

Poly-L-lactic acid for HIV-1 facial lipoatrophy: 48-week follow-up

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Objectives

Poly-L-lactic acid (PLA) injections modestly increase objectively assessed facial thickness but not facial soft tissue volume (FSTV) over 24 weeks. The durability of this response has not been well defined objectively.

Methods

HIV-infected lipoatrophic adults were randomized to four open-label PLA treatments administered every 2 weeks from week 0 (immediate group, $n = 50$) or from week 24 (deferred group, $n = 50$). Endpoints included FSTV assessed by computed tomography, facial lipoatrophy severity, quality of life (QoL) and safety. Analyses were by intention to treat.

Results

Between weeks 24 and 48, soft tissue thickness increased modestly in injection planes, at the maxillary [mean 0.9 mm; 95% confidence interval (CI) 0.3–1.5 mm; $P = 0.007$] and base of nasal septum levels (mean 0.4 mm; 95% CI 0.1–0.8; $P = 0.021$), but not in untreated areas ($P = 0.79$ and $P = 0.24$). PLA durability assessed at week 48 in immediate group participants showed a mean change in FSTV of 14 cm^3 (95% CI -1 to 29 cm^3 ; $P = 0.060$) and increased tissue depth at the maxillary ($P < 0.0001$), base of nasal septum ($P < 0.0001$) and mandibular ($P = 0.0035$) levels. At week 48, clinicians and patients subjectively assessed facial lipoatrophy severity as reduced in immediate participants (83 and 91%, respectively), and the Mental Health scale score of the Short Form-36 Health Survey improved significantly in immediate participants relative to deferred participants ($P = 0.027$). Subcutaneous injection-site nodule incidence at 48 weeks was 10%.

Conclusions

PLA treatment benefits were durable, with objectively assessed modest increases in facial volume and tissue thickness sustained over 48 weeks in injection planes but not in other facial areas. Improvements in some QoL domains were maintained.

Keywords: HIV, lipoatrophy, poly-L-lactic acid

Accepted 19 August 2008

Introduction

Lipoatrophy of subcutaneous adipose tissue in the limbs, face and buttocks, and accumulation of adipose tissue in the intra-abdominal space, dorsocervical region and the breasts are major features of HIV lipodystrophy [1,2].

*See Appendix A.

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Facial lipoatrophy, the most distressing manifestation, can be stigmatizing, severely affecting quality of life (QoL) and self-esteem, and may result in reduced antiretroviral (ARV) adherence [3]. Although use of the newer nonthymidine nucleoside reverse transcriptase inhibitors is associated with less lipoatrophy [4], in the absence of proven therapies, management of established fat loss can be challenging as reversal is slow [5–7].

An array of injectable filling agents has been marketed for soft tissue augmentation and many of these are used for aesthetic management of HIV facial lipoatrophy [8].

Poly-L-lactic acid (PLA; Sculptra™; Dermik Laboratories, Bridgewater, NJ, USA), a synthetic, biodegradable, immunologically inert, resorbable polymer, approved in Europe and the USA for use in HIV facial lipoatrophy, is used most commonly. Although open-label studies have demonstrated PLA safety in HIV-infected adults [9–18], PLA efficacy has been objectively assessed in only one randomized clinical trial [19]. This open-label, multicentre study compared immediate *vs.* deferred PLA injections in adults with moderate to severe facial lipoatrophy. The study's primary objective was to determine the effect of four bilateral PLA treatments administered every 2 weeks on facial soft tissue volume (FSTV) over 24 weeks using volumetric computed tomography (CT). At 24 weeks, although PLA had not increased FSTV, significant but clinically modest improvements in objectively assessed tissue thickness at the planes of injection were demonstrated. We report here longer term efficacy, safety and durability.

Methods

Participants

Details of participants' eligibility, randomization and baseline characteristics have been reported previously in the 24-week primary efficacy comparison [19].

All participants provided written, informed consent following approval by the local human research ethics committee at each site.

Interventions

At baseline, 100 eligible patients were randomized to receive four open-label PLA treatments [one vial (150 mg) per cheek] every 2 weeks with a minimum 14-day interval between treatments commencing either at week 0 (immediate group; $n = 50$) or following a delay period of 24 weeks (deferred group; $n = 50$). At weeks 0, 2, 4 and 6, immediate group participants received bilateral PLA injections at a single surgical location in each of the four participating Australian states according to a common protocol [19]. Following completion of the 24-week study visit, the deferred group also received four bilateral PLA injections at weeks 25, 27, 29 and 31 at the four surgical locations protocolled. Management guidelines for PLA-related adverse events included treatment delay or termination. PLA cessation was mandatory for grade 4 (very severe or life-threatening) events considered definitely, probably or possibly related to PLA. Antiretroviral therapy (ART) changes were permitted for on-study adverse events or virological failure.

Assessments

Assessments performed to week 24 have been published previously [19]. All participants were seen at weeks 36 and 48. Additionally, deferred group participants were seen at weeks 26, 28, 30 and 32 for a post-procedure and safety review. Safety assessments included physical examination, recording of clinical adverse events and concomitant drugs and measurements of plasma HIV-1 RNA and T-lymphocyte subsets. Women of child-bearing potential in the deferred group had serum β -human chorionic gonadotrophin testing immediately prior to PLA commencement. At week 48, spiral CT of the head was performed with subsequent volumetric assessment using three-dimensional (3D) post-processing software to quantify total FSTV of the region defined superiorly by the mid-orbit and inferiorly by the angle of the mandible [19]. Four protocol-defined bony landmarks were identified on four axial images and with the measurement tool baselines were drawn at the level of the mandible, the base of the nasal septum, the maxilla and the orbit. From each baseline the maximum distance to the skin line was recorded as the mandible, base of nasal septum, maxilla and orbit measurements, respectively. Other objective body composition measures collected at each visit were weight, body mass index (BMI), and hip and waist circumferences. Subjective measures of lipodystrophy severity were recorded independently by clinicians and patients at each time-point. Each body region was scored according to a standardized system (0 for none, 1 for mild, 2 for moderate or 3 for severe) [20,21].

Health-related QoL was self-reported using the Short Form (SF)-36v2 Health Survey at weeks 36 and 48 [22]. Self-satisfaction with appearance and weight was assessed using the Multidimensional Body-Self Relations Questionnaire-Appearance Scales (MBSRQ-AS), a standardized measure of body image attitudes [23]. ARV adherence was assessed using a standardized self-report form [24]. Participants recorded whether they took 'all', 'most', 'about half', 'very few', or 'none' of their medication during the preceding 7 days.

Statistical analysis

When the week 24 primary efficacy analysis did not demonstrate a significant change in FSTV, the Protocol Steering Committee requested that an interim analysis be performed on all data to week 48 to evaluate PLA durability, safety and tolerability. Moreover, if there was no significant change in FSTV, the study should be terminated. An analysis plan was finalized prior to database closure. The week 48 statistical analysis was

conducted when all randomized participants had completed at least 48 weeks of follow-up, or had permanently withdrawn from follow-up. Changes from baseline in efficacy endpoints were summarized at each study visit. Time windows were defined by the mid-point between nominal study weeks, except for facial CT scans which were performed within 4 weeks of week 48; if more than one measurement of a parameter were available in a time window, the mean value was used. Efficacy analyses compared the randomized treatment groups on an intention-to-treat basis in terms of change from baseline to week 48 and included all participants with baseline data and at least one follow-up assessment. A last-value-carried-forward approach was utilized for participants lost to follow-up. Secondary analyses used only available data. Continuous endpoints were investigated using analysis of variance or nonparametric equivalents and binary endpoints were assessed by χ^2 tests or logistic regression. All significance tests were two-sided and not adjusted for multiple comparisons.

PLA durability at week 48, as measured by CT, was assessed in the immediate group only. A pooled analysis based on available data assessed change from baseline to 24 weeks post-treatment in FSTV and facial linear measurements. Baseline data for the deferred group were week 24 data (immediately prior to PLA start).

Serious adverse events, adverse events associated with PLA or leading to changes in ART, and all grade 3 or 4 clinical adverse events were summarized at each study visit by treatment group. Events associated with PLA modification or cessation were summarized. An ARV adherence score was calculated as described previously [24]. Subgroup analyses were based on the following strata: age, patient-assessed facial lipoatrophy severity, baseline protease inhibitor (PI) and thymidine nucleoside reverse transcriptase inhibitor (NRTI) use, and surgeon. Differences in outcome between randomized treatment arms were assessed with tests of interaction between treatment and strata.

Univariate and multivariate linear regressions were used to determine predictors of PLA efficacy, defined on the basis of a change in FSTV greater than the pooled median change 24 weeks after PLA initiation, and predictors of an increase in linear measurements (base of nasal septum and maxillary levels) 24 weeks after PLA initiation. The following variables were assessed as predictors: baseline demographic characteristics, ARV treatment, CD4 cell count and HIV-1 viral load, smoking status, skin tanning type (Fitzpatrick scale) [25], treatment group (immediate/deferred), baseline FSTV, baseline and week 24 limb fat mass and percentage, and change in limb fat mass and percentage at week 24 assessed by dual-energy X-ray

absorptiometry (DEXA). Baseline characteristics for deferred participants were week 24 data, except for body composition data where week 0 and week 24 were utilized as no week 48 DEXA was protocolled. Multivariate models considered all variables with a P -value ≤ 0.1 in initial analyses, and used forward stepwise methods. All analyses were performed using STATA Statistical Software version 10 (Stata Corporation, College Station, TX, USA).

Results

One hundred participants (50 immediate; 50 deferred) contributed to the week 24 randomized comparison. Subsequently, three participants (two immediate and one deferred) withdrew consent (patient choice), and one (immediate) was lost to follow-up (Fig. 1). Most (92%) participants were men, 35% had AIDS, and all were receiving ART: 65 were receiving a PI-based regimen and 14 a thymidine NRTI. Mean \pm standard deviation (SD) baseline FSTV was $388 \pm 71 \text{ cm}^3$ in the immediate group and $393 \pm 69 \text{ cm}^3$ in the deferred group [19].

Forty-eight of the 49 deferred participants (98%) received four bilateral PLA treatments. One participant required only three treatments (six vials) for adequate facial correction. Twenty-five ARV drugs were stopped in 16 participants (16%; 10 immediate and six deferred). Six agents were discontinued for virological failure (two immediate participants), seven for toxicity (six participants; four immediate and two deferred), and the remaining 12 (48%) for regimen simplification. The drugs discontinued most commonly were lamivudine (seven participants; four immediate and three deferred), lopinavir/ritonavir (four immediate) and tenofovir (three immediate). Thymidine NRTI therapy was stopped in two participants (one immediate and one deferred), and no participant ceased PI therapy. No participant received any additional intervention or procedure for lipodystrophy. There was no death, new AIDS-defining event, or protocol violation. Data for 100 participants (50 immediate and 50 deferred) were available for the intention-to-treat analysis.

Efficacy: objective measures

Between weeks 24 and 48, tissue thickness in injection planes, at base of nasal septum and maxillary levels, increased significantly [mean 0.4 mm; 95% confidence interval (CI) 0.1–0.8 mm; $P = 0.021$ and mean 0.9 mm; 95% CI 0.3–1.5 mm; $P = 0.007$, respectively] in immediate group participants, but there was no change at the untreated orbital and mandibular levels (Table 1 and Fig. 2). PLA durability, assessed in immediate group participants at 48 weeks, showed a mean change in FSTV of 14 cm^3 (95% CI

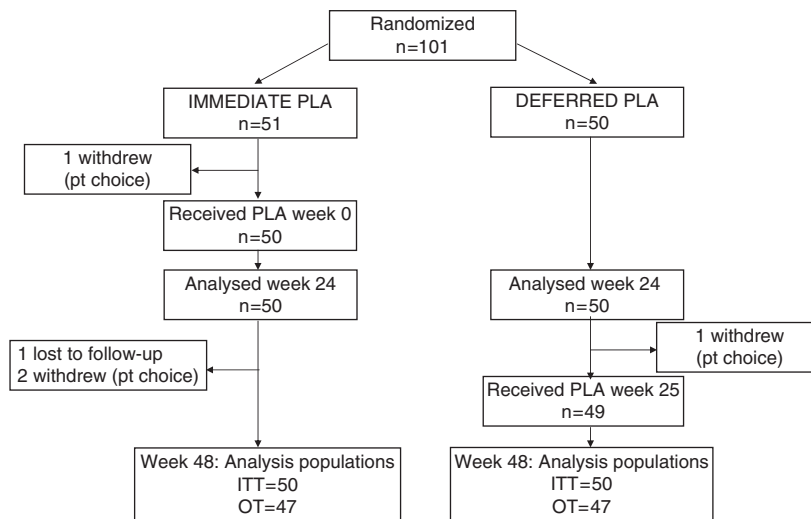


Fig. 1 Patient follow-up.

Table 1 Change in objective facial measures in immediate participants

	Baseline (<i>n</i> = 50) Mean (SD)	Change between weeks 24 and 48 (<i>n</i> = 47)*			Week 48 change from baseline (<i>n</i> = 50) [†]		
		Mean (%)	95% CI	<i>P</i>	Mean (%)	95% CI	<i>P</i>
Facial soft tissue volume (cm ³)	388 (71)	14 (4)	−1 to 29	0.060	14 (4)	−1 to 29	0.060
Linear measurements (mm) [‡]							
Mandible	21 (5)	0.4 (2)	−0.3 to 1.3	0.24	1.0 (4)	0.3–1.6	0.0035
Base of nasal septum	28 (4)	0.4 (2)	0.1–0.8	0.021	1.7 (6)	1.1–2.2	<0.0001
Maxilla	12 (3)	0.9 (8)	0.3–1.5	0.007	3.1 (27)	2.4–3.8	<0.0001
Orbit	13 (3)	0.1 (1)	−0.4 to 0.5	0.79	0.1 (1)	−0.4 to 0.7	0.59

*Includes all subjects with week 24 data (intention to treat).

[†]Includes all subjects with week 0 data (intention to treat).

[‡]Mean of left- and right-sided measurements.

CI, confidence interval; SD, standard deviation.

−1 to 29 cm³; *P* = 0.060; Table 1) and increased tissue depth at maxillary, base of nasal septum and mandibular levels (Table 1).

Pooled 24-week analysis using available data (*n* = 96) demonstrated a significant mean change from baseline in FSTV (15 cm³; 95% CI 5–24 cm³). PLA increased tissue thickness at the maxilla and base of nasal septum levels (mean 1.2 mm; 95% CI 0.8–1.5 and 2.5 mm; 95% CI 2.1–2.9 mm, respectively), but there was no change in thickness at the untreated orbit and mandibular levels (mean 0.8 mm; 95% CI 0–1.5 and −0.3 mm; 95% CI −0.9 to 0.3 mm, respectively). Analyses to investigate predictors of a good 24-week volumetric response to PLA, defined as an FSTV change greater than the overall pooled median change (12.6 cm³) 24 weeks post-treatment, produced inconsistent data. In multivariate analysis, independent predictors of a volumetric response (> 12.6 cm³) were deferred treatment group (*P* = 0.002), and a baseline FSTV above the median

(*P* = 0.031). Predictors of a greater increase in tissue thickness at the maxillary level were surgical site (*P* = 0.009), and Fitzpatrick skin types IV–VI (*P* = 0.001). There were no significant predictors of a tissue thickness increase at the base of nasal septum level.

A 24-week treatment delay did not impact PLA efficacy. At week 48, the mean change in FSTV was 14 cm³ (95% CI −1 to 29 cm³) in the immediate group and 18 cm³ (95% CI 5–30 cm³) in the deferred group, a between-group difference of −4 cm³ (95% CI −22 to 16 cm³; *P* = 0.71; Fig. 3). These represent changes in FSTV of 4 and 5%, respectively (between group difference −1%; *P* = 0.66). There was no between-group difference in mean change in tissue depth in injection planes (maxilla, *P* = 0.22; base of nasal septum, *P* = 0.44; Fig. 2). Tissue thickness at the untreated orbital and mandibular levels did not differ (*P* = 0.11 and *P* = 0.40, respectively) (Fig. 2). Treatment efficacy, assessed by change in FSTV at week 48, did not

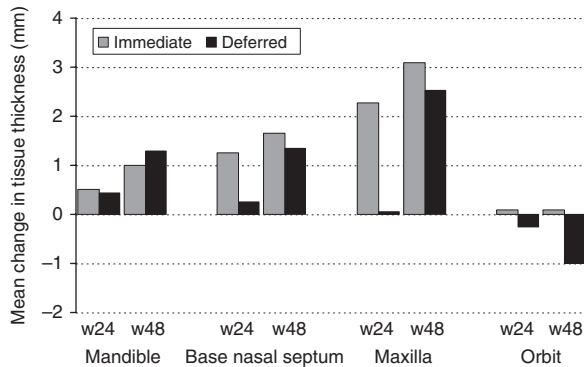


Fig. 2 Change from baseline to study weeks in facial linear measurements.

differ significantly between any subgroup (data not shown). At week 48, there was no between-group difference in plasma viral load ($P = 0.40$), CD4 lymphocyte counts ($P = 0.53$), self-reported ARV adherence ($P = 0.75$), or any objective body composition measure [weight ($P = 0.81$), BMI ($P = 0.91$), waist circumference ($P = 0.72$), or waist-to-hip ratio ($P = 0.40$)].

Efficacy: subjective measures

At week 48, patients and clinicians perceived sustained improvements in facial lipoatrophy severity in immediate participants, with 83 and 91%, respectively, assessing severity as reduced (Fig. 4). There was no difference in any other clinician- or patient-assessed subjective measure of lipodystrophy or its severity at week 48 in immediate participants. In the deferred group, facial lipoatrophy severity was assessed as reduced by 82% of deferred PLA recipients and 88% of clinicians at week 48 (Fig. 4). There was no between-group difference in patient- or clinician-assessed facial lipoatrophy severity at week 48 ($P = 0.70$ and 0.50 , respectively) (Fig. 4), or any other clinician- or patient-assessed subjective measure of lipodystrophy or its severity.

At week 48, change from baseline in scores for Mental Health and Social Functioning scales of the SF-36 Health Survey in the immediate group were higher than those observed at week 24 (data not shown). At week 48, the mean change in the Mental Health score differed significantly in the immediate group relative to the deferred group (5.2 and -3.7 , respectively; $P = 0.027$). There was a trend for a greater mean change in the score for Social Functioning in the immediate group relative to the deferred group (6.1 and -3.3 , respectively; $P = 0.078$). There was no between-group difference in the Physical Component Summary score ($P = 0.14$), but there was a trend for immediate group participants to have a greater increase in

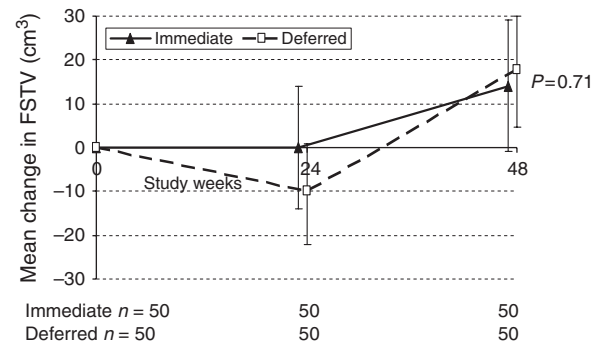


Fig. 3 Change from baseline to week 48 in facial soft tissue volume (FSTV).

the Mental Health Component Summary score ($P = 0.072$). There was no between-group difference in any of the five MBSRQ-AS-assessed body self-image subscale scores at week 48.

Safety/tolerability

The majority (98%) of deferred participants experienced at least one product/procedure-related adverse event, most commonly pain/discomfort (73%), oedema (65%) and erythema (49%). Adverse events were similar in frequency, grade, onset time and duration to those reported by immediate group participants [19]. At week 48, three palpable and one visible subcutaneous noninflammatory injection site nodules and one papule were ongoing in four deferred participants (8%). At week 24, five injection site subcutaneous noninflammatory nodules and one papule had been ongoing in six immediate participants (12%). Between weeks 24 and 48, one nodule and one papule resolved spontaneously and one late-onset nodule and two papules (three participants) were diagnosed. In total, 96 of the 99 participants (97%) who received PLA experienced at least one product/procedure-related adverse event (Table 2). At week 48, eight nodules (seven palpable and one visible) and two papules remained ongoing in 10 participants (10%).

There were 10 serious adverse events in seven participants (three immediate and four deferred). No event was associated with PLA, and no other grade 4 event was considered to be definitely, probably or possibly related to PLA.

Discussion

Following four bilateral PLA treatments in HIV-infected, ARV-experienced adults with moderate or severe facial lipoatrophy, clinically modest increases in objectively

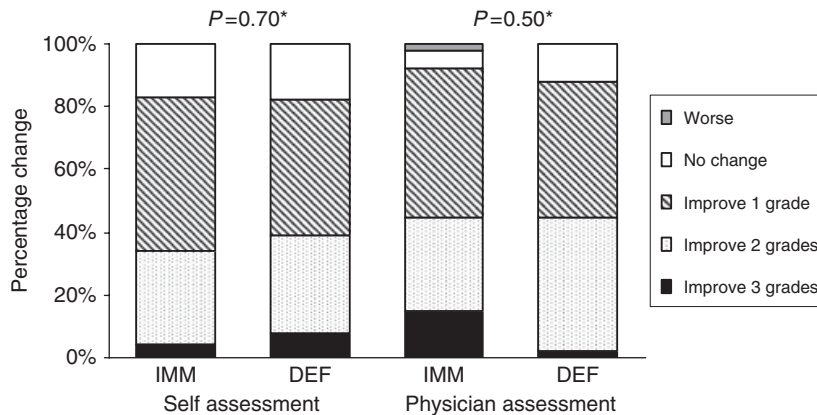


Fig. 4 Percentage change in subjective facial lipoatrophy severity at week 48.

*P value for immediate (IMM) group *vs.* deferred (DEF) group

Table 2 Overall procedure/product-related adverse events to week 48

Event	% Grades 1 & 2 (n = 392)*	Median time to onset (days)	Median duration (days)	% Grades 3 & 4 (n = 392)*	Median time to onset (days)	Median duration (days)
Pain/discomfort [†]	73	0	2	4	0	2
Oedema [‡]	64	0	3	7	0	2
Erythema [‡]	50	0	2	4	0	2
Ecchymosis [‡]	9	0	3	1	0	6.5
Pruritus [‡]	8	0	2	-	-	-
Inflammation [‡]	6	0	2	-	-	-
Haematoma [‡]	1	0	5	-	-	-
Nodule (> 10 mm)	7	1.5	76.5 [§]	-	-	-
Papule (< 10 mm)	4	4	7.5	-	-	-

*Based on total number of treatment procedures (immediate plus deferred groups).

[†]Grades 1 and 2, 1–5 on visual analogue scale; grades 3 and 4, 6–10 on visual analogue scale.

[‡]Grades 1 and 2, < 50 mm; grades 3 and 4, 50–85 mm.

[§]Eight nodule and two papule events were ongoing at week 48.

assessed facial soft tissue thickness around the planes of injection, but not facial volume, were demonstrated out to week 48. Clinicians and patients perceived sustained treatment benefits with significant improvements in facial lipoatrophy severity assessed at week 48 in participants treated at baseline. A 24-week treatment delay did not impact change in FSTV or facial soft tissue thickness compared with immediate treatment. Differences in some QoL scores were observed. Subcutaneous nodule incidence at 48 weeks was 10%.

Between weeks 24 and 48 there was a gradual but significant increase in tissue depth in two planes, the maxilla and the base of the nasal septum, in early PLA recipients. These increases can only be interpreted as a durable PLA treatment benefit as they were not accompanied by improvement in untreated facial areas. Gradual increases in facial thickness are consistent with the mechanism of action of PLA [26,27], which differs from the more immediate benefits achieved with the use of nonbiodegradable filling agents such as polyacrylamide gel [16] or polyalkylimide gel [28].

At week 48, mean tissue depth had increased to 3.1 mm at the maxillary level and 1.7 mm at the base of the nasal septum in early PLA recipients. These changes, while lower than the week 48 changes reported in some studies [9,11,17], are comparable to those reported in others [13,14]. However, cross-study comparisons of PLA efficacy for HIV facial lipoatrophy are problematic because of the heterogeneity of these studies. To date, all PLA studies have been open-label, varying enormously in terms of the number of treatments administered, study subjects, and facial lipoatrophy severity and its assessment. Only one earlier study utilized a validated lipodystrophy assessment tool [29] to assess facial lipoatrophy severity [10]. PLA studies lack objective lipodystrophy data. Validated measures of facial soft tissue thickness or volume for assessing and/or comparing treatment efficacy are also lacking. Measurement methods employed have included ultrasonography [9,14,17], callipers [11], and 3D photography with 3D computerized reconstruction of the face [13], none of which has been validated. Collectively, these factors demonstrate the lack of scientifically valid data that relate

to this treatment approach, and assist in explaining the broad inter-study variability in PLA treatment outcomes.

This is the first study to use FSTV, an unbiased objective measure, to assess treatment benefits following soft tissue augmentation. The increase in FSTV observed in deferred participants 24 weeks after PLA initiation contrasts with the lack of change observed at 24 weeks in participants treated immediately. However, at week 48 FSTV had increased in immediate PLA recipients and was not different between groups. This disparity is probably attributable to variability in the procedure and/or the extent of the area of PLA injection relative to the facial volume. Accurate measurement of facial volume necessitated the single operator at each of the nine national scanning sites to reconstruct the data sets at 24 and 48 weeks to mirror baseline image parameters. Failure to adhere to this requirement could produce measurement error. Additionally, the mid-orbit and the angle of the mandible, which constituted the upper and lower landmarks for FSTV, respectively, produced a volume substantially greater than the area of PLA injection. As the improvements in tissue thickness in injection planes were modest, the resultant volumetric increases may have been difficult to detect, especially if the procedure was more variable than expected.

The pooled 24-week analysis confirmed a PLA treatment benefit with significant but modest increases in facial thickness around the planes of injection and in FSTV. Between weeks 24 and 48, one participant in each arm ceased stavudine therapy. Given the slow rate of lipoatrophy reversal following thymidine NRTI cessation [30,31], we do not believe that this therapy change is likely to have impacted study results. These data are supported by no change in any objective body composition parameter.

The objectively assessed increases in both FSTV and facial soft tissue thickness were perceived by both patients and clinicians, with most assessing improvements in apparent facial lipoatrophy severity that were sustained at week 48. Clinician- and patient-perceived facial lipoatrophy severity did not differ between participants treated at baseline and those treated after week 24. Subjectively assessed lipodystrophy and its severity were also assessed as not different, and this finding was supported by no between-group difference in any objective body composition measure.

Reliable and validated instruments measured the impact of treatment on health-related QoL (SF-36) and body self-image (MBSRQ-AS) [32]. Between weeks 24 and 48, scores for Mental Health and Social Functioning scales of the SF-36 continued to improve in participants who received PLA at baseline, demonstrating ongoing patient-

perceived treatment benefits. It is likely that these improvements accounted for the differences in health-related QoL outcomes observed at week 48, with improved Mental Health and a trend towards increased Social Functioning in the immediate group. In contrast, the MBSRQ-AS assessment of psychological state showed that scores for body-self image and self-satisfaction with weight and appearance were not different between the groups.

Safety data suggest that PLA injections are safe and well tolerated over 48 weeks. Overall product/procedure-related adverse events were transient and of low grade, comparable with those reported previously in this population [9,13,33]. No severe or serious adverse event was associated with PLA. While most subcutaneous noninflammatory injection-site nodules resolved spontaneously during the study, there were several late-onset nodules. Histological examination of these nodules was not undertaken. At week 48, the incidence of injection site nodules was 10%, although incidences ranging from 0 to 52% have been reported in previous studies [9,11–16,18,33]. Incidences were higher in early studies where PLA injection volumes were 3–4 mL [9,15,33]. Less concentrated solutions have lower viscosity and so promote more even PLA dispersal and reduced nodule formation [34], as demonstrated here and in other recent studies [12,14,16]. Differences in nodule incidence may also reflect differences in study design. In the current study, clinicians actively sought and palpated for nodules/papules, while others may have relied solely on patient report. Nodule onset times were consistent with those reported previously [13,35]; however, data on nodule duration are incomplete as many remained ongoing at study closure [9,13,17,33].

This study has its limitations. Most participants were white men, a reflection of the Australian HIV epidemic. The absence of a control group after week 24 means that we cannot confirm that the increases in facial soft tissue thickness and volume were exclusively attributable to PLA treatment and not to generalized improvements in lipoatrophy *per se*. However, this is unlikely as tissue thickness at the untreated orbit level, which did not increase over the study period, served as a control. There is no information describing normal FSTV in men, and hence we are unable to assess to what extent facial volume approached normality. However, overall our results suggest that FSTV is not an ideal measure.

In conclusion, this multicentre, open-label study of PLA treatment is the first to demonstrate objectively assessed clinically modest increases in facial volume and soft tissue thickness that were sustained over 48 weeks in injection planes but not in other facial areas. Patient-perceived benefits included aesthetic improvement and enhanced

social functioning and QoL; however, psychological benefits were greater in those treated at baseline. The cost of soft tissue augmentation is substantial as third-party providers contribute minimally. It is encouraging to know that treatment delays, necessitated on financial grounds, would not be expected to impact outcomes adversely. The optimal treatment approach for HIV facial lipoatrophy is currently unknown. Research to define and compare the most efficacious filling agents for this distressing condition will require use of validated diagnostic criteria and/or tools to assess lipoatrophy severity and validated measures of facial soft tissue thickness or volume.

Acknowledgements

We thank all participants for their time and commitment. The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government Department of Health and Ageing and affiliated with the Faculty of Medicine, The University of New South Wales, Sydney, Australia. Financial support for this work was received from Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Merck Sharp & Dohme, Roche Products, AIDS Council of New South Wales, and New South Wales Department of Health. Study treatment was provided by Sanofi-Aventis.

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Appendix A

Study investigators

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