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● *Original Contribution*

COMPARABILITY OF ECHOGRAPHIC AND TOMOGRAPHIC ASSESSMENTS OF BODY FAT CHANGES RELATED TO THE HIV ASSOCIATED ADIPOSE REDISTRIBUTION SYNDROME (HARS) IN ANTIRETROVIRAL TREATED PATIENTS

AQ1-2

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Abstract—To assess the comparability of ultrasonographic (US) subcutaneous fat thickness (SFT) measurements in comparison with computed tomography (CT) at reference points (RPs) representative of HIV related adipose redistribution syndrome (HARS) in patients treated with antiretrovirals. US and CT measurements were compared in nine patients with clinical reports of HARS. We obtained the best resolution of facial (at deepest point of Bichat pad), brachial (in the dorsal face of arm) and crural SFT (at mid thigh) by means of minimal transducer pressures avoiding potential biases such as stand off pads pressure on the skin and artefacts due to too abundant quantity of gel. CT scans were obtained in the same RP where US measurements were performed such as identified by means of metallic skin markers. Median US measurement of facial SFT was 8.8 mm (95% CI: 3.1 to 13.4), 3.95 mm (95% CI: 2.62 to 5.84) for brachial SFT and 4 mm (95% CI: 3.4 to 9.4) for crural SFT. Median CT assessments of facial SFT was 8.7 mm (95% CI: 3.5 to 13.5), 4.2 mm (95% CI: 2.6 to 5.88) for brachial SFT and 5 mm (95% CI: 3.9 to 10.3) for crural SFT, with no significant difference at each RP. A linear regression showed good CT/US comparability at each RP, with no significant deviation from linearity ($p > 0.10$). US shows to be highly comparable with CT, excluding invaliding biases as the transducer pressure on the skin. Given the proven efficacy on the HARS assessments, if well standardized, US could be a reliable method, simpler than CT in the management of body fat changes related to HARS. (E-mail: steinman@imaging.robarts.ca)

Key Words: **Ultrasonography, Lipodystrophy, HIV infection, Antiretrovirals, Body fat changes.**

INTRODUCTION

Abnormal body fat changes (BFCs) and related metabolic alterations are frequently documented in subjects infected with human immunodeficiency virus (HIV) during the treatment with highly active antiretroviral therapies (HAART) (Bogner et al. 2001; Mallon et al. 2003) and are described as HIV associated adipose redistribution syndrome (HARS) (Carr 2003; Carr et al. 1998; Lichtenstein 2005; Lichtenstein et al. 2007).

If the predominant increase of visceral adipose tissue (VAT), lipohypertrophy (LH) and the related metabolic alterations lead to the increased cardiovascular risk (Friis-Moller et al. 2003; Grinspoon et al. 2005; Hadigan et al. 2003), the decrease of subcutaneous adipose tissue (SAT), lipoatrophy (LA) is a relevant social problem for its disfiguration and stigmatizing consequences, often so evident as to discourage the adherence to therapy with an increased risk of failure (Gripshover 2003). AQ: 3

The current clinical diagnoses based on subjective perception of patient and objective assessments of clinicians showed considerable risk of misdiagnoses, particularly in the initial and less severe stages.

On the other hand, the too sophisticated elaboration of lipodystrophy score by the Case Definition group study (Carr et al. 2003), the limited availability, the high costs and the risk for ionizing exposure of Dual Energy X-ray absorptiometry (DEXA) (Cavalcanti et al. 2005; AQ: 4

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Yang et al. 2004) and computed tomography (CT) (Engelson et al. 1999; Schambelan 2002; Schwenk 2002; Padilla et al. 2004; Yoshizumi et al. 1999) used to elaborate the score suggest the usefulness of alternative methods.

Ultrasound (US) show advantages that could make it an ideal imaging tool in the assessment of HARS (Martinez et al. 2000; Asensi et al. 2004; Gulizia et al. 2005, 2006; Asensi et al. 2006; Padilla et al. 2007). However, some authors have suggested that it could underestimate the SAT losses because of the transducer pressure on the skin, particularly in patients with facial LA (Carey et al. 2005; Padilla et al. 2007).

The aim of this study was to assess the comparability of US SAT measurements at reference points (RPs) representative of BFCs related to more disabling lipoatrophic findings observed during the HARS in comparison with CT assessments, the current gold standard tool (Padilla et al. 2004; Schambelan 2002; Yoshizumi et al. 1999).

PATIENTS AND METHODS

Nine adult HIV patients treated with HAART, with no active AIDS-defining illness and documented HARS, were enrolled.

A series of SFT assessments by means of US and CT were performed from our US Unit and the Institute of Radiology of Pavia between the January 2005 and July 2005, as part of a study for which Appropriate Ethics Committee approval was obtained. Informed consent was obtained from each enrolled patient.

Non-obese HIV infected patients were selected as identified by body-mass index (BMI) <27 kg/m^2, chosen to avoid possible biases as not-lipodystrophic obesity and to select patients with more likelihood to be affected by LA (Muurahainen 1999).

US assessment of fat thickness was always performed by the same physician, an experienced sonologist (GR), blinded to the patient's data, using high-frequency transducers (7.5–13 MHz) of EUB 6500 (HITACHI Medical Systems) and an Accuvix XQ (Sedas Medical technologies). AQ: 5 AQ: 6

Subcutaneous fat thickness (SFT) has been assessed at three RPs, avoiding any pressure on the underlying skin in the supine position, without any stand-off pad and using minimal quantity of gel to obtain the best resolution of epidermidis and derma included in the SFT measurements.

The US assessments were performed only when a well-defined horizontal hyperechoic line of epidermidis was obtained:

(1) Facial LA was assessed at deepest point of Bichat pad, using a left nasogenian transversal scan SFT from the external line of hyperechoic rim of malar bone to the hyperechoic line of epidermidis (Fig. 1a). F1
(2) Brachial LA: the assessment of upper limb SFT was performed with a dorsal scans of arm and an anterior flexion of the right elbow joint in a 90° angle, using a longitudinal scan, 10 cm above the elbow, from the external rim of superficial fascia of triceps to the hyperechoic line of epidermidis (Fig. 1b).
(3) Crural LA: long scan at 15 cm above the rotula, from external rim of superficial fascia of right quadriceps to the hyperechoic line of epidermidis (Fig. 1c).

US RPs were identified based on their representation of clinically based BFCs. Three measurements were obtained for each RP; mean value was considered for statistical analysis. CT assessment of SFT was always performed by the same physician blinded to the patient's data using a Somatom Balance, Siemens Medical Solutions. AQ: 7 AQ: 8

After a preliminary debate with our radiologists, we choose to obtain CT scans of each RPs identification where the US measurements were performed by means of metallic skin markers (Fig. 2a and b). F2

Statistical analysis

Mean and 95% CI of clinical and demographic data were obtained; moreover, median and 95% CI of single measurement were assessed.

A t-test and a Mann-Whitney test, respectively, were performed to assess significant statistical differences of clinical and demographic features and all SFT assessments by US and CT. A Passing and Bablok regression was performed to evaluate the comparability of US and CT measurements. Regression equations were obtained with relative intercept A and slope B and their 95% CI. Null hypothesis was tested at a level of p of 0.05. Statistical analyses were performed with MEDCALC statistical software (Broekstraat 52 B-9030 Mariakerke, Belgium).

RESULTS

Study population: mean age in males was 40.8 y (95% CI: 37.7 to 43.8); mean age in females was 41 years (95% CI: 32.7 to 49.3).

Mean BMI in males and females HIV subjects were 20.3 kg/m^2 (95% CI: 16.8 to 23.8) and 23.6 kg/m^2 (95% CI: 17.8 to 29.4), respectively.

No significant differences were shown between males and females HIV positives. CD4 T lymphocytes titer in HIV infected showed median of 314 cells/mmc (95% CI: 159 to 467) in males and 603 cells/mmc (95% CI: 348 to 638) in females, respectively.

Mean duration of HIV infection was 13.5 y (95% CI: 5.4 to 21.6) for males and 12.7 y (95% CI: 5.1 to

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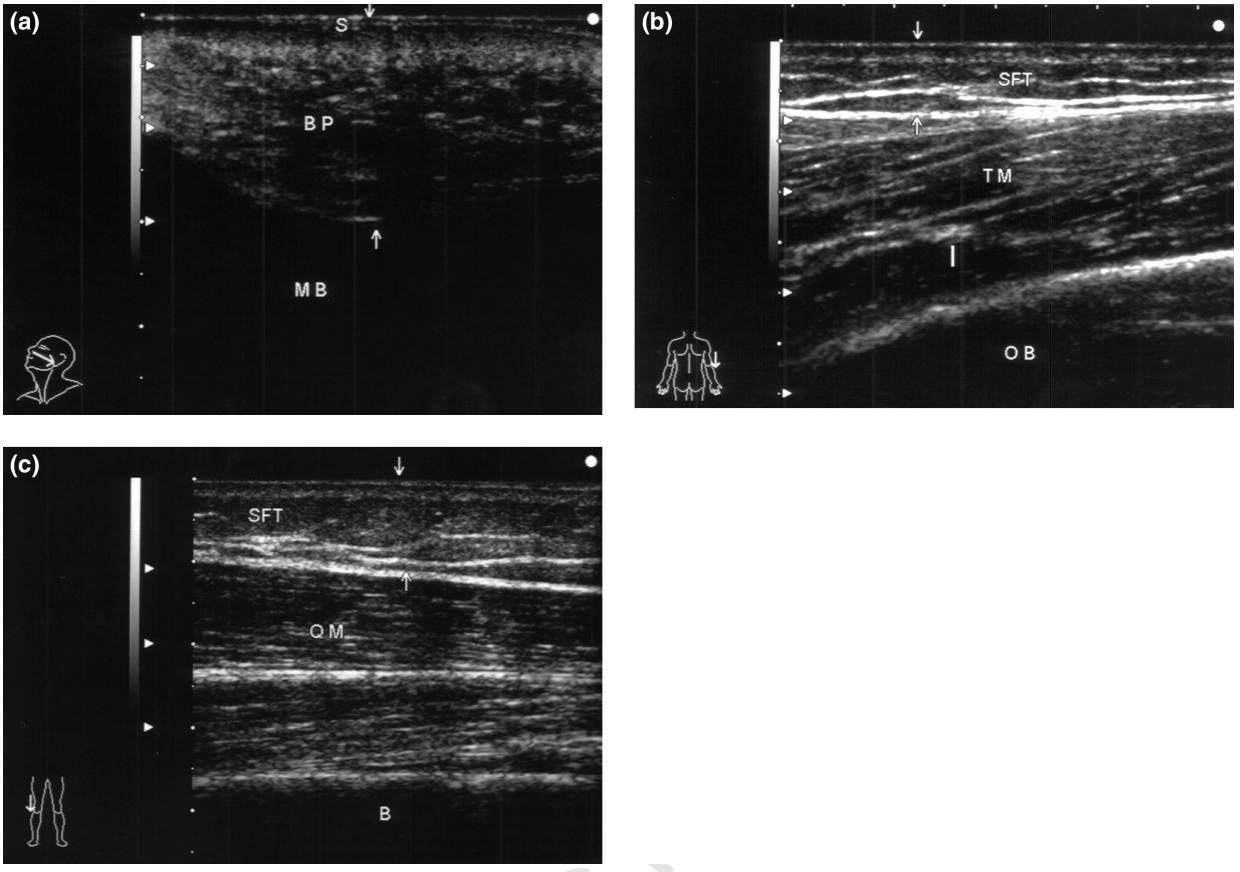

Fig. 1. Sonographic "skin reference points" to measuring cutaneous lipoatrophy. US scan with 7.5 to 13 MHz linear transducers is performed without pressing the underlying skin. (A) Facial reference point: SFT is measured with a left nasogenian transversal scan from the malar bone (MB) to the skin (S) on deepest point of Bichat pad (BP). (B) Upper limb reference point: SFT is measured with a long scans 10 cm above the right elbow from superficial wall of triceps muscle (T M) upper omeral bone (OB) to the skin. (C) Lower limb reference point: SFT is measured with long scans 15 cm above the rotula from the superficial wall of quadriceps muscle (QM) upper the femoral bone (B) to the skin.

20.3) for females, whereas mean duration of HAART was 11 years (95% CI: 9.2 to 12.8) and 9.5 y (95% CI: 9.5 to 12.8) for males and females, respectively. No significant differences were shown based on gender.

All patients were treated with HAART; regimen with 1 PI and 2 NRTIs was administered in four (44.4%) patients, two (22.2%) were treated with regimens PIs and NRTIs free, respectively. Administration of d4T was documented in the pharmacological history of patients in four (44.4%) cases.

HARS US findings. Median facial SFT was 8.8 mm (95% CI: 3.1 to 13.4) with a median upper limb SFT of 3.95 mm (95% CI: 2.62 to 5.84) and a median lower limb SFT of 4 mm (95% CI: 3.4 to 9.4).

HARS CT findings. Median facial SFT was 8.7 mm (95% CI: 3.5 to 13.5) with a median upper limb SFT of 4.2 mm (95% CI: 2.6 to 5.88) and a median lower limb SFT of 5 mm (95% CI: 3.9 to 10.3).

The comparison of CT and US SFT measurements showed no statistically significant differences for each RP. Features of enrolled patients are described in Table 1. T1

As summarized in Fig. 3a, b and c, a Passing and Bablok regression showed good CT/US comparability at each RP, with no significant deviation from linearity ($p > 0.10$): F3

Facial SFT- regression equation: y = −0.45 (95% CI −0.27 to 1.46) + 0.99 × (95% CI −0.86 to 1.07). Brachial SFT- regression equation: y = 0.07 (95% CI −0.82 to 0.67) + 1.04 × (95% CI −0.89 to 1.3). Crural SFT- regression equation: y = −0.66 (95% CI −0.56 to 0.93) + 0.98 × (95% CI 0.91 to 1.2).

DISCUSSION

HARS is a multifactorial syndrome in which several findings could be described separately or concurrently from generalized (central obesity) or focused LH (dor-

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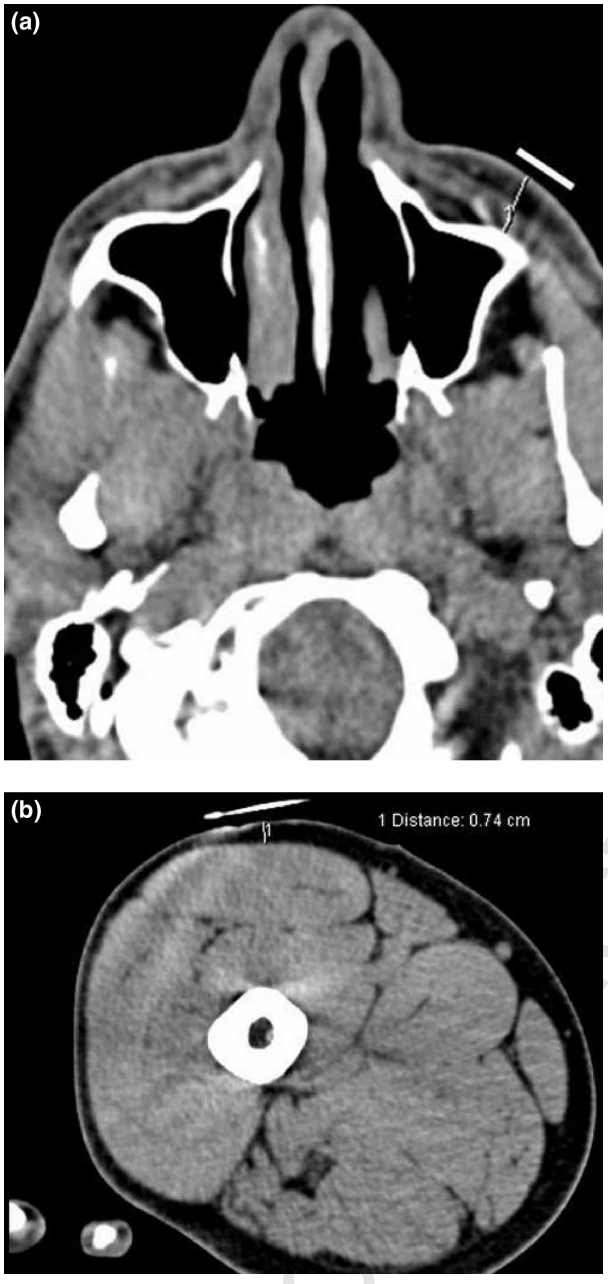

Fig. 2. Tomographic measurements of marked facial (A) and lower limb (B) SFT at reference points corresponding to skin areas where sonographic assessments were performed.

socervical lipomatosis, gynecomastia) to the predominant or mixed LA with facial, brachial and/or crural or buttock LA. The same stigmatizing SFT losses could be generalized or focused (Gripshover 2003; Lichtenstein 2005; Lichtenstein et al. 2007); the diagnosis of BFCs requires, therefore, imaging tools able to assess every body area. AQ: 9

The lack of ionizing radiations, low cost, availability, simplicity and being acceptable to patients suggest that US could be a more practical method than CT and DEXA and an ideal tool, especially in the early identification of HARS.

US accuracy in the assessment of HARS has been demonstrated by several authors, including our group (Martinez et al. 2000; Asensi et al. 2004; Gulizia et al. 2005, 2006; Padilla et al. 2007). Moreover, our and other observations (Martinez et al. 2000) documented good interobserver reliability, little intraobserver variability (less than 5%) and a good correlation with the HARS grading scale (Asensi et al. 2006).

In our opinion, however, the good perspectives of US require the standardization of measurement techniques and the identification of common RPs acknowledged from all authors.

Several BFCs are described in the HARS, and obviously more potential RPs have been studied, also by means of CT and US comparisons (Padilla et al. 2007), such as the omental fat thickness or perirenal fat diameter for the assessment of lipohypertrophic findings of HARS (Martinez et al. 2000; Asensi et al. 2004, 2006; Gulizia et al. 2005, 2006). On the other hand, if cervical lipomatosis had been well studied by means of US (Piliero et al. 2003; Palacios et al. 2007), it would be a less common type of fat redistribution in this population. AQ: 10

In the current study, we focused our attention on the more representative and disabling damages described in the daily practice. Based on clinically different presentations of LA, we identified three RPs representative of facial, brachial and crural LA.

Lastly, because the US anatomy of SFT is comparable at each body area, good comparability between US and CT in the assessment of SFT observed at chosen RPs AQ: 11

Table 1. Demographic, clinical, echographic and tomographic features of series for HIV lipoatrophic patients

Features	Mean (95% CI)	
Male		
No. patients	4	
Age, y	40.8 (37.7-43.8)	
BMI, kg/m^2	20.3 (16.8-23.8)	
Duration of HIV, y	13.5 (5.4-21.6)	
Duration HAART, y	11 (9.2-12.8)	
CD4, cells/mmc	314 (159- 467)	
Female		
No. patients	5	
Age, y	41 (32.7-49.3)	
BMI, kg/m^2	23.6 (17.8-29.4)	
Duration of HIV, y	12.7 (5.1-20.3)	
Duration HAART, y	9.5 (9.5-12.8)	
CD4, cells/mmc	603 (348- 638)	
	US	CT
SFT, mm	Median (95% CI)	Median (95% CI)
Facial	8.8 (3.1-13.4)	8.7 (3.5-13.5)
Brachial	3.95 (2.62-5.84)	4.2 (2.6-5.88)
Crural	4 (3.4-9.4)	5 (3.9-10.3)

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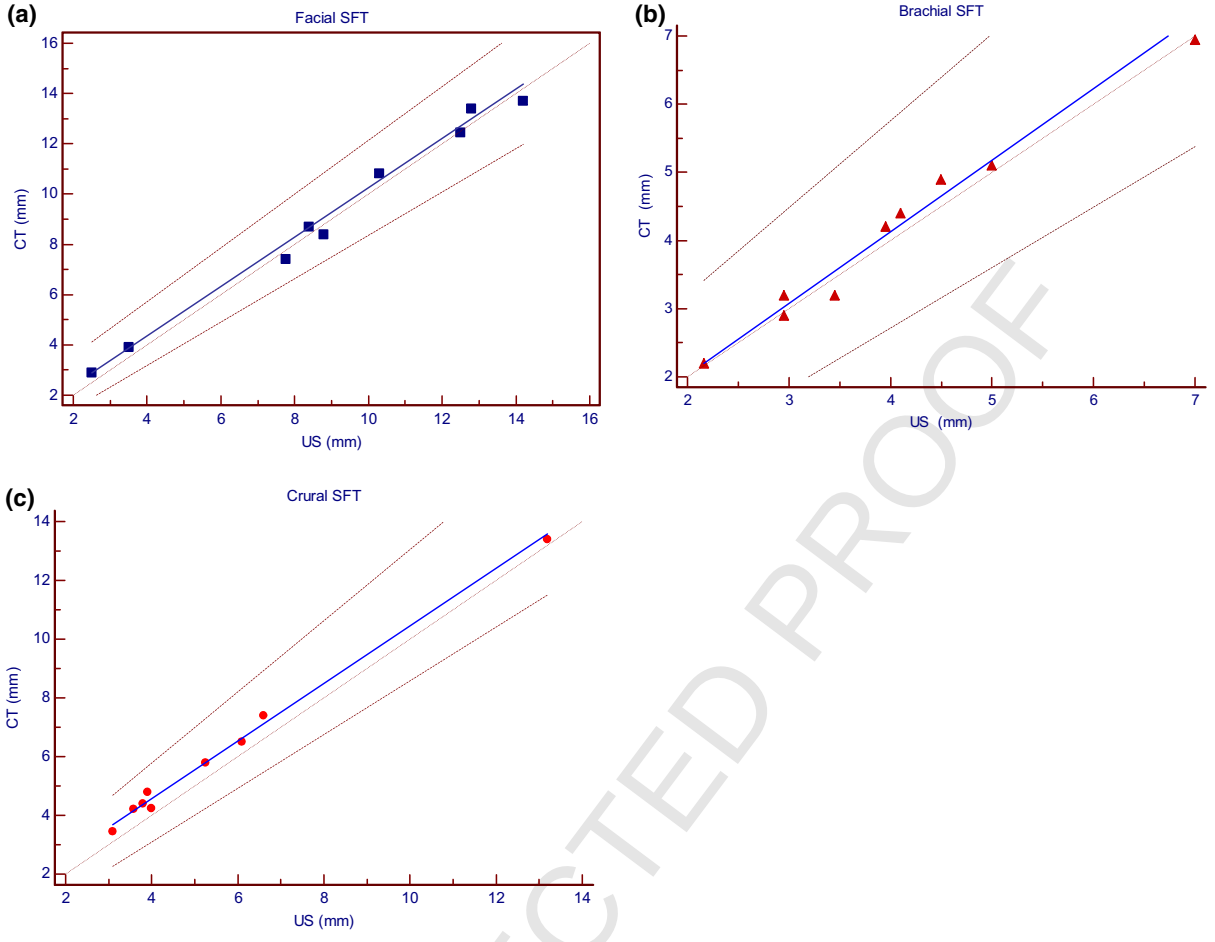

Fig. 3. Scatter diagrams and regression line of facial (A), brachial (B) and Crural (C) SFT assessments by means of ultrasound and tomography. (Passing and Bablok Regression showed no significant deviation from linearity [$p > 0.10$].)

(particularly in the upper and lower limbs) suggests the reliability of US measurements for each of BFCs described in the HARS.

A well-defined procedure in the measurement technique of SFT at RPs to be reproducible in clinical HARS presentation, such as we have suggested in the Patients and Methods section, seems to confirm the ability of US to identify LA, allowing an early diagnosis and preventing advanced stages in which HARS is less reversible or more invaliding by means of serial re-assessments in the routinely visits of HIV patients.

In this regard, diagnostic thresholds of LA have recently been reported (Martinez et al. 2000; Asensi et al. 2004, 2006; Gulizia et al. 2005, 2006; Padilla et al. 2007) at each RPs, but the same identification of SFT losses in the serial re-assessments could be a valid guide to identify the BFCs, alternatively other more sophisticated imaging tools.

Recently, discordant evidences were proposed on effective accuracy of US and on its poor correlation with CT due to the transducers pressure on the skin, partially related to the too peripheral assessment of facial SFT performed; in our opinion this is not representative of clinical findings of facial LA and the choice to compare CT assessments of crural SAT and US measurements of facial SFT (Carey et al. 2005; Gulizia et al. 2006).

Although in our investigation we did not perform a comparison with standardized CT procedures for the assessment of SAT based on the measurement of its section areas or volume (Gellett et al. 2001; Padilla et al. 2004; Schwenk 2002) as being our aim to assess the reliability of US-based SFT measurements, we show that US is comparable with CT with a high agreement between the US and CT measurements performed at same RPs.

The good comparability between the CT and US measurements excludes any relevance of the US transducers pressure on the underlying skin and confirms the reliability of our measurement technique, beginning with the careful identification and measurement of RPs to avoiding any potential bias such as the pressure offered by stand-off pads in the skin and taking care to exclude

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artefacts due to a too abundant quantity of gel to obtaining the best resolution of SFT, such as we have proposed, with minimal transducer pressure.

Although the limited number of enrolled patients suggests wariness in our conclusions, Milinkovic et al. (2003) and other authors (Padilla et al. 2007) reported a good correlation between US and CT SFT measurements and, if confirmed by larger studies, it could enforce the good perspectives of US to obtain reliable assessments of BFCs related to LA in HIV patients treated with antiretrovirals.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

AQ1— Included first names.

AQ2— Please verify affiliation for Giovanna Ferraioli and Carlo Filice. Are they both affiliated with the Division of Infectious and Tropical Diseases, University of Pavia?

AQ3— Word edit: “disfiguration” (instead of “disfigurating”) OK?.

AQ4— Spelling edit: “absorptiometry” (instead of “absorbimetry”) OK?

AQ5— Please provide city/state (if located in the USA) or city/country (if located outside the USA) for Hitachi Medical Systems.

AQ6— Please provide city/country for Sedas Medical technologies.

AQ7— Word edit: “representation” (instead of “representativity”) OK?

AQ8— Please provide city/state or city/country for Siemens Medical.

AQ9— Word edit: “body area” (instead of “body district”) OK?

AQ10— Edit OK? The meaning is not clear.

AQ11— Word edit: “structure” (instead of “anatomy”) OK?

AQ12— What is meant by “invaliding”? Do you mean “invalidating”?

AQ13— What is meant by “alternatively” in this context? Do you want to say “instead of”?

AQ14— Are these proceedings of a meeting? Please provide publisher, editor, and page numbers.

AQ15— Are these proceedings of a meeting? Please provide publisher, editor, and page numbers.

AQ16— Are these proceedings of a meeting? Please provide publisher, editor, and page numbers.