



NATIONAL CENTRE IN HIV
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AN ANALYSIS OF THE CORRELATION BETWEEN THE SEVERITY OF INJECTION SITE REACTIONS AND THE AMOUNT OF SUBCUTANEOUS FAT IN THE ALLIANCE COHORT

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Introduction

The unique mode of action of enfuvirtide (ENF; FUZEON[®], formerly T-20), the only approved HIV-1 fusion inhibitor, means that it is effective against HIV that has developed resistance to all other classes of approved antiretrovirals.¹ It therefore offers a valuable alternative treatment option for patients harbouring drug-resistant virus. Two large Phase III studies (TORO 1 and TORO 2) showed that ENF (90 mg *bid* subcutaneously) added to an optimized background antiretroviral regimen significantly improved virologic response, increased the time to virologic failure, and increased CD4 count in extensively pretreated, HIV-1-infected individuals compared with an optimized background regimen alone over 48 weeks.^{2–4} The safety and efficacy of ENF have been shown to be durable out to 96 weeks.⁵

ENF is the only approved antiretroviral medication that is administered by subcutaneous injection. Injection site reactions (ISRs) were the most common adverse events reported in the Phase III trials over 48 weeks, occurring in 98% of patients using ENF.⁶ Most reactions were mild and did not limit the activities of daily living, and only 4.4% of patients discontinued treatment because of ISRs over 48 weeks.⁴ Most patients were satisfied with the ease of injection of ENF, and acceptance of self-injection was not associated with baseline clinical characteristics such as height, weight or body mass index.⁷

Manifestations of a reaction may include pain and discomfort, induration, erythema, nodules and cysts, pruritus and ecchymosis.⁶ However, the aetiology of these reactions is unknown and observations have been reported from biopsy studies which differed in design and implementation, studying ISRs in those starting ENF, or those with long-term use.^{8–10}

Objective

To assess whether the severity of ISRs to ENF administration among patients in the ALLIANCE trial was correlated with the amount of subcutaneous fat measured in patients at baseline.

Methods

- The ALLIANCE trial (ML16992) is a 48-week, single-arm, open-label, multicentre study designed to assess the safety and efficacy of switching patients with current or historical treatment-limiting toxicities attributed to NRTI therapy to a new combination regimen of antiretroviral therapy containing ENF and excluding NRTIs. A total of 59 HIV-1-infected, triple-class-experienced, ENF-naïve patients were enrolled. Patients received ENF 90 mg *bid* subcutaneously together with an optimized NRTI-sparing background regimen. Further study details and primary 48-week results are described elsewhere.¹¹
- Limb fat was assessed at baseline and at weeks 24 and 48 by a dual energy X-ray absorptiometry (DEXA) scan.
- ISRs were assessed at every study visit (weeks 2, 4, 8, 12, 24, 36 and 48) using standardized questions. ISRs were graded for severity from 1 to 4, with grade 4 being the most severe.
- The time trend for proportion of people with ISRs was assessed by generalized estimating equation modelling, accounting for repeated measures within individuals.
- The associations between ISRs (any reaction [defined as any sign/symptom \geq grade 1], grade 2–4 reactions and grade 3/4 reactions) over 48 weeks, and baseline limb fat mass (categorized as tertiles: < 2.70 kg, 2.70–4.29 kg or \geq 4.30 kg) were assessed by generalized estimating equation modelling, accounting for repeated measures within individuals. Data points where baseline limb fat mass or ISR data were missing were excluded.
- The relationship between limb fat percent (categorized as tertiles: < 10.5%, 10.5–16.5% or > 16.5%) and ISRs was tested by logistical regression at weeks 24 and 48.

Results

- The baseline characteristics of the 59 patients enrolled in the ALLIANCE study are shown in Table 1.
- Fifty-two patients (88%) remained on ENF at week 48. Two patients (3.4%) discontinued for hypersensitivity to ENF. Other reasons for discontinuation were loss to follow-up (one patient), withdrawal of consent (one patient), treatment failure (one patient) and death from disease progression (two patients).

Table 1. Patient baseline characteristics (n = 59)

Age (mean \pm SD, years)	46.8 \pm 8.8
Male, n (%)	57 (97)
Caucasian, n (%)	56 (95)
CDC classification C, n (%)	35 (59)
HIV RNA (median [range], log ₁₀ copies/ml)	4.8 (1.7–5.9)
CD4 cell count (median [range], cells/mm ³)	158 (2–1150)
Duration of prior antiretrovirals (median [range], years)	8.7 (5.1–12.7)
Number of prior antiretrovirals (median)	13
NRTI toxicities ^a (current or previous), n (%)	
Lipodystrophy	39 (66)
Peripheral neuropathy	20 (34)
Anaemia/neutropenia	12 (20)
Others	53 (90)

^a some patients reported more than one treatment-limiting toxicity

Limb fat measurements

- Results of the body composition DEXA scans conducted at baseline are presented in Table 2.
- The median peripheral (total limb) fat mass at baseline was 3.38 kg (range 0.58–13.25 kg) and the median percentage of limb fat tissue was 12.89% (range 2.7–34.8%). These values fall close to the midpoint of the mid-tertile category identified for each parameter for statistical analysis.
- Significant elevations in total lean and fat mass were observed for the trunk, arms and body as a whole at week 48. Similarly, small but significant increases in percentage fat were observed in both central and peripheral body compartments.¹¹
- Patients experienced a significant increase from baseline in both peripheral fat mass and percent over the course of the study. The mean (SD) change from baseline in peripheral fat mass was 74 g (849 g) at week 24 and 381 g (1,239 g) at week 48, while the absolute mean (SD) change from baseline in limb fat percentage was 0.9% (4.8%) at week 24 and 2.6% (6.2%) at week 48.

Table 2. Body composition DEXA scan results (mean [SD]) at baseline (n = 59)

Arm	Fat tissue (%)	14.9 (8.9)
	Fat mass (g)	1,214 (896)
	Lean mass (g)	6,460 (1,317)
Leg	Fat tissue (%)	12.8 (7.6)
	Fat mass (g)	2,807 (2,086)
	Lean mass (g)	17,836 (3,148)
Total limb	Fat tissue (%)	27.7 (15.6)
	Fat mass (g)	4,021 (2,858)
	Lean mass (g)	ND
Trunk	Fat tissue (%)	22.0 (9.6)
	Fat mass (g)	8,433 (5,192)
	Lean mass (g)	27,524 (4,397)
Total body	Fat tissue (%)	18.1 (8.2)
	Fat mass (g)	13,084 (7,967)
	Lean mass (g)	55,356 (8,464)

ND, not determined

Injection site reactions

- ISR data were missing for one patient and one patient reported no ISRs for the entire duration of the study.
- Overall, 98% of patients experienced one or more local ISRs over the course of the study. Between 77% and 96% of patients for whom data are available reported ISRs at each study visit and, overall, 89% of ISR assessments revealed one or more reactions (Table 3).
- The most frequent types of ISR were induration (reported by 61–88% of patients at each study visit), which was generally categorized as 'slight', and erythema (reported by 46–70% of patients at each visit), which were most commonly of a small size (< 25 mm). Pruritus, nodules and cysts, and ecchymosis were less commonly reported reactions.
- At each study visit, the majority of patients who reported ISRs had between one and five reactions evident, and the duration of individual ISRs was most commonly \leq 3 days.

Association between injection site reactions and baseline

- Univariate analysis revealed no significant association between the level of baseline limb fat of study participants (< 2.70 kg, 2.70–4.29 kg or \geq 4.30 kg) and the likelihood of them experiencing one or more ISRs over the course of the study (Table 3).

Table 3. Incidence of ISRs (any grade) over 48 weeks and baseline limb fat mass

Baseline limb fat mass (kg)	Number of assessments	ISR reported (any grade)		OR ^a	95% CI	p-value	p trend
		Yes (%)	No (%)				
< 2.70	127	113 (89%)	14 (11%)				
2.70–4.29	116	107 (92%)	9 (8%)	1.42	0.33–6.04	0.634	
\geq 4.30	132	113 (86%)	19 (14%)	0.77	0.22–2.67	0.683	0.675
Overall	375	333 (89%)	42 (11%)				

OR, odds ratio; CI, confidence interval

^a from generalized estimating equation modelling, accounting for repeated measures within individuals

- There was an overall statistically significant trend towards a higher incidence of more severe ISRs with lower levels of baseline limb fat mass (Table 4 and 5).
- A lower risk of grade 2–4 ISRs during the study was identified in patients who had a limb fat mass of \geq 4.3 kg at baseline (OR 0.35 [95% CI 0.14–0.84], $p = 0.019$; Table 4).
- One in three ISR assessments in patients with low levels (< 2.70 kg) of limb fat at baseline revealed a reaction of grade 3/4 severity, compared with 22% and 16% of assessments in patients with baseline limb fat mass values in the middle and upper tertiles, respectively (Table 5).
- Univariate analysis suggests that patients who had a limb fat mass of \geq 4.3 kg at baseline were significantly less likely to experience grade 3/4 ISRs during the study than patients who had less peripheral fat at baseline (OR 0.40 [95% CI 0.19–0.86], $p = 0.018$; Table 5). This difference remained significant when adjusting for study week (OR 0.38 [95% CI 0.17–0.83], $p = 0.015$).
- Limb fat percent greater than 16.5% was protective against grade 3/4 ISRs at weeks 24 and 48 (OR 0.17, $p = 0.027$ and OR 0.21, $p = 0.031$, respectively).

Table 4. Association between grade 2–4 ISRs over 48 weeks and baseline limb fat mass

Baseline limb fat mass (kg)	Number of assessments	Grade 2–4 ISR reported		OR ^a	Univariate			Adjusted ^b				
		Yes (%)	No (%)		95% CI	p-value	p trend	OR ^a	95% CI	p-value	p trend	
< 2.70	127	105 (83%)	22 (17%)									
2.70–4.29	116	80 (69%)	36 (31%)	0.46	0.18–1.17	0.102		0.46	0.18–1.17	0.104		
\geq 4.30	132	82 (62%)	50 (38%)	0.35	0.14–0.84	0.019	0.019	0.33	0.13–0.81	0.016	0.016	
Overall	375	267 (71%)	108 (29%)									

OR, odds ratio; CI, confidence interval

^a from generalized estimating equation modelling, accounting for repeated measures within individuals;

^b adjusted for visit week

Table 5. Association between grade 3/4 ISRs over 48 weeks and baseline limb fat mass

Baseline limb fat mass (kg)	Number of assessments	Grade 3/4 ISR reported		OR ^a	Univariate			Adjusted ^b				
		Yes (%)	No (%)		95% CI	p-value	p trend	OR ^a	95% CI	p-value	p trend	
< 2.70	127	42 (33%)	85 (67%)									
2.70–4.29	116	26 (22%)	90 (78%)	0.60	0.29–1.25	0.171		0.58	0.27–1.22	0.149		
\geq 4.30	132	21 (16%)	111 (84%)	0.40	0.19–0.86	0.018	0.017	0.38	0.17–0.83	0.015	0.014	
Overall	375	89 (24%)	286 (76%)									

OR, odds ratio; CI, confidence interval

^a from generalized estimating equation modelling, accounting for repeated measures within individuals;

^b adjusted for visit week

Discussion

- Peripheral fat wasting is common among people treated with HAART and can have a significant impact on a patient's quality of life.¹² It is one of a constellation of complications associated with the lipodystrophy syndrome, which was reported as a current or historical treatment-limiting toxicity in two-thirds of our study participants at baseline.
- The initiation of twice-daily injection of ENF did not reduce the level of health-related quality of life experienced by our study participants and one variable – overall health – showed a small but significant improvement at week 48.¹¹ This finding may in part be attributable to the favourable changes in peripheral fat levels seen in patients over the course of the study.
- Although most people experience ISRs to ENF administration, it is likely that several factors influence the incidence and severity of ISRs.
 - Injection technique is particularly important. When initiating treatment with ENF, patients should receive comprehensive training on injection technique, and a range of preparation and administration support materials are available to help patients and their caregivers minimize the chances of ISRs (see www.fuzeon.com).
 - In addition, a number of specific interventions, such as post-injection massage of the injection site,¹³ have been reported to ameliorate these reactions in some patients.
- Recent consensus recommendations include a basic outline of good ENF injection technique and a list of various interventions that may alleviate some of the most common injection-related problems.¹⁴
- Subcutaneous fat in the periphery correlates with subcutaneous fat assessed in the abdomen which may be accompanied by visceral (intra-abdominal) fat accumulation.¹⁵ Therefore, abdominal subcutaneous atrophy can occur with truncal obesity due to visceral abdominal fat accumulation. Reduced ISRs following abdominal injections may reflect improving quantities of subcutaneous fat.
- The most common sites for injection are the abdomen, upper thighs and upper arms, because there is enough subcutaneous fat to allow the patient to pinch enough skin to give the injection correctly. The association seen in our study between total limb fat levels at baseline and severity of ISRs may reflect an increased ability to inject subcutaneously in patients who have a greater amount of peripheral fat. ISRs may be worse when the injection is given deeper than it should be, leading to intramuscular administration, and this is more likely in patients who have a thinner layer of subcutaneous fat tissue.

Conclusion

- In the ALLIANCE trial, 98% of patients experienced one or more local ISRs to ENF administration. Reactions were generally mild and lasted for less than 3 days, and no patient discontinued treatment because of ISRs.
- Over 48 weeks, the likelihood of experiencing a local reaction to ENF injection was similar between patients, regardless of the amount of peripheral subcutaneous fat they had at baseline.
- The severity of ISRs appeared to be lower in patients with greater levels of peripheral fat at baseline.
- Increased peripheral fat at baseline (\geq 4.3 kg) was associated with a decreased incidence of grade 3/4 ISRs in this study group (OR 0.40, $p = 0.017$), and also offered a protective effect against ISRs of grade 2–4 severity (OR 0.35, $p = 0.019$).
- These findings may reflect an increased ability to inject subcutaneously in patients with more peripheral fat.

ALLIANCE Investigators

The ALLIANCE Study Group included Hugo Reé, Jo Murray at AIDS Medical Unit (Queensland [Qld]), David Orth, David Youds at Brunswick St General Practice (Qld), Tony Allworth, Natalie Gerns at Royal Brisbane Hospital (Qld), John Quin, Gary Keogh at Bigge Park Clinic, Liverpool Hospital (New South Wales [NSW]), Dominic Dwyer, Emma Keating, Maggy Piper at Westmead Hospital (NSW), Nicholas Doong, Jeff Hudson at Burwood General Practice (NSW), Andrew Carr, Karen MacRae at St Vincent's Hospital (NSW), Robert Finlayson, Wilma Goodyear at Taylor Square Private Clinic (NSW), Robert McFarlane, Robyn Vale at 407 Doctors (NSW), Cassy Workman, Jacinta Parrem, Vanessa Rees at AIDS Research Initiative (NSW), Mark Kelly, Jega Sarangapani at Albion Street Clinic (NSW), Jonathan Anderson, Julie Patching, Kaye Lowe at Carlton Clinic (Victoria [Vic]), Norm Roth, Helen Wood at Prahran Market Clinic (Vic), Alan Street, Janine Roney at Royal Melbourne Hospital (Vic), Jenny Hoy, Anne Mijch, Janine Roney at The Alfred Hospital (Vic), John Dyer, Mark Boyd, Trish Roberts, Robyn Tanti at Flinders Medical Centre (South Australia), Martyn French, Jo Clemmons, Susie Stewart at Royal Perth Hospital (Western Australia), and Mark Bloch, Rohan Holland, Samantha Miller at Holdsworth House General Practice (NSW), Janaki Amin, Gillian Hales, Sean Emery at University of NSW, John Miller, Roche Australia.

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