disorder at VHA facilities, or be referred by VHA on a cost basis to outside facilities for such treatment, if it would improve the patient's mental health.

4. ACTION

- a. **Facility Director.** The facility Director, or designee, is responsible for ensuring that:
- (1) Facility policy is written, published, and in place to allow eligible veterans to receive treatment for AIFL according to the following procedures:
- (2) Approved AIFL therapies are available at the facility if treatment is to be administered at the facility. The FDA has classified SculptraTM and Radiesse® as devices rather than medications; VA has accordingly classified these as prosthetic devices. SculptraTM and Radiesse® are normally ordered and purchased by placing a consult with the Prosthetics Service in the Computerized Patient Record System (CPRS) by the clinician who is to administer treatment (from the Dermatology, Plastic Surgery, or Otolaryngology Service). Manufacturers of these products offer patient access programs that may allow acquisition at decreased cost. *NOTE:* providers are encouraged to contact the manufacturers using the respective Web sites (www.sculptra.com and www.radiesse-fl.com) for additional information.
 - (3) Sterility of these products is verified as outlined in current VHA policy.
 - b. Chief of Staff. The facility Chief of Staff is responsible for ensuring that:
- (1) All primary care providers for HIV+ patients are trained to recognize AIFL, properly assess its severity and its psychological consequences, and make appropriate referrals.
- (2) The Dermatology, Plastic Surgery, Otolaryngology staff are trained, competent, and privileged to administer (inject) appropriate materials.
 - (3) If there is no in-house expertise, appropriate referrals are made to outside providers.
- (4) Appointment, on an as-needed basis, of an *ad hoc* Facial Lipoatrophy Assessment Committee to adjudicate the need for AIFL therapy in the event of a disagreement on this issue.
 - c. **Referring HIV Provider.** The referring HIV provider is responsible for:

- (1) Determining whether the patient has facial lipoatrophy of sufficient severity that the patient's mental health is substantially impaired due to depression, stigmatization or social isolation and is willing to undergo Sculptra™ or Radiesse® treatment.
 - (2) Documenting the extent and severity of lipoatrophy.
- (a) Digital photography, although not required, can facilitate documentation. If photographs are obtained, they should be stored into CPRS to provide a record of progression of facial lipoatrophy justifying treatment, the patient's baseline condition before therapy, and the response to therapy (see subpar. 5b).
- (b) Consultation regarding technical aspects of digital photography and transfer of images into the CPRS should be obtained from the medical media department of the facility, or from the VistA Imaging Capture Web site at http://vaww.vistau.med.va.gov/VistaU/vistaimaging/Capture/Capture.htm.
- (c) Verbal informed consent is sufficient for digital images used solely for treatment purposes; however, use of such images for other purposes (e.g., education) requires documentation of written informed consent using VA Form 10-3203, Consent for Use of Picture and/or Voice or other appropriate form, (see VHA Privacy Fact Sheet vol. 5, no. 2, at: http://vaww.vhaco.va.gov/privacy/Communications/FactSheetVol05No2.doc).
- (3) Determining whether HIV medications associated with lipoatrophy (particularly thymidine analogues, such as stavudine) are part of the patient's regimen, and whether these medications can be safely replaced with other HIV medications that are less likely to cause lipoatrophy (see subpar. 5c). *NOTE:* Because new data may become available showing some or all of these agents are just as likely to be associated with facial lipoatrophy, providers need to consult the VA's HIV Web site (www.hiv.va.gov) and the peer-reviewed medical literature for up-to-date information on antiretroviral agents associated with facial lipoatrophy.
- d. <u>Treatment Procedures.</u> Appropriate Treatment Procedures are available. Veterans who meet criteria for, and who desire to proceed with, treatment must be referred to the local or regional VA dermatology, plastic surgery, or otolaryngology, or clinic for initial evaluation.
- (1) SculptraTM or Radiesse® are only to be administered by a dermatologist, plastic surgeon, or an otolaryngologist with appropriate training and experience in use of these products.
- (2) Exclusion criteria include: abnormal coagulation parameters, a history of a clinically significant bleeding disorder, concomitant treatment with high-dose aspirin, or an anticoagulant in the case of Radiesse®, concomitant receipt of interferon. *NOTE:* The safety and effectiveness of these products have not been established in women who are pregnant or lactating, or in individuals with a history of keloid formation or hypertrophic scarring.
- (3) The decision to proceed with injections must be made by the local Dermatology, Plastic Surgery, or Otolaryngology Service. In the event of a disagreement with the indications for

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initial treatment, continuation of initial corrective therapy, or a need for retreatment, the patient can be referred to a *ad hoc* Facial Lipoatrophy Assessment Committee (appointed by the Chief of Staff) for evaluation either in person or by evaluation of current images (see subpar. 4c2).

- (4) Prior to initiating treatment, signature informed consent must be obtained from the patient as outlined in VHA Handbook 1004.1.
- (5) Treatment would be limited to a total of three injections at 2 to 6 week intervals for SculptraTM and a total of three injections (one initial and two follow-up) for Radiesse®.
- (6) Following completion of initial correction of deformity, the patient should normally not be considered for retreatment for 6 months.
- e. <u>Patient Education.</u> Patient Education must be provided prior to any Sculptra[™] or Radiesse® treatment. The physician administering the treatments must:
 - (1) Obtain signature informed consent from the patient.
- (2) Provide education and appropriate counseling regarding the procedure, risks and realistic expectations as to what may be achieved (or may not be achieved) by Sculptra[™] or Radiesse® treatment.
- (3) Discontinue treatment if the patient fails to comply with the follow-up protocol, misses appointments, resulting in the loss or wastage of material, or receives treatment of the same facial areas with soft tissue fillers of any other type.
- f. <u>Referral to other facilities</u>. Referral to other facilities when necessary. For VA facilities at which there is limited access to clinicians with appropriate expertise for administering these products, referral to another VA facility with access to such clinicians or fee-based referral to a non-VA provider is permitted.

5. REFERENCES

- a. Echavez M, Horstman W. "Relationship Between Lipoatrophy and Quality of Life." <u>AIDS</u> Reader 15:369-75: 2005.
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- c. Moyle GJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, Hay P, Fakoya A, Murphy M, Scullard G, Leen C, Reilly G; RAVE (Randomized Abacavir versus Viread Evaluation) Group UK. "A Randomized Comparative Trial of Tenofovir DF or Abacavir as Replacement for a Thymidine Analogue in Persons with Lipoatrophy." <u>AIDS.</u> 20:2043-50: 2006.

- d. Radiesse Package Insert. 2006.
- e. Sculptra Package Insert. 2005.
- f. Silvers, SL, Eviatar, JA, Echavez, MI, and Pappas, AL. "Prospective Open-Label 18-Month Trial of Calcium Hydroxylapatite (Radiesse) for Facial Soft Tissue Augmentation in Patients with HIV-associated Lipoatrophy: One year Durability," <u>Plastic and Reconstructive Surgery Journal</u>. 118(3 Suppl):34S-45S: 2006.
- g. Valantin MA, Aubron-Olivier C, Ghosn J, Laglenne E, Pauchard M, Schoen H, Bousquet R, Katz P, Costagliola D, Katlama C. "Polylactic Acid Implants (New-Fill) to Correct Facial Lipoatrophy in HIV-infected Patients: Results of the Open-label Study VEGA," <u>AIDS.</u> 17:2471-7: 2003.
- **6. FOLLOW-UP RESPONSIBILITY:** The Public Health Strategic Healthcare Group (13B) is responsible for the content of this directive. Questions may be addressed to the Director, National Clinical Public Health Programs at (202) 461-7249, or at publichealth@va.gov.
- **7. RECISSIONS:** None. This VHA Directive expires January 31, 2013.

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ATTACHMENT A

COMPARISON OF SCULPTRA AND RADIESSE

AGENT	Sculptra	Radiesse
FILLER	Poly-L-lactic acid	Calcium hydroxylapatite
APPROVED	July 2004	December 2006
HOW SUPPLIED	Sterile freeze-dried preparation in vials; reconstituted with sterile water to 3-5 milliliter (mL).	0.3 and 1.3 ml syringe
COST PER VIAL (May 2007)	\$900 per vial	\$200 per 1.3 mL syringe; (mean initial volume in clinical trials – 4.8 mL)
CLINICAL TRIALS USED FOR FOOD AND DRUG ADMINISTRATION (FDA) APPROVAL	Effectiveness: Two open-label studies enrolling 80 patients with antiretroviral-induced facial lipoatrophy (AIFL) (baseline adipose thickness 0 - 2.7 mm). Mean age 41- 45 years; 72-84 percent white, 93-98 percent male; majority of patients reported to have Fitzpatrick score of I-III. Follow-up 12 through 96 weeks. Patients received 3 to 5 treatments with a maximum of 4 mL injected into each check at each treatment. Safety: Two open-label studies enrolling 198 patients; 52 week follow-up.	Effectiveness and Safety: One prospective open-label multicenter trial enrolling 100 patients with AIFL (severity 2 or greater on Facial Lipoatrophy Severity Scale). Mean age 48 years; 56 percent white; 94 percent male; 51 percent Fitzpatrick score of IV- VI. Follow-up 18 months. 78 percent of patients received three treatments. Mean initial treatment volume 4.8 mL
PATIENTS EXCLUDED FROM CLINICAL TRIALS USED FOR FDA APPROVAL	Patients with abnormal coagulation parameters, concomitant treatment with Non-steroival Anti-inflammatory Drugs (NSAIDS) or aspirin, or active facial skin disease; history of keloid formation or hypertrophic	Patients with a history of a bleeding disorder, use of topical or systemic corticosteroids or anabolic steroids, concomitant receipt of anti-platelet agents, anti-inflammatory agents, thrombolytics, or interferon, history of keloid formation or
	scarring; pregnancy or lactation.	hypertrophic scarring; pregnancy or lactation.

COMPARISON OF SCULPTRA AND RADIESSE (continued)

	Sculptra	Radiesse
BASIS FOR FDA	Mean increase of 7 millimeter	Mean increase of $2.4 - 2.7$
APPROVAL	(mm) in facial adipose thickness	mm in cheek thickness at 6
	at 96 weeks. Improved self-	months. Improvement in
	perception; no improvement in	Global Aesthetic
	quality of life in one study,	Improvement Scale and
	improved "Hospital Anxiety	patient satisfaction.
	and Depression Scale" in	
	another study.	
USUAL NUMBER OF	Three to six injections at 2 to 6	One. Follow-up treatments at
TREATMENTS	week intervals; One or two vials	1 month and 6 months after
	per treatment.	initial treatment may be
		necessary to maintain
		therapeutic results.
ADVERSE EVENTS	Safety data from 277 patients	Safety data from 117 patients
	Ecchymosis (21 percent)	Ecchymosis (64 percent)
	Edema (10 percent)	Edema (99 percent)
	Local discomfort (13	Local discomfort (37
	percent)	percent)
	Erythema (2 percent)	Erythema (55 percent)
	Subcutaneous papules (up to	Pruritis (21 percent)
	52 percent; mean onset 7 months)	
DURABILITY OF	In the largest effectiveness	91 percent of patients rated as
RESPONSE	study, 43 percent of patients had	improved or better at 18
	total cutaneous thickness of at	months post-treatment (see
	least 10 mm at 96 weeks (see	subpar. 5f in the Directive).
	subpar. 5g in the Directive.).	
COMMENTS	Subcutaneous papules were	In a radiographic study of 58
	palpable, but non-visible; in	patients, there was no
	largest study, resolved in 6 of	indication that Radiesse®
	22 patients by week 96.	potentially masked abnormal
		tissues or was interpreted as
		tumors on Computed
	yyaya hurna nayar tang: II: White	Tomography scans

Fitzpatrick score – I: White, always burns, never tans; II: White, always burns, minimal tan; III: White, burns minimally, tans gradually; IV: Light brown, burns minimally, tans well; V: Brown, rarely burns, tans profusely; VI: Dark brown or black, never burns, tans deeply Facial Lipoatrophy Severity Scale (see subpar. 5f in the Directive). Global Aesthetic Improvement Scale (see subpar. 5f in the Directive).