Effects of Liraglutide, a Glucagon-Like Peptide-1 Analogue, on Metabolic Abnormalities and Body Weight in HIV-infected Subjects with or without Type 2 Diabetes

Ramesh Saeedi[1], Parisa Dabirvaziri[2], Negar Fouladi Nashta[3], Masoud Yousefi[4], Silvia Guillemi[3,5], Julio Montaner[3,4], Jiri Frohlich[1,2], Marianne Harris[3,4], and Greg Bondy[1,2,3,4,*]

[1]Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
[2]Healthy Heart Program Prevention Clinic, St. Paul's Hospital, Vancouver, BC, Canada
[3]AIDS Research Program, Providence Health Care Institute, Vancouver, BC, Canada
[4]Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[5]Department of Family Practice, University of British Columbia, Vancouver, BC Canada

*Corresponding author: Gregory Bondy, MD, FRCPC, B180- 1081 Burrard Street, Vancouver, BC, V6Z 1Y6, Canada, Tel: 604-806-8192; Fax: 604-806-8590; E-mail: gbondy@provedencehealth.bc.ca

Abstract

Objectives: To evaluate the effects of six-month liraglutide treatment on antiretroviral therapy (ART)-induced HIV-associated lipodystrophic syndrome (HALS) including diabetes mellitus (DM), lipodystrophy, and dyslipidemia in HIV-infected subjects with and DM.

Methods: We performed a retrospective case-control study in which medical records of lipodystrophic HIV-infected subjects and HIV-uninfected obese subjects with or without DM who were treated with liraglutide for 6 months were analyzed. A group of HIV-uninfected obese subjects served as controls. Subjects were separated into 4 groups: lipodystrophic HIV-infected subjects without DM (HIV-DM) (N=30), lipodystrophic HIV-infected subjects with DM (HIV+DM) (N=32), obese subjects without DM (obese-DM) (N=32), and obese subjects with DM (obese+DM) (N=53). Changes in body weight, blood pressure (BP), and glucose and lipid profiles were investigated over 6 months of liraglutide treatment.

Results: Body weights were significantly reduced in all groups except HIV–DM. Glucose profile mainly improved in the obese+DM group. Liraglutide treatment of HIV–DM subjects tended to decrease low density lipoprotein cholesterol (LDL-C) and total cholesterol/ high density lipoprotein cholesterol (TC/HDL-C). In HIV+DM subjects, there was a tendency to lower BP, TC, and non-HDL-C in response to liraglutide. In obese-DM subjects, liraglutide tended to lower TC/HDL, triglyceride (TG), logTG/HDL, non-HDL-C and LDL-C. In obese-DM subjects, fasting blood glucose (FBG) and TC were significantly reduced. In obese+DM subjects, liraglutide treatment tended to lower BP, non-HDL-C, FBG, and logTG/HDL-C.

Conclusions: Six months of liraglutide treatment of HIV-infected subjects resulted in weight loss, which was statistically significant only in subjects with diabetes; it also improved several metabolic abnormalities associated with HALS.

Keywords: GLP-1 analogue; HIV; Diabetes; Body weight; Metabolic abnormalities

Abbreviations

ApoB: Apolipoprotein B; ART: Antiretroviral Therapy; BMI: Body Mass Index; BP: Blood Pressure; DM: Diabetes Mellitus; FBG: Fasting Blood Glucose; GLP-1: Glucagon-like Peptide-1; HbA1c: Glycated Haemoglobin; HDL-C: High Density Lipoprotein Cholesterol; HALS: HIV-Associated Lipodystrophic Syndrome; HIV: Human Immunodeficiency Virus; IDC: Immunodeficiency Clinic; LDL-C: Low Density Lipoprotein Cholesterol; TC: Total Cholesterol; TG: Triglyceride.

Introduction

The widespread use of antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection has prolonged survival of HIV-infected patients [1]. However, use of ART has been associated with development of HIV-associated lipodystrophic syndrome (HALS), characterized by several metabolic abnormalities including lipodystrophy (body fat redistribution), insulin resistance, diabetes mellitus (DM), and dyslipidemia; all are major risk factors for an increase in incidence of cardiovascular disease [2,3]. For the majority of the patients, these changes in body composition have adversely affected their quality of life, led to low self-esteem, and caused poor medication adherence [4]. Furthermore, HALS-associated metabolic changes may increase the risk of cardiovascular disease [2,3]. Medical therapies, such as recombinant growth hormone releasing factor analogues and metformin, have modest effects on body composition in HIV-infected subjects and/ or have significant metabolic side-effects [5,6].

Liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, has 97% homology to the peptide hormone secreted in the lower part of small intestine which stimulates glucose-dependent endogenous insulin secretion, reduces glucagon secretion, and promotes weight loss by increasing satiety [7,8]. It was initially developed for the treatment of DM. In addition to its blood glucose lowering properties, it also promotes weight loss, reduces subcutaneous fat, reduces systolic blood pressure (sBP) and improves cardiovascular risk profile in patients with and without DM [9-12]. In a case report of a patient with HIV-associated type 2 diabetes, liraglutide use improved glycemic control and lipodystrophy [13]. In this retrospective case- control study, we assessed the effect of 6 months liraglutide treatment on metabolic abnormalities and body weight in lipodystrophic HIV-infected patients with or without diabetes.

Methods

This retrospective case-control study was carried out in lipodystrophic HIV-infected subjects seen at the Immunodeficiency Clinic (IDC)- HIV metabolic Clinic at St. Paul's Hospital, Vancouver, BC, Canada. A group of HIV-negative obese subjects recruited from Healthy Heart Prevention Clinic at St. Paul's Hospital, Vancouver, BC, Canada served as controls. Obesity was defined as body mass index (BMI ≥ 30 kg/m^2). We performed chart review including demographic, clinical, and laboratory data of all patients who were prescribed liraglutide between January 2010 and December 2013. Patients were classified into 4 groups: lipodystrophic HIV-infected subjects without DM (HIV-DM), lipodystrophic HIV-infected subjects with DM (HIV+DM), 32 non-DM obese subjects (obese-DM), and 53 DM obese subjects (obese+DM). All patients initially started liraglutide, 0.6 mg once daily for a week, by subcutaneous injection. Then the dose was increased to 1.2 mg once daily and maintained for 6 months. The primary outcome measure was change in body weight at the end of the study. Secondary endpoints were changes in fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein B (ApoB), non HDL-C, log(TG/HDL-C), TC/HDL-C, and sBP after 6 months of liraglutide therapy. The protocol and informed consent were approved by the institutional Ethics Board.

Statistical analysis

Data were expressed as mean ± standard deviation (M ± SD), after checking the normality of the variables' distributions unpaired t-tests or Mann-Whitney tests were used to determine the differences in patient characteristics between HIV-infected and uninfected subjects. Bonferroni's correction applied to avoid the multiple comparison error and p value less than 0.001 was considered to be statistically significant. All statistical calculations were performed with SPSS software package.

Results

Patient demographics and baseline characteristics

Baseline characteristics of the study population are summarized in Tables 1 and 2. At baseline, subjects with HIV+DM had significantly higher FBG, HgA1c, and log (TG/HDL-C) as compared to HIV-DM subjects. In the HIV+DM group, TG tended to be higher and LDL-C tended to be lower than the HIV-DM group.

Among HIV-negative obese patients, subjects with DM were older than non-DM subjects, had significantly higher FBG and HgA1c as compared to non-DM subjects. When compared to obese-DM subjects, Obese+DM subjects had significantly lower LDL-C. Also there TC and HDL-C tended to be lower in Obese+DM than obese+DM subjects.

Overall, HIV-infected subjects and HIV-uninfected subjects with DM were more likely to receive metformin as compared to their counterparts without DM. Obese+DM subjects were more likely to receive combination therapy for DM than HIV+DM (64% vs. 26%). More DM subjects with and without HIV were on lipid lowering medications compared to their non-DM counterparts.

All, except one with and one without DM, HIV-infected subjects were receiving ART. All patients receiving ART had undetectable HIV-RNA (<40 copies/ml) (Table 3). The HIV-DM subjects were more likely to be receiving a protease inhibitors containing HAART as compared to those with DM (96% vs. 68%). There was no significant differences in CD4 counts among HIV(+) subjects with and without DM.

Effects of liraglutide on body weight and metabolic parameters

Table 4 shows the effect of 6 months of treatment with 1.2 mg of liraglutide on body weight, sBP, glycemic control, and lipid profile. Liraglutide treatment resulted in significant weight loss in obese subjects with and without DM as well as in HIV+DM subjects. In addition, there was a trend in reduction in weight in HIV-DM subjects. The treatment showed a trend to lower sBP only in DM patients with and without HIV. It had no effect on diastolic BP (dBP) in any group.

Liraglutide treatment showed a tendency to improve glycemic control only in patients without HIV. Treatment of HIV-DM subjects with liraglutide tended to decrease LDL-C and TC/HDL-C. In HIV+DM, liraglutide tended to decrease TC and non-HDL-C. In the obese-DM group, while TC was significantly reduced, there were lower LDL-C, non-HDL-C, TG, TC/HDL-C, and Log (TG/HDL-C) trend in response to liraglutide. Liraglutide treatment of the obese+DM subjects tended to lower non-HDL-C and log (TG/HDL-C).

Comparison between HIV-infected subjects and HIV-uninfected subjects

When all HIV-infected subjects were compared to non-infected controls, liraglutide tended to reduce HgA1c and FBG only in controls. However, there were no other differences between weight, lipid profile, or BP among HIV-infected and control groups (data not shown).

Discussion

HALS is observed frequently among HIV-infected patients [2,3]. Changes in body fat redistribution in HIV-infected subjects include regional lipohypertrophy and lipoatrophy [2,3]. Metabolic changes including insulin resistance, DM, dyslipidemia characterized by elevated LDL-C and TG and decreased HDL-, may be a consequence of changes in body fat redistribution [2,3]. In this retrospective case-control study, we found that six months treatment with 1.2 mg of liraglutide of lipodystrophic HIV-infected subjects with and without DM resulted in reduction of body weight, which was significant only in those with DM; it also improved several metabolic parameters. To our knowledge, this is the first report showing liraglutide effect on metabolic parameters as well as body weight changes in HIV-infected subjects with and without DM.

A major finding of the present study was the effect of liraglutide on body weight of lipodystrophic HIV–infected subjects. Six months of liraglutide treatment of HIV+DM resulted in a significant weight loss by mean of 4.4 kg (Table 4). In HIV- DM group, it also led to a modest but not significant, reduction in body weight (mean reduction of 2.4 kg). This difference may be due to a number of factors such as type of ART (96% of the HIV-DM subject received a protease inhibitor-containing ART, vs 68% in the HIV+DM), duration of HIV, or use of other medications. In our study, 65% of HIV+DM vs. 30% of HIV-DM were on metformin. Metformin is known to cause weight loss in patients with and without diabetes. Metformin may have an additional benefit when combined with liraglutide, as previously shown in non-HIV-infected patients with DM [7].

Liraglutide treatment of obese+DM subjects led to a significant reduction in body weight (mean reduction of 4.0 kg), consistent with other studies [14]. It also resulted in significant weight loss (mean reduction of 7.3 kg) in obese-DM group. This finding is higher than is reported in the literature [10]. This discrepancy may be due to the difference in life style, use of metformin and other hypoglycemic agents (21% of our subjects were taking metformin), duration or dose of liraglutide, study design, or other factors. Interestingly, as shown in the Tables 1 and 4, even though 54% of obese+DM subjects and 21% of obese-DM were on metformin, the weight loss effect of liraglutide seems to be more in obese- DM than those obese+DM. The reason for this might be due to other factors such as changes in life style, concomitant use of other antiglycemic agents in obese+DM group, or other unknown factors.

	HIV-DM	HIV+ DM	Obese-DM	Obese+DM
Men/women	28/2	29/3	21-Nov	30/23
Age (years)	54 (5.8)	56 (8.2)	49 (11.6)	58 (9.2)
Body weight (Kg)	100.3 (20.7)	97.6 (12.1)	106.5 (27.1)	102.6 (20.2)
sBP (mmHg)	125.0 (16.0)	126.2 (13.6)	126.7 (14.7)	128 (14.7)
dBP (mmHg)	78.8 (10.4)	75.6 (8.6)	79.4 (10.9)	75.1 (8.9)
Smoking				
Non-smoker	11 (36%)	14 (43%)	17 (53%)	29 (54%)
Ex-smoker	12 (40%)	12 (37%)	12 (37%)	16 (30%)
Current smoker	7 (23%)	6 (18%)	2 (6%)	6 (11%)
Exercise				
Sedentary	10 (33%)	10 (31%)	10 (31%)	24 (45%)
1-3X per week	12 (40%)	12 (37%)	10 (31%)	19 (35%)
≥ 4X per week	8 (26%)	10 (31%)	12 (37%)	10 (18%)
Prestudy antidiabetic treatment				
Monotherapy				
Metformin	9 (30%)	21 (65%)	7 (21%)	29 (54%)
Sulfonylurea	0 (0%)	7 (21%)	0 (0%)	16 (30%)
Thiazolodinedions	0 (0%)	2 (6%)	0 (0%)	8 (15%)
Insulin	0 (0%)	5 (15%)	0 (0%)	9 (16%)
DPP-4	0 (0%)	3(9%)	0 (0%)	13 (24%)
Combination therapy	0 (0%)	18 (26%)	0 (0%)	34 (64%)
Prestudy antihypertensive treatment	11 (36%)	19(59%)	14 (43%)	40 (75%)
Prestudy lipid lowering medication				
Monotherapy				
Statin	10 (33%)	22 (68%)	15 (46%)	35 (66%)
Fibrate	1 (3%)	5 (15%)	1 (3%)	10 (18%)
Ezetrol	1 (3%)	5 (15%)	3 (9%)	11 (20%)
Combination therapy	1 (3%)	9 (28%)	2 (6%)	11 (20%)
Others	9 (3%)	10 (31%)	8 (25%)	17 (32%)

Table 1: Baseline characteristics of the studied population

Data are mean (SD) or n, unless otherwise noted. Others; include antipsychotic medication, thyroid medication

As we shown in the Table 1, the percentages of subjects in HIV+ DM using metformin are 35% more than HIV-DM. However, there is also 33% difference in non-HIV control groups on metformin, and the weight loss effect of liraglutide seems to be more in both non-HIV control groups than in HIV groups. We speculate that such differences in HIV and non-HIV subjects may be due to HIV infection itself, type of ART, use of other medications, or other unknown factors.

Liraglutide has been shown to improve glycemic control in patients with DM which is consistent with our finding [9,12-16]. In our study there was a 0.5% statistically significant reduction in HgA1c in obese+DM subjects. Interestingly, liraglutide treatment of HIV+DM did not improve their glycemic control, possibly due to effects of other medications such as ART, HIV infection, higher insulin resistance, or lower concomitant use of other antidiabetic agents (26% of HIV+DM subjects were on combination antidiabetic drugs while 64% of obese-DM subjects were on combination treatment). In addition, due to the retrospective nature of our study, we did not have HbA1c measurements in all subjects.

In this study, liraglutide treatment showed a trend to lower sBP in both DM groups. The effect of liraglutide on BP is not consistent with some studies showing improvement [12-17] and others showing no effect [8]. We can speculate that the reduced sBP may be, at least in part, related to weight loss since HIV infected and non-infected subjects with DM lost more weight.

In addition to the beneficial effects on body weight, liraglutide appears to significantly lower certain lipid parameters such as TC, LDL-C, and TG [18]. In the current study, we found that in obese+DM subjects, liraglutide treatment tended to lower non-HDL-C, and log (TG/HDL-C). It also had a beneficial effect on lipid profile in obese-DM subjects with a significant reduction in TC and tendency to lower LDL-C, non-HDL-C, TG, TC/HDL-C, and log (TG/HDL-C). The differences between our study and others may be due to the dose and duration of treatment with liraglutide, concomitant use of other lipid-lowering medication, or changes in lifestyle. In HIV-infected patients, there was a trend in improvement in some of the lipid parameters including TC and non-HDL-C in HIV+DM group

	HIV-DM	HIV+ DM	Obese-DM	Obese+DM
FBG (mmol/L)	5.8 (1.2)	7.8 (2.5)*	5.7 (0.8)	9.0 (2.8)*
	N=25	N=30	N=32	N=49
HgA1c	5.7 (0.5)	7.2 (1.2)*	6.1 (0.5)	7.7 (1.2)*
	N=14	N=25	N=15	N=50
TC (mmol/L)	4.6 (1.3)	4.6 (1.2)	5.2 (1.1)	4.6 (1.16)$
	N=29	N=32	N=32	N=53
HDL-C (mmol/L)	1.2 (0.5)	1.0 (0.3)	1.2 (0.4)	1.05 (0.27)$
	N=29	N=32	N=32	N=53
Non-HDL-C (mmol/L)	3.3 (1.5)	3.6 (1.3)	4.0 (1.0)	3.56 (1.15)
	N=28	N=32	N=32	N=53
LDL-C (mmol/L)	2.6 (0.9)	2.1 (0.8)$	3.0 (1.0)	2.34 (1.1)*
	N=25	N=23	N=26	N=44
TG (mmol/L)	2.4 (1.9)	4.7 (5.5)$	2.6 (2.0)	3.3 (2.8)
	N=26	N=30	N=32	N=53
TC/HDL-C	4.3 (1.1)	5.3 (3.2)	4.5 (1.5)	4.4 (1.3)
	N=29	N=32	N=32	N=53
apo(B) (g/L)	1.0 (0.3)	0.8 (0.2)	1.0 (0.2)	0.89 (0.16)
	N=8	N=11	N=11	N=11
log(TG/HDL-C)	0.2 (0.3)	0.5 (0.4)*	0.2 (0.4)	0.41 (0.34)
	N=26	N=30	N=32	N=52

Table 2: Baseline Lipid Profiles

Data are mean (SD).

$p<0.05 as compared to its counterpart; *p<0.001 as compared to its counterpart

	HIV-DM	HIV+DM
CD4 lymphocyte count (cells/mm³)	610.4 (268.5)	591.9 (246.7)
	N=24	N=21
Viral load	46.7 (8.3)	40.8 (3.9)
	N=23	N=21
Prestudy ART treatment		
PI	29 (96%)	22 (68%)
Raltagravir	9 (30%)	10 (31%)
NRTI	27 (90%)	24 (75%)
NNRTI	9 (30%)	13 (40%)
None	1 (3%)	1 (3%)

Table 3: Baseline characteristics of ART

Data are mean (SD) or n (%).

	HIV-DM	HIV+ DM	Obese-DM	Obese+DM
Weight loss (Kg)				
N	30	32	31	51
Mean change (SD)	-2.4 (12.5)	-4.4 (6.0)	-7.3 (10.5)	-4.0 (5.3)
95% CI	2.3 to 7.1	2.2 to 6.6	3.4 to 11.1	2.4 to 5.4
p value	0.3	p<0.001	p<0.001	p<0.001
sBP (mmHg)				
N	23	27	14	24
Mean change (SD)	-2.2 (15.6)	-5.6 (13.8)	-7 (13.2)	-8.8 (17.6)
95% CI	-4.5 to 8.9	0.2 to 11.1	-0.6 to 14.6	1.3 to 16.2
p value	0.5	p<0.05	0.7	p<0.05
dBP (mmHg)				
N	23	27	14	24
Mean change (SD)	-3.09 (10.3)	-0.5 (8.3)	-0.4 (12.6)	-1.2 (0.9)
95% CI	-1.4 to 7.5	-2.7 to 3.8	-7.1 to 8.0	-2.7 to 5.1
p value	0.17	0.7	0.9	0.53

FBG (mmol/L)				
N	22	25	31	48
Mean change (SD)	-0.3 (0.9)	-0.03 (2.48)	-0.5 (0.5)	-1.1 (2.9)
95% CI	-0.1 to 0.6	-1 to 1.06	0.2 to 0.6	0.3 to 1.2.0
p value	0.17	0.95	p<0.001	p<0.05
HgA1c				
N	6	22	15	47
Mean change (SD)	-0.05 (0.3)	-0.1 (0.6)	-0.3 (0.4)	-0.5 (0.9)
95% CI	-0.2 to 0.3	-0.2 to 0.4	0.1 to 0.6	0.2 to 0.8
p value	0.7	0.45	0.004	p<0.001
TC (mmol/L)				
N	29	31	31	51
Mean change (SD)	-0.04 (1.06)	-0.3 (0.9)	-0.5 (0.7)	-0.6 (2.5)
95% CI	-0.3 to 0.4	0.00 to 0.7	0.3 to 0.8	-0.14 to 1.3
p value	0.8	p<0.05	p<0.001	0.11
LDL-C (mmol/L)				
N	19	19	26	42
Mean change (SD)	-0.2 (0.4)	-0.09 (0.6)	-0.2 (0.5)	-0.1 (0.6)
95% CI	0.03 to 0.4	-0.2 to 0.4	0.02 to 0.5	-0.09 to 0.3
p value	p<0.05	0.54	p<0.05	0.33
HDL-C (mmol/L)				
N	27	31	31	51
Mean change (SD)	0.05 (0.6)	0.1 (0.3)	0.04 (0.1)	0.02 (0.2)
95% CI	-0.3 to 0.2	-0.2 to 0.03	-0.01 to 0.08	-0.07 to 0.03
p value	0.7	0.1	0.1	0.4
non-HDL-C (mmol/L)				
N	27	31	32	51
Mean change (SD)	-0.3 (1.0)	-0.6 (1.3)	-0.6 (1.2)	-0.32 (1.1)
95% CI	-0.1 to 0.7	0.1 to 1.1	0.2 to 1.1	0.02 to 0.6
p value	0.2	p<0.05	p<0.05	p<0.05
TG (mmol/L)				
N	24	27	31	51
Mean change (SD)	-0.3 (1.5)	-1.3 (4.1)	-0.7 (1.1)	-0.6 (2.4)
95% CI	-0.3 to 0.9	-0.3 to 2.9	0.3 to 1.1	-0.1 to 1.2
p value	0.3	0.12	p<0.05	0.9
TC/HDL-C				
N	19	20	28	43
Mean change (SD)	-0.3 (0.6)	-0.7 (2.4)	-0.4 (0.7)	-0.3 (1.4)
95% CI	0.00 to 0.6	-0.4 to 1.9	0.1 to 0.6	-0.1 to 0.7
p value	p<0.05	0.19	p<0.05	0.17
log(TG/HDL-C)				
N	23	27	30	51
Mean change (SD)	-0.08 (0.2)	-0.1 (0.3)	-0.09 (0.2)	-0.1 (0.2)
95% CI	-0.01 to 0.2	0.00 to 0.3	0.02 to 0.1	0.01 to 0.1
p value	0.06	0.06	p<0.05	p<0.05

Table 4: Changes in body weight, blood pressure, glycemic control and lipid profile with lariglutide treatment
Only values of p<0.001 are significant (see the statistical analysis)

and LDL-C and TC/HDL-C in HIV-DM group. Decrease in some of the lipid parameters, possibly due to missing of data. The reasons that we did not see much beneficial effect in lipid parameters in HIV-infected subjects as we observed in non-HIV subjects could be due to concomitant use of ART, changes in lifestyle, type and dose of statin, lack of measurement of lipid parameters in all patients, or other undefined factors. Overall the improvement in lipid parameters by administration of liraglutide observed in current study may have beneficial effect on cardiovascular risk profile.

The present study has a number of limitations mainly due to its retrospective and non-randomized nature. Complete blood work data was not available in all patients. Furthermore, patients received concomitant medications that may have affected the measured outcomes. However, all the study participants were on a stable medication regimen and not changes in ART or other medications occurred during the study period.

In conclusion, liraglutide treatment of HIV-infected subjects with and without DM resulted in weight loss, and improvement in some metabolic parameters. These beneficial effects of liraglutide in these subjects may improve HALS and by doing so, it may improve cardiovascular risk profile.

References

1. Bittar R, Giral P, Aslangul E, Assoumou L, Valantin MA, et al. (2012) Determinants of low-density lipoprotein particle diameter during antiretroviral therapy including protease inhibitors in HIV-1-infected patients. Antivir Ther 17: 855-860.

2. de Waal R, Cohen K, Maartens G (2013) Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. PLoS One 8: e63623.

3. Kosmiski LA, Kuritzkes DR, Lichtenstein KA Glueck DH, Gourley PJ, et al. (2001) Fat distribution and metabolic changes are strongly correlated and energy expenditure is increased in the HIV lipodystrophy syndrome. AIDS 15: 1993-2000.

4. Lenert LA, Feddersen M, Sturley A, Lee D (2002) Adverse effects of medications and trade-offs between length of life and quality of life in human immunodeficiency virus infection. Am J Med 113: 229-232.

5. Lo JC, Mulligan K, Noor MA, Lee GA, Schwarz JM, et al. (2004) The effects of low-dose growth hormone in HIV-infected men with fat accumulation: a pilot study. Clin Infect Dis 39: 732-735.

6. Sheth SH, Larson RJ (2010) The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials. BMC Infect Dis 10: 183-193.

7. Drucker DJ, Nauck MA (2006) The incretin system: glucagon-likepeptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368: 1696-1705.

8. Knudsen LB, Nielsen PF, Huusfeldt PO, Johansen NL, Madsen K, et al. (2000) Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. J Med Chem 43: 1664-1669.

9. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, et al. (2009) Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 32: 84-90.

10. Suzuki D, Toyoda M, Kimura M, Miyauchi M, Yamamoto N, et al. (2013) Effects of Liraglutide, a Human Glucagon-like Peptide-1 Analogue, on Body Weight, Body Fat Area and Body Fat-related Markers in Patients with Type 2 Diabetes Mellitus. Intern Med 52: 1029-1034.

11. Rigato M, Fadini GP (2014) Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. Diabetes Metab Syndr Obes 7: 107-120.

12. Oldadapo AO, Barner JC, Rascati KL, Strassels SA (2012) A retrospective database database analysis of neuropathic pain and oral antidiabetic medication use and adherence among Texas adults with type 2 diabetes enrolled in Medicaid. Clin Ther 34: 605-613.

13. Diamant M, van Agtmael M (2012) Liraglutide treatment in a patient with HIV and uncontrolled insulin-treated type 2 diabetes. Diabetes Care 35: e34.

14. Mulligan CM, Harper R, Harding J, McIlwaine W, Petruckevitch A, et al. (2013) A retrospective audit of type 2 diabetes patients prescribed liraglutide in real-life clinical practice. Diabetes Ther 4: 147-151.

15. Marre M, Shaw J, Brändle M, Bebakar WM, Kamaruddin NA, et al. (2009) Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med 26: 268-278.

16. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, et al. (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 374: 39-47.

17. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, et al. (2009) Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 374: 1606-1616.

18. Plutzky J, Garber AJ, Falahati A, Toft AD, Poulter NR (2009) The once-daily human GLP-1 analogue, liraglutide, significantly reduces markers of cardiovascular risk in type 2 diabetes: a meta-analysis of six clinical trials. Eur Heart J 30: 917-919.