Fosamprenavir/ritonavir and Nelfinavir have Comparable Effects on Body Fat Changes in Antiretroviral-naïve Patients: 48-Week Results from the SOLO Study.

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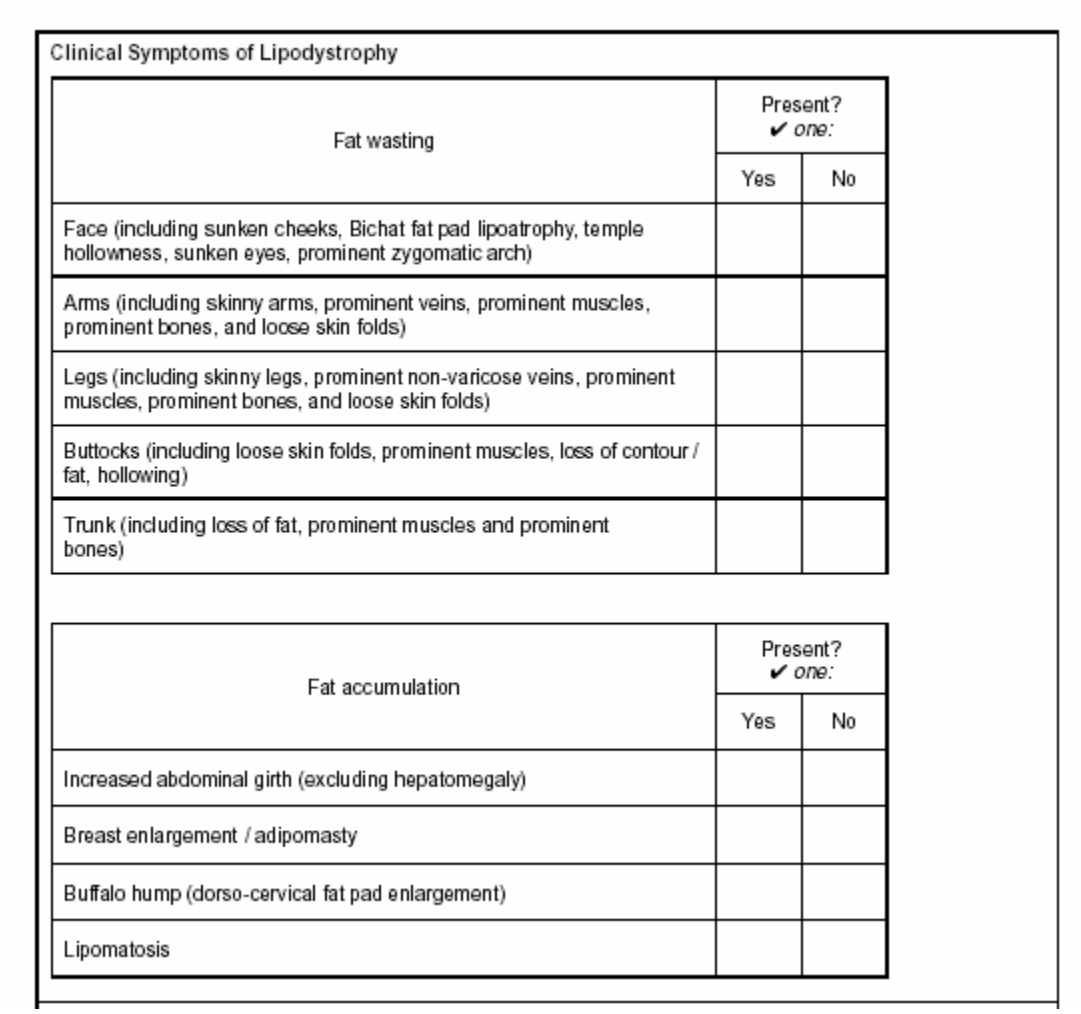
Introduction: Body composition changes are characterized by the selective loss of subcutaneous fat (lipoatrophy) from the face and the extremities, and/or the accumulation of fat around the dorso-cervical area, neck, abdomen and trunk which has been associated with HAART. However, for HIV-1 infected patients naïve to HIV therapy, the symptoms of lipoatrophy may be pre-existent in the extremities and peripheral body areas as an adverse effect of HIV-1 infection itself[1]. To date, minimal prospective data from cohorts or from randomised, comparative trials on the incidence of body composition changes (BCC) have been presented on ART-naïve subjects initiating HAART.

Methods: SOLO was a randomized study in antiretroviral therapy-naïve, HIV-infected adults which compared the efficacy and safety of fosamprenavir/ritonavir once-daily (FPV/r Lexiva ®, Telzir ®; N=322) with Nelfinavir twice-daily (NFV; N=327), each administered with Abacavir/lamivudine. Body composition changes (BCC) were assessed by targeted clinical assessment of symptoms consistent with fat redistribution or BCC. This was evaluated by physician observation using a standardized GSK questionnaire, (as shown in Figure 1) at the Baseline (BL)/Day 1 visit, Week 24, Week 48 and every 16 weeks thereafter until the study was completed.

Figure 1. Sample APV 30002 (SOLO) Lipodystrophy Questionnaire



Clinical Symptoms of Lipodystrophy

Fat wasting	Present? ✔ *one:*	
	Yes	No
Face (including sunken cheeks, Bichat fat pad lipoatrophy, temple hollowness, sunken eyes, prominent zygomatic arch)		
Arms (including skinny arms, prominent veins, prominent muscles, prominent bones, and loose skin folds)		
Legs (including skinny legs, prominent non-varicose veins, prominent muscles, prominent bones, and loose skin folds)		
Buttocks (including loose skin folds, prominent muscles, loss of contour / fat, hollowing)		
Trunk (including loss of fat, prominent muscles and prominent bones)		

Fat accumulation	Present? ✔ *one:*	
	Yes	No
Increased abdominal girth (excluding hepatomegaly)		
Breast enlargement / adipomasty		
Buffalo hump (dorso-cervical fat pad enlargement)		
Lipomatosis		

At BL, detailed information about the subjects' personal (diabetes, tobacco and alcohol intake, exercise habits) ands family history was collected. Blood pressure, weight and waist to hip ratio was also measured at the Baseline visit, Week 24, 48 and every 16 weeks thereafter.

Results:

Table 1. Baseline Characteristics

	FPV/r QD + ABC/3TC N= 322	NFV BID + ABC/3TC N=327
Age (years) Median	**36**	**36**
Sex		
Females, n (%)	**96 (30)**	**78 (24)**
Males, n (%)	**226 (70)**	**249(76)**
Race, n (%)		
White	**163 (51)**	**178 (54)**
Black	**122 (38)**	**109 (33)**
Asian	**5 (2)**	**7 (2)**
American Hispanic	**24 (7)**	**25 (8)**
Other	**8 (2)**	**8 (2)**
Disease Category		
Asymptomatic	**182 (57)**	**172 (53)**
Symptomatic, not AIDS	**73 (23)**	**81 (25)**
AIDS	**67 (21)**	**73 (22)**
Missing	**0**	**1 (<1)**
Median Plasma HIV-1 RNA (Log_{10} copies/mL)	**4.78**	**4.83**
Median CD4+ Count (cells/mm^3)	**166**	**177**

A total of 649 subjects were enrolled from the US, Europe, South Africa and Australia. Demographic characteristics were well matched in the two groups. Overall, median baseline (BL) CD4 was 170 cells/μL and the median HIV-1 RNA was 4.81 $\log_{10}$ copies/mL. The low entry median CD4+ cell counts and the high percentage (21-22%) of subjects with CDC defined AIDS illustrates that the study population was at an advanced disease state at entry. There were no subjects who discontinued the study due to BCC. Overall, approximately 10% of the subjects enrolled changed their backbone NRTI during the study duration due to intolerance.

Figure 2. Incidence of Body Composition Changes reported Based on Questionnaire responses at BL and Week 48 in the two treatment groups

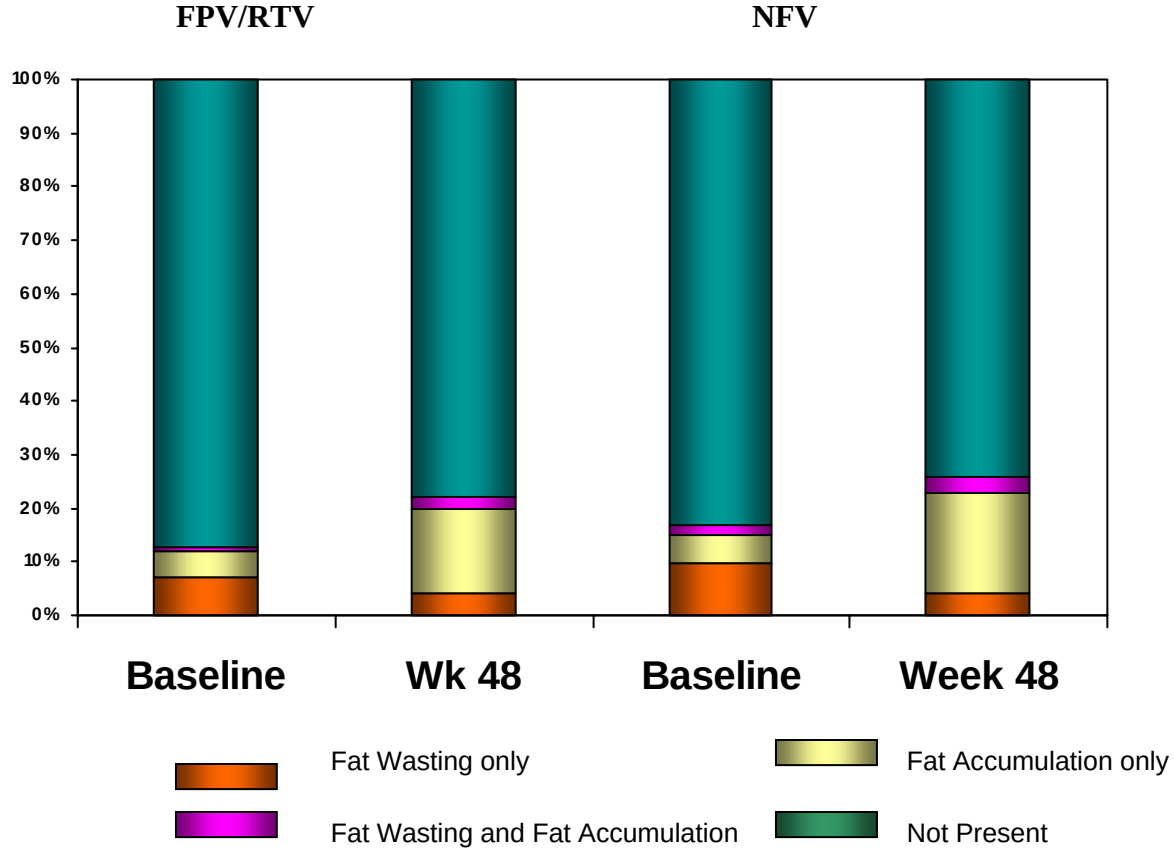


Figure 2 demonstrates the incidence of BCC over the 48 week study period in both arms of study.

40/321 (12%) and 52/325 (16%) of subjects reported at least one BCC at BL in the FPV/r and NFV groups, respectively, with the majority of these subjects reporting fat wasting (25/321 (8%) and 37/325 (11%), respectively. Of note, 14/30 (47%) and 16/35 (46%) of subjects with BCC at BL did not report any BCC at wk 48, in the FPV/r and NFV groups, respectively.

Of subjects who did not report fat wasting at baseline, only 4% (9/215, and 9/232) reported fat wasting at wk 48 in both groups. Of subjects who did not report fat accumulation (FA) at BL, 15% (33/219) and 18% (44/238) reported signs of FA at wk 48 in the FPV/r and NFV groups.

Table 2. Frequency of Specific Clinical Signs and Symptoms of Fat Redistribution APV30002 Safety Population

Clinical Symptoms of Lipodystrophy	908/RTV QD N=322 n (%)	NFV BID N=327 n (%)
Facial wasting:		
Present at Baseline: n	15	26
Absent at Week 48	12 (80)	20 (77)
Absent at Baseline: n	218	247
Present at Week 48	6 (3)	6 (2)
Present at WD	3 (6)	2 (5)
Leg wasting		
Present at Baseline: n	9	18
Absent at Week 48	7 (78)	14 (78)
Absent at Baseline: n	224	255
Present at Week 48	4 (2)	3 (1)
Present at WD	3 (2)	2 (5)
Increased abdominal girth		
Present at Baseline: n	13	18
Absent at Week 48	5 (38)	6 (33)
Absent at Baseline: n	220	255
Present at Week 48	34 (15)	43 (17)
Present at WD	4 (8)	3 (7)
Breast enlargement		
Present at Baseline: n	2	5
Absent at Week 48	0	2 (40)
Absent at Baseline: n	231	268
Present at Week 48	9 (4)	13 (5)
Present at WD	1 (2)	2 (5)
Fat lump on back of neck (buffalo hump)		
Present at Baseline: n	2	1
Absent at Week 48	1 (50)	0
Absent at Baseline: n	231	272
Present at Week 48	3 (1)	3 (1)
Present at WD	0	0
Lipomatosis		
Present at Baseline: n	2	2
Absent at Week 48	1 (50)	1 (50)
Absent at Baseline n	231	271
Present at Week 48	1 (<1)	1 (<1)
Present at WD	0	1 (2)

Of those subjects who reported facial and leg wasting at study entry, a majority of those subjects reported an absence of these symptoms after 48 weeks of therapy.

The median baseline body weight was 69.8kg (FPV/r group) and 69.9kg (NFV group). A median increase in body weight of 3kg at Week 48 was observed in both groups. (Body weight at Week 48: FPV/r median 74.5 kg, IQ range 49.5-136.2 and NFV arm a median 73.7 kg IQ range of 40.5-200).
There was a median increase from BL in hip and waist circumference of 2 cm in the FPV/r group and 3 cm in the NFV group, respectively. Median Waist/hip ratio did not

change over 48 weeks in both study arms (0.0 in both groups). No median changes in systolic (0.0mmHg in both groups) or diastolic blood pressure (0.0mmHg in both groups) were observed. Use of steroids was similar between both the FPV/r (24%) and NFV (23%) containing arms of the study.

Subgroup Analyses

The treatment arms were well balanced with respect to the different symptoms of BCC. Therefore, for the subgroup analyses values for both treatment arms are presented combined.

Analysis by baseline viral load and CD4 cell count

Table 3 Summary of Lipodystrophy by Visit and Baseline Viral Load (both treatment groups combined)

Assessment	Lipodystrophy Symptom	<=10,000 copies/ml	>10,000 - <=100,000 copies/ml	>100,000 copies/ml
Baseline	Any	4/63 (6%)	24/327 (7%)	64/256 (25%)
	Fat Wasting	1/63 (2%)	10/327 (3%)	51/256 (20%)
	Fat Accumulation	3/63 (5%)	16/327 (5%)	18/256 (7%)
	None	59/63 (94%)	303/327 (93%)	192/256 (75%)
Week 24	Any	7/55 (13%)	32/282 (11%)	52/215 (24%)
	Fat Wasting	2/55 (4%)	9/282 (3%)	19/215 (9%)
	Fat Accumulation	3/55 (5%)	27/282 (10%)	37/215 (17%)
	None	48/55 (87%)	250/282 (89%)	163/215 (76%)
Week 48	Any	11/47 (23%)	48/253 (19%)	57/188 (30%)
	Fat Wasting	4/47(9%)	13/253 (5%)	13/188 (7%)
	Fat Accumulation	9/47 (19%)	41/253 (16%)	47/188 (25%)
	None	36/47 (77%)	205/253 (81%)	131/188 (70%)

Please note that percentages may not add up to 100 as some subjects reported both fat wasting and fat accumulation

At baseline the >100,000 group has a higher proportion of subjects reporting fat wasting. In the <=10,000 and >10,000-<=100,000 groups the proportion of subjects reporting fat wasting remains fairly stable throughout the study. However, the proportion of subjects in the >100,000 reporting fat wasting decreases at Week 24 and then again at Week 48 to a rate comparable with the other two arms. The proportion of subjects reporting fat accumulation increases over time in all three groups with a slightly higher proportion in the >100,000 group at both Week 24 and Week 48.

Table 4 Summary of Lipodystrophy by Visit and Baseline CD4 Cell Count (both treatment groups combined)

Assessment	Lipodystrophy Symptom	<200 cells/mm3	>=200 cell/mm3
Baseline	Any	67/357 (19%)	25/284 (9%)
	Fat Wasting	51/357 (14%)	11/284 (4%)

	Fat Accumulation	22/357 (6%)	15/284 (5%)
	None	290/357 (81%)	259/284 (91%)
Week 24	Any	57/305 (19%)	33/243 (14%)
	Fat Wasting	20/305 (7%)	10/243 (4%)
	Fat Accumulation	43/305 (14%)	27/243 (11%)
	None	248/305 (81%)	210/243 (86%)
Week 48	Any	72/265 (27%)	43/220 (20%)
	Fat Wasting	16/265 (6%)	14/220 (6%)
	Fat Accumulation	61/265 (23%)	35/220 (16%)
	None	193/265 (73%)	177/220 (80%)

Please note that percentages may not add up to 100 as some subjects reported both fat wasting and fat accumulation

At baseline the <200 group has a higher proportion of subjects reporting fat wasting but at both Week 24 and Week 48 the proportion of fat wasting is similar between the two groups. At week 48 the proportion of fat accumulation is now slightly higher in the <200 group, although both groups showed an increase in the proportion of fat accumulation over time.

Analysis by Gender

Table 3 Summary of Lipodystrophy by Visit and Gender (both treatment groups combined)

Assessment	Lipodystrophy Symptom	Females	Males
Baseline	Any	22/173 (13%)	70/473 (15%)
	Fat Wasting	13/173 (8%)	49/473 (10%)
	Fat Accumulation	11/173 (6%)	26/473 (5%)
	None	151/173 (87%)	403/473 (85%)
Week 48	Any	47/133 (35%)	69/355 (19%)
	Fat Wasting	7/133 (5%)	23/355 (6%)
	Fat Accumulation	43/133 (32%)	54/355 (15%)
	None	86/133 (65%)	286/355 (81%)

Please note that percentages may not add up to 100 as some subjects reported both fat wasting and fat accumulation

At Wk 48 the proportions of fat wasting were low and similar between the males and females. However, at Wk 48, 32% (43/133) of females reported fat accumulation compared to 15% (54/355) of males.

Analysis by Race

Table 4 Summary of Lipodystrophy by Visit and Ethnic Origin (both treatment groups combined)

Assessment	Lipodystrophy Symptom	Black	White	Other*
Baseline	Any	34/229 (15%)	51/340 (15%)	7/77 (9%)
	Fat Wasting	21/229(9%)	36/340 (11%)	5/77 (6%)
	Fat Accumulation	16/229 (7%)	18/340 (5%)	3/77 (4%)
	None	195/229 (85%)	289/340 (85%)	70/77 (81%)
Week 48	Any	55/180 (31%)	51/251 (20%)	10/57 (18%)
	Fat Wasting	9/180 (5%)	21/251 (8%)	0
	Fat Accumulation	49/180 (27%)	38/251 (15%)	10/57 (18%)
	None	125/180 (69%)	200/251 (80%)	47/57 (82%)

*Other includes Asian, American Hispanic and Other
Please note that percentages may not add up to 100 as some subjects reported both fat wasting and fat accumulation

At Week 48 the proportion of subjects reported fat wasting was low and similar between the different ethnic groups. All groups reported an increase in fat accumulation over time and at Week 48 the proportion of black subjects reporting fat accumulation was greater than the other groups.

Discussion

- These are the first prospective BCC data from a controlled clinical trial for FPV/r. Of note, in this therapy naïve population, FPV/r and NFV were combined with the ABC/3TC backbone.
- Overall, a low rate of fat wasting was observed over 48 weeks, comparable in both arms.
- No differences in rates of BCC were detected when the two arms were pooled and the incidence of fat wasting was analyzed by baseline viral load, baseline CD4 cell count and gender or race
- Both low baseline CD4 cell count and high viral load was associated with higher proportion of subjects reporting fat wasting at baseline.
- The proportion of subjects in both the >100,000 group and the CD4 cell count <200cells/mm3 group who reported fat wasting decreased at Week 24 and then again at Week 48
- Upon analysis of the incidence of fat accumulation by gender, there was a notable trend of increased incidence in females by Week 48[3]
- An increase in body weight combined with no change in waist/hip ratio was observed in both groups
- The use of ABC/3TC as a background NRTIs as first line regimen may have substantially contributed to the low number of reported fat wasting signs and symptoms.
- A continuous low rate of fat wasting has been demonstrated over a 120 week period of FPV/r treatment[2] (see abstract No L787).

Conclusion

- When combined with the ABC/3TC backbone, both the FPV/RTV and the NFV containing arms had comparable effects in BCC over the 48 week study duration with a low incidence of fat wasting in both arms
- Decreases in the proportion of fat wasting over time were observed in subjects with advanced HIV disease (viral load >100,000 or CD4 cell count <200cells/mm3) who initiated a first line therapy with ABC/3TC plus FPV/r or NFV
- Females had an increased incidence of fat accumulation over 48 weeks of the study
- There were no effects of race or gender seen on the incidence of fat wasting.
- Overall, these data of incidence of and changes in BCC over time may be attributed to a general overall improvement in health and nutrition in response to treatment of the HIV disease state and a potential reversal of HIV associated changes in these therapy naïve patients.

References

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