

Research: Treatment

Reducing risk of Type 2 diabetes in HIV: a mixed-methods investigation of the STOP-Diabetes diet and physical activity intervention

A. D. Duncan^{1,2,3} , B. S. Peters^{1,3}, C. Rivas⁴ and L. M. Goff² 

¹Department of Immunology, Infection and Inflammatory Diseases, King's College London, ²Department of Diabetes and Nutrition, King's College London, ³Department of HIV Medicine, Guy's and St. Thomas' Hospital NHS Foundation Trust and ⁴Institute of Education, University College Hospital, London, UK

Accepted 5 February 2019

Abstract

Aim To conduct a mixed-methods feasibility study of the effectiveness and acceptability of an individualized diet and physical activity intervention designed to reduce the risk of Type 2 diabetes experienced by people living with HIV.

Methods Participants with impaired fasting glucose and HIV were invited to take part in a 6-month diet and physical activity intervention. Individualized advice to achieve 10 lifestyle goals was delivered monthly. Diabetes risk was assessed pre- and post-intervention by measurement of the glucose and insulin response to a 3-h meal tolerance test. Six-month change was analysed using paired *t*-tests. Research interviews exploring the acceptability of the intervention and factors influencing behaviour change were conducted with those who participated in the intervention, and those who declined participation.

Results The intervention ($n=28$) significantly reduced the following: glucose and insulin, both fasting and postprandial incremental area under the curve (glucose 7.9% and 17.6%; insulin 22.7% and 31.4%, respectively); weight (4.6%); waist circumference (6.2%); systolic blood pressure (7.4%); and triglycerides (36.7%). Interview data demonstrated the acceptability of the intervention. However, participants expressed concern that deliberate weight loss might lead to disclosure of HIV status or association with AIDS-related illness. The belief that antiretroviral medications drove diabetes risk was associated with declining study participation or achieving fewer goals.

Conclusions We have demonstrated the beneficial effects of a lifestyle intervention in mitigating the increased risk of Type 2 diabetes associated with HIV. Future interventions should be designed to further reduce the unique barriers that prevent successful outcomes in this cohort.

Diabet. Med. 00: 1–10 (2019)

Introduction

Antiretroviral therapy, used to suppress HIV replication, has markedly improved life expectancy for people living with HIV; however, some antiretroviral drugs are associated with an increased risk of Type 2 diabetes and several other chronic comorbidities through interference with GLUT-4-mediated transport, potassium signalling within β cells, and suppression of endogenous hepatic gluconeogenesis [1]. HIV itself confers specific risk for Type 2 diabetes, as does the duration of infection and degree of immunosuppression, with HIV-

associated inflammation thought to upregulate chemokines involved in insulin regulation [2]. Traditional diabetes risk factors, such as obesity, whilst characteristically much less prevalent in the early years of the HIV epidemic, are becoming increasingly common as the HIV phenotype changes from one of wasting and premature death to one of obesity and increased life expectancy. Type 2 diabetes is reported to be up to four times more prevalent in HIV than non-HIV populations, with a relative risk of 2.4 for people living with HIV in London and no observed difference by ethnicity [3].

Diet and exercise interventions are highly effective in preventing Type 2 diabetes in cohorts without HIV [4,5]. Achieving diet and physical activity behaviour change is challenging [6]. Specific barriers to behaviour change exist in HIV, including stigma, isolation and body image [7], which should be considered when designing lifestyle interventions. To

Correspondence to: Alastair Duncan. E-mail: alastair.duncan@gstt.nhs.uk
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

What's new?

- People living with HIV have a disproportionately high risk of Type 2 diabetes.
- Significant barriers to diet and lifestyle behaviour change exist within HIV, including stigma, isolation and body image challenges, which should be taken into consideration when designing diabetes prevention interventions.
- We have demonstrated that an individualized diet and physical activity intervention significantly reduced Type 2 diabetes risk in a cohort of adults who were HIV positive. Our qualitative data provided rich insight into the complexity of supporting healthful behaviour change in HIV, highlighting a range of factors that act to motivate individuals or prevent behaviour change.

date few diet and exercise interventions have been undertaken in HIV, focusing predominantly on cardiovascular risk, and demonstrating little impact on markers of diabetes risk [8–10].

The aim of the present mixed-methods exploratory investigation was to evaluate the feasibility and effectiveness of delivering an intensive diet and physical activity intervention for reducing Type 2 diabetes risk in people with HIV and impaired fasting glucose (IFG), to inform the design of a full-scale trial. Qualitative methods have been used to understand patients' experience of the intervention and explore barriers to and facilitators of behaviour change in order to better understand how to support positive changes in this cohort. They provide important context for a better understanding of the quantitative data to inform future work.

Participants and methods

Study design

We conducted a mixed-methods exploratory study, comprising a single-arm 6-month diet and physical activity intervention aimed at improving glucose tolerance and semi-structured interviews aimed at understanding patients' experience of the intervention, to characterize enablers of and barriers to behaviour change in people with HIV and IFG. The study received UK National Health Service Research Ethics approval (13-LO-1543). All participants provided informed consent.

Participants

Men and women (age ≥ 18 years) diagnosed with both HIV and IFG (6.0–6.9 mmol/l), attending routine outpatient appointments at three London HIV clinics, were invited to participate. Ineligibility criteria included: contraindications for dietary change or exercise; liver function tests ≥ 2.5 times above the upper reference range; hepatitis B or C co-infection; or use of

medicines that might interfere with glucose homeostasis (e.g. corticosteroids). Recruitment and data collection took place between February 2014 and September 2015.

Intervention

The intervention goals were informed by two diabetes prevention trials [11,12], with dietary goals based on the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) approaches. Individualized advice on how to achieve 10 goals (Table 1) was delivered by a research dietitian (A.D.) in six one-to-one monthly visits, held in a Clinical Research Facility, and one telephone contact on day 14. Each contact was 30 min in duration. Monthly targets to achieve goals were agreed jointly by the research dietitian and the participant, and individualized according to physical, social, cultural and medical needs. Motivational interviewing and cognitive behaviour therapy techniques, such as goal-setting and self-monitoring, were used to promote and support behaviour change. Weight, waist circumference, body composition, dietary 24-h recall and step count were measured at each visit and used for motivational counselling.

Procedures

Participants attended a baseline and endpoint (24 weeks) assessment visit. The primary outcome was change in glucose incremental area under the curve (iAUC), measured by a 3-h meal tolerance test. Participants attended in a fasting state. They were also asked to refrain from exercise, smoking and alcohol for 24 h beforehand, and to consume three standard meals containing carbohydrates the day before. On arrival, a cannula was inserted into the antecubital fossa vein. A baseline fasting blood sample was drawn for measurement of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, insulin, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). After this, the participant consumed the liquid meal (200 g Fortisip Compact™, providing 60 g carbohydrate, 19 g protein and 18 g fat) within 120 s, with blood sampling at 5, 10, 15, 30, 60, 90, 120, 150 and 180 min for the assessment of glucose, insulin, GIP and GLP-1 levels.

Height (m) and weight (kg) were measured using calibrated electronic equipment and used to calculate BMI, and waist circumference (cm), defined as the midpoint between the lowest rib and the supra-iliac crest, was categorized using International Diabetes Federation (IDF) criteria [13]. Body composition was measured using a Quadscan 4000 multifrequency bioelectrical impedance analyser (Bodystat, Douglas, Isle of Man, UK). Hypertension was recorded if the individual was prescribed antihypertensive medicines or had a mean of three blood pressure values $>140/80$ mmHg. Quality of life was assessed using the HIV/AIDS Targeted Quality of Life questionnaire [14]. Physical activity was recorded using the International

Table 1 Details of the 10 diet and physical activity intervention goals and the methods of individualization

	Standardized goal	Individualization
1. Energy restriction	Daily energy deficit of 600 kcal	Individual energy requirement estimated using standard equations based on age, weight, gender and physical activity. Daily energy deficit of 600 kcal prescribed and meal plans and portion restriction guidance provided.
2. Weight reduction	Achieve 7% weight loss in 6 months, or until BMI of 22.5 kg/m ² achieved	Personalized discussion of achievability and acceptability of weight loss target. Monthly targets mutually agreed, based on expected weight loss of 0.5 kg per week.
3. Waist reduction	Aim to reduce waist size to achieve International Diabetes Federation target: < 90 cm for Asian, 94 cm other men; < 80 cm for women	Personalized discussion of achievability and acceptability of waist targets. If unrealistic to achieve these targets within 6 months, then aim for a 7% reduction.
4. Limit saturated fat	Saturated fat to comprise <10% of mean total daily energy intake	Individualized dietary advice tailored to ethnicity, food habits, socioeconomic status, lifestyle patterns, access to food, cooking ability, and medical issues. Habitual food habits, dietary intake and shopping habits assessed through a 24-h recall interview. Feedback provided to participant on relevant food groups and cooking methods; food swaps, portion size guidance and healthier cooking methods advised and backed up with written handouts. Achievable dietary goals agreed and written advice provided.
5. Monounsaturated fat	Monounsaturated fat to comprise >15% of mean total daily energy intake	
6. Wholegrains	>50% of carbohydrate intake from wholegrains	
7. Restrict added sugar	Restrict added sugar to 25g per day or less	
8. Sodium restriction	<6 g salt daily (<2.5 g sodium per day)	
9. Fruit and vegetables	≥7 portions fruit and vegetables daily	
10. Steps per day	10 000 steps per day, building gradually by 1000 steps per day until goal achieved or exceeded	Methods of achieving target based on lifestyle, motivation, medical issues and external factors.

Physical Activity Questionnaire [15]. Activity was calculated as metabolic equivalent of task (MET) min per day. At baseline, participants were issued with a Yamax CW-600 digi-walker™ pedometer to record daily step count throughout the intervention. Dietary intake was assessed using a 5-day food diary (including one weekend day); nutritional analysis was conducted using Nutritics™ software. Ten-year cardiovascular risk was estimated using the QRisk2-2015 tool [16].

Baseline demographic, social and medical data were collected from medical records and patient interviews. Ethnicity, sexuality, employment status and education level were self-defined. Financial struggle was self-categorized using a tool validated in chronic illness [17]. Cardiovascular disease (CVD) was defined as including coronary heart and peripheral vascular diseases, stroke and transient ischaemic attacks. Current use of statins was recorded. Known duration of HIV infection and of antiretroviral therapy were measured from the dates of the first known positive HIV antibody test and first use of any antiretroviral drug, respectively. Lipodystrophy was defined as current or historic by participant recall and/or physician diagnosis from the medical notes. Hepatic steatosis, diagnosed using standard clinical definitions [transient elastography ultrasonography (FibroScan™) with an attenuation >250, biopsy or MRI scan], weight change in the 12 months after initiation of antiretroviral drugs, and CD4 count nadir were recorded.

Laboratory analysis

Plasma glucose was measured by glucose oxidase assay (Advia 2400; Siemens Healthcare, Erlangen, Germany). Serum insulin concentration was measured by immunoassay using chemiluminescent technology (Advia Centaur; Siemens Healthcare). GLP-1 and GIP (total) concentrations were measured by fluorescent ELISA methods (EGLP-35K and EZHGIP-54K; Merck Millipore, Burlington, MA, USA).

Data analysis

The iAUC was calculated using the trapezoidal method for glucose, insulin, GLP-1 and GIP response in the meal tolerance test. Homeostatic model assessment of insulin resistance (HOMA-IR) [18] and the oral glucose insulin sensitivity index (OGIS) were used to estimate insulin resistance [19]. The following antiretroviral drugs were categorized as those most associated with the development of insulin resistance: zidovudine; didanosine; stavudine; zalcitabine; indinavir; and high-dose ritonavir [20,21]. Metabolic syndrome was defined using IDF criteria [13].

Sample size

A principal aim of this exploratory study was to estimate effect size for a future definitive trial. A sample size of 30 would

enable an informative estimate of the standard deviation (SD) of the change in glucose iAUC and for other continuous outcomes collected. A 95% CI for the SD would range from 0.775 to 1.32 times higher than the obtained estimate of the SD.

Statistical analysis

Data were analysed per protocol using IBM SPSS, version 22. For variables with a normal distribution, arithmetic means and SD values are presented. Paired *t*-tests were used to determine the effects of the intervention, and significance levels were set at 0.05 with two-tailed tests. Chi-squared and ANOVA tests were used to compare goal attainment by ethnicity.

Semi-structured research interviews

Participants were purposively sampled to include: those who completed the intervention; those who withdrew; and those who declined participation. Additionally, for maximal diversity, non-white participants were purposively sampled. The interviewer, a research dietitian experienced in HIV care and trained in qualitative research techniques, used a topic guide to structure the interview and ensure key themes were covered. The topic guide, although initially informed by observations from clinical experience and published literature, was designed to be flexible. It evolved through the study, reflecting the iterative nature of the work. Given the potential for the interviewer and interviewee to have a clinical or research relationship, emphasis was placed on confidentiality, with explicit reassurance that healthcare would not be affected by any response. Participants were encouraged to speak freely. Open questions, active listening and follow-up questions were used to probe or expand themes. To minimize bias the interviewer remained blinded to intervention results until completion of interviews. Interviews were digitally recorded and professionally transcribed verbatim.

Interview analysis

Following familiarization with the first three interview transcripts, possible themes and sub-themes were identified and coded through discussion by three of the authors (A.D., L.G. and C.R.) using short statements to capture the meaning of the theme. Thematic analysis was partly deductive, based on existing literature and clinical observation, and partly inductive considering new topics emerging from the data. For further analysis the data were imported into NVivo11™ software (QSR International). Using the Framework approach, the entirety of the interview data were summarized in matrix cells, with themes and sub-themes in columns and participants in rows, promoting cross-case and cross-theme analysis [22]. Themes were continually contrasted and combined or modified to fit new data added; this process informed further

data collection. Parallel collection and analysis of data enabled assessment of saturation of themes, where significantly different coded themes were no longer emerging and contributing to generation of new meaning. Recruitment to interview ceased at this point [23]. Coding and analysis, conducted primarily by the research dietitian (A.D.), was discussed a number of times with other authors (L.G. and C.R.) and also checked by participants to maximize reliability and validity [24].

Results

Cohort characteristics

Participant recruitment is summarized in Fig. 1; 33 participants were recruited, three were withdrawn after diagnosis with Type 2 diabetes at baseline and two withdrew their participation, resulting in 28 completing the intervention. The baseline clinical, anthropometric and socio-demographic characteristics of the 28 participants who completed the intervention are presented in Table 2.

Intervention

The results of the intervention are shown in Table 3. Fasting glucose and insulin significantly reduced following the intervention, as did glucose and insulin iAUC (18%, $P=0.023$ and 31%, $P=0.017$, respectively). In addition, HOMA-IR and OGIS, both improved post-intervention, and a significant reduction in GIP iAUC ($P=0.006$) was observed.

Participants achieved significant improvements in weight, waist circumference, percentage body fat, systolic and diastolic blood pressure, triglycerides, HDL cholesterol, 10-year cardiovascular risk and life satisfaction score.

A median of five goals were achieved; 22% of participants achieved six or more. The most frequently achieved goal, reducing sodium intake to <2.5 g per day, was attained by 82% of participants, 61% achieved restriction of added sugar intake, 57% achieved 10 000 steps per day and restriction of saturated fat intake, whereas only 14% achieved the monounsaturated fat intake goal. We investigated goal attainment according to ethnicity (white vs non-white) to try and understand if the intervention was more or less acceptable and achievable according to ethnicity. Overall, the mean number of goals achieved did not differ by ethnicity. There was a non-significant trend for white participants to be more likely to achieve the target reduction in waist circumference ($P=0.07$). Non-white participants were statistically significantly more likely to achieve a reduced saturated fat intake ($P=0.004$) and demonstrated a trend to achieve a reduced sugar intake ($P=0.07$). There was no statistically significant difference in achievement of other goals.

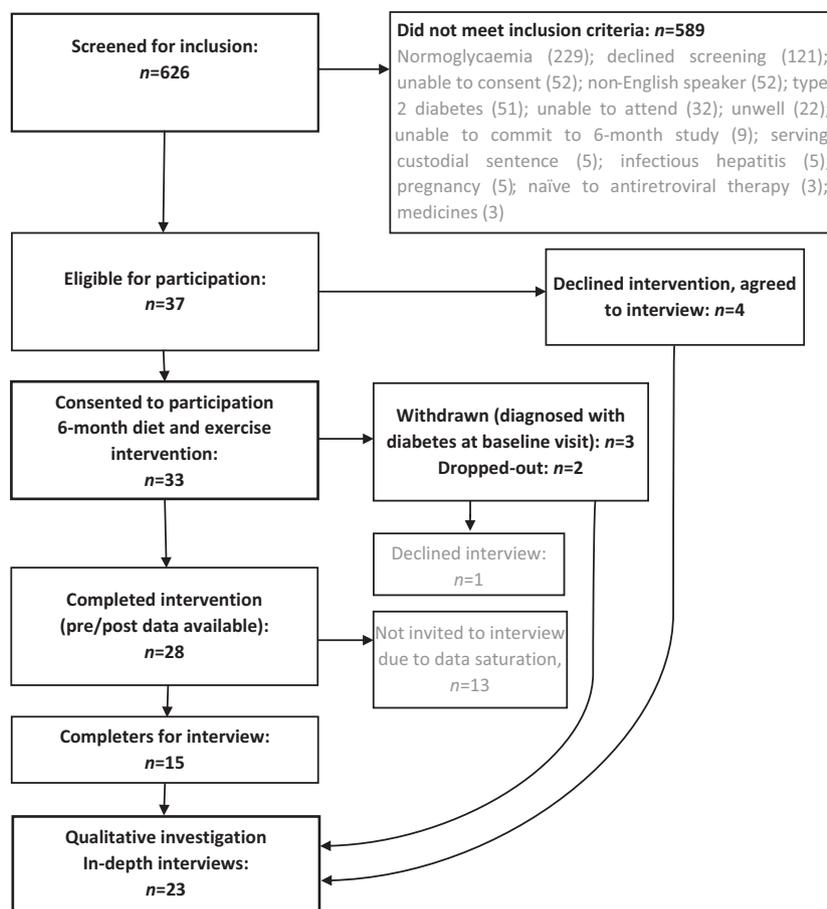


FIGURE 1 Consort diagram of participant recruitment.

Interviews

Data saturation was reached at interview 23. The mean (range) duration of interviews was 44 (26–81) min. Participants found the intervention acceptable, particularly appreciating improved knowledge and skills, motivational interviewing, stepwise goal-setting with tools such as pedometers to aid achievement, and monthly support. They perceived the intervention to have potential to impact a wide range of health concerns:

‘It doesn’t just get rid of belly fat, it is good for the heart and for one mentally as well’.

[Interviewee 9, male, age 60 years].

Those who declined to take part in the intervention, however, described monthly appointments as burdensome. Flexibility in future appointment scheduling was frequently mentioned.

In relation to the potential for behaviour change, the coding frame was categorized at the highest level into general and HIV-specific enablers of and barriers to behaviour change, described below.

Barriers to and enablers of behaviour change

Analysis of our interview data suggested that the positive changes in behaviour experienced by the majority of participants were related to motivation associated with a sense of control regarding diabetes prevention, although additional layers of complexity were recognized.

Body image and HIV stigma

Body shape changes secondary to HIV-associated lipodystrophy syndrome affected body image and limited the opportunity to exercise:

‘My stomach. Every time I go to the gym people think I’m pregnant because of the lipodystrophy.’

[Interviewee 4, female, age 55 years].

Interviewees across ethnicities worried that planned weight loss might lead to disclosure of HIV status or be associated with HIV-related illness:

‘If I lose weight... the first thing they will point at, that one has got AIDS. Because of the weight you have lost.’

[Interviewee 7, female, age 49 years].

Table 2 Baseline characteristics of intervention participants

Total number of participants	28
Age, years	54.0 ± 8.1
Men, n (%)	21 (75)
Ethnicity, n (%)	
White	17 (61)
Black African	7 (25)
Black Caribbean	3 (11)
South Asian	1 (4)
Sexuality, n (%)	
Heterosexual	11 (39)
Homosexual	12 (43)
Not disclosed	5 (18)
BMI, kg/m ²	30.5 ± 6.7
Central obesity (IDF definition), n (%)	25 (89)
Fasting glucose, mmol/l	6.4 ± 0.3
Hypertension, n (%)	16 (57)
Metabolic syndrome, n (%)	22 (79)
Hepatic steatosis, n (%)	17 (61)
Cardiovascular disease	1 (4)
Statin: current use, n (%)	14 (50)
Smoking status, n (%)	
Current	2 (7)
Ex	8 (29)
Never	18 (64)
Duration HIV infection, years	15.6 ± 8.4
CD4 nadir, cells/mm ³	205 ± 133
Duration of antiretroviral therapy, years	10.6 ± 6.4
Antiretroviral medication associated with Type 2 diabetes risk, n (%)	13 (46)
% weight gain after antiretroviral medication initiation	7.0 ± 5.8
Lipodystrophy, n (%)	5 (18)
Family history of Type 2 diabetes, n (%)	16 (57)
Working / Student, n (%)	16 (57)
Unemployed, n (%)	10 (36)
Retired, n (%)	2 (7)
Financial struggle, n (%)	3 (11)
Further education, n (%)	20 (71)

IDF, International Diabetes Federation. Data are mean ± SD, unless otherwise stated.

Loss of cultural identity

A significant barrier to weight reduction was the perceived loss of cultural identity; participants of African origin described being overweight as culturally desirable:

'I said, "Oh look how big I am". They said, "Oh no, you're not big, that is the good right thing".... They said, "no, no, no, don't lose weight."

[Interviewee 14, female, age 51 years].

This was echoed among gay men who self-identified as 'bears' (a sub-section of gay men who reject idealized lean muscularity, and are more likely to be bearded, hairier, heavier and more masculine than gay men in general [25]):

'My partner likes me being a bigger guy, yeah.'

[Interviewee 23, male, age 41 years].

This contrasted with a cultural pressure for some gay men to achieve a lean physical aesthetic:

'Well, I looked at myself side on in the mirror and I thought would you sleep with you and I thought no I wouldn't.'

[Interviewee 9, male, age 60 years].

HIV-related fertility

Participants who achieved fewer intervention goals and those who declined participation believed HIV medicines conferred their increased diabetes risk and considered prevention measures futile:

'As you get older and you're on these [HIV] drugs, this [diabetes] is just going to happen. There's nothing you can do. You can try to be healthy but you're not going to avoid it.'

[Interviewee 22, male, age 46 years].

'I have a problem because of the HIV medication I'm taking because I know it makes me put on weight.'

[Interviewee 6, male, age 40 years].

HIV-specific enablers

A desire to avoid adding to pill or disease burden motivated change among those who achieved more goals:

'To have to start diabetes medicines as well, on top of the HIV ones, I thought, that is going to be very hard.'

[Interviewee 8, female, age 48 years].

Some believed that diabetes prevention was achievable and less burdensome than living with HIV:

'Diabetes is a disease but I know it can be easily tackled with food without taking any medicine. But HIV is not like that.'

[Interviewee 16, male, age 71 years].

Discussion

In this exploratory investigation we have shown the beneficial effects of a 6-month intensive individualized diet and activity intervention on markers of Type 2 diabetes risk in people with HIV and prediabetes. Our intervention, which targeted moderate weight loss through energy restriction and increased physical activity, alongside reductions in saturated fat, sugar and salt and increases in wholegrains and fruit and vegetables, significantly improved a number of cardiometabolic risk factors including fasting and post-load glycaemia, body weight, waist circumference, blood pressure, triglycerides, and HDL cholesterol. Through our qualitative data we gained an insight into the experiences of participants undertaking the intervention and identified a range of barriers and enablers to diet and physical activity behaviour change that people with HIV and prediabetes reported. We recognized HIV-specific barriers, including fear

Table 3 Primary and secondary outcome data in study participants ($n=28$) at baseline and after 6 months' participation in a diet and physical activity intervention for diabetes prevention

	Baseline Mean \pm SD	Post-intervention Mean \pm SD	Change, %	P^*
Fasting glucose [†] , mmol/l	6.3 \pm 0.4	5.8 \pm 0.7	-7.9	0.003
Glucose iAUC [†] , mmol/l \times min	255 \pm 165	210 \pm 149	-17.6	0.023
Fasting insulin [†] , pmol/l	100.1 \pm 70.1	77.1 \pm 61.7	-22.7	0.021
Insulin iAUC [†] , pmol/l \times min	1870 \pm 1350	1283 \pm 1109	-31.4	0.017
Fasting GIP [†] , ng/l	41.0 \pm 60.3	29.6 \pm 20.0	-27.8	0.359
GIP iAUC [†] , ng/l \times min	36078 \pm 20677	27020 \pm 14369	-25.1	0.006
Fasting GLP-1 [†] , pmol/l	19.5 \pm 21.1	14.7 \pm 13.7	-24.6	0.252
GLP-1 iAUC [†] , pmol/l \times min	1391 \pm 1213	1790 \pm 2260	28.7	0.416
HOMA-IR [‡] , HOMA score	3.93 \pm 2.89	2.88 \pm 2.47	-26.7	0.011
OGIS [‡] , Mari method, mmol/min/m ²	315 \pm 62	360 \pm 64	14.3	0.002
Weight, kg	88.8 \pm 15.8	84.7 \pm 15.6	-4.6	<0.001
Waist, cm	107.1 \pm 14.1	100.5 \pm 12.2	-6.2	<0.001
Body fat ^{**} , % total body mass	29.3 \pm 9.6	27.6 \pm 9.1	-5.8	0.010
Systolic blood pressure, mmHg	135 \pm 13	125 \pm 20	-7.4	0.006
Diastolic blood pressure, mmHg	81 \pm 11	74 \pm 10	-8.6	0.006
Total cholesterol, mmol/l	4.88 \pm 0.95	4.72 \pm 0.86	-3.3	0.155
LDL cholesterol, mmol/l	2.78 \pm 0.83	2.70 \pm 0.88	-2.9	0.429
HDL cholesterol, mmol/l	1.27 \pm 0.45	1.43 \pm 0.45	12.6	0.002
Triglycerides, mmol/l	2.07 \pm 1.37	1.31 \pm 0.59	-36.7	0.002
Energy Balance [§] , kcal/day	51 \pm 571	-424 \pm 499	NA	<0.001
Walking [¶] , min/week	1705 \pm 1571	2605 \pm 2087	52.8	0.015
Total activity [¶] , MET min	3405 \pm 2519	5186 \pm 3611	52.3	<0.001
10-year cardiovascular risk ^{††} , %	9.6 \pm 7.3	8.3 \pm 6.4	-13.5	0.001
Satisfaction with life ^{‡‡} , % score	64.8 \pm 27.3	76.2 \pm 22.0	17.6	0.004
Overall quality of life ^{‡‡} , % score	75.3 \pm 25.4	80.5 \pm 23.7	6.9	0.060

CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostatic model of assessment of insulin resistance; iAUC, incremental area under the curve; MET, metabolic equivalent of task; NA, not applicable; OGIS, oral glucose sensitivity index.

^{*}Paired-samples *t*-test to estimate significance of change in mean.

[†]Measured by 3-h frequently sampled liquid meal tolerance test.

[‡]Measured using data from the 3-h frequently sampled liquid meal tolerance test.

[§]Estimated energy intake (5-day food diaries) minus estimated total energy expenditure (standard equations).

[¶]Assessed using the International Physical Activity Questionnaire.

^{**}Measured using bioelectrical impedance analysis.

^{††}Estimated by the QRisk2 (2015) tool.

^{‡‡}Assessed by the HIV/AIDS Targeted Quality of Life questionnaire.

of disclosure of HIV status or HIV-related illness associated with weight loss, which had an impact on the acceptability of the intervention. These qualitative data will inform intervention design for a future definitive trial.

The improvements in fasting glucose, BMI and blood pressure achieved in the present study were both statistically and clinically significant. A recent meta-analysis of 'real-world' diabetes prevention lifestyle interventions, many of which were of uncontrolled study designs, reported overall reductions in weight of 2.5 kg and fasting plasma glucose of 0.09 mmol/l, which were associated with a 29% reduction in diabetes incidence [5]. The reductions that our participants demonstrated were of a greater magnitude, which is reassuring given the complex aetiology of HIV-associated diabetes and history of exposure to antiretroviral drugs associated with dysglycaemia, and suggests that lifestyle interventions are an effective means by which to prevent or delay diabetes onset in people with HIV. In their review, as well as estimating overall effects, Galaviz *et al.* [5] evaluated the lifestyle interventions according to mode of delivery

(group education by community members, group education by healthcare professionals, one-to-one education by healthcare professionals, and technology-based delivery). By far the most common delivery was group-based by a healthcare professional, with one-to-one delivery being the least commonly used delivery. Interestingly, in their subgroup analyses, they showed that group-based education by either community members or healthcare professionals was more effective at facilitating diabetes prevention, weight loss and reductions in fasting plasma glucose than either one-to-one or technology-based delivery. The effectiveness of our intervention, which was one-to-one and delivered by a healthcare professional, may relate to the intensity of our intervention, which has been recognized as a key determinant of weight loss success [4], and may be greater than those included in the Galaviz *et al.* review, as often within one-to-one interventions contact time is reduced because of cost implications. We did not evaluate the cost of delivering our intervention, however, we believe that six 30-min appointments with a health professional is not significantly different

from current clinical practice. Future trials may wish to investigate retaining the intensity of our intervention when delivered in a more cost-effective group setting.

To date, diet and exercise interventions in HIV cohorts have primarily focused on reducing cardiovascular disease risk rather than diabetes. Fitch *et al.* [10] used an intensive 12-month lifestyle intervention, with and without metformin, to mitigate cardiovascular risk. In contrast to our findings, beneficial changes in weight, waist circumference and fasting glycaemia were only achieved when metformin was used, with no benefit from lifestyle alone. Compared to our investigation, the participants exhibited a lesser degree of baseline hyperglycaemia and there was a lack of weight loss in the lifestyle arm, which may explain some of the differences with our findings. A more recent randomized trial, which also aimed to mitigate cardiovascular risk in participants stable on antiretroviral therapy, used a 3-year highly intensive multidisciplinary intervention focused on dietary change and smoking cessation, with aerobic exercise encouraged [27]. The intervention resulted in a small decrease in LDL cholesterol and 10-year cardiovascular risk but did not change BMI, triglycerides, insulin or glucose levels. These findings are in direct contrast to our intervention, where we observed no impact on LDL cholesterol, possibly as a result of statin use by 50% of our participants, but significant changes in the other measures. Baseline BMI was considerably higher in our intervention and the weight loss we observed may partially explain the differences in findings.

Within our exploratory study we did not perform detailed assessments of the potential mechanisms by which our intervention significantly improved the glucose tolerance of our participants. Nearly a third of our participants achieved the waist circumference targets, which may have been associated with loss of visceral fat, which is a known driver of insulin resistance. Considering our biochemical results, which showed significant reductions of both fasting and postprandial glycaemia, as well as fasting triglyceride levels, we would also hypothesize that our intervention may have reduced hepatic fat deposition and improved hepatic insulin sensitivity. We did not measure inflammatory markers, which are strongly linked with insulin resistance, but it would be relevant to look at these also in future investigations.

Achieving lifestyle behaviour change is challenging and highly complex in any patient group. In our study only 22% of participants achieved six or more goals; however, we did observe that goals were partially achieved. For example, 22% of participants achieved the 7% weight loss goal, whereas the mean weight loss across the intervention was 4.6%. Despite this, we were still able to show significant benefits to diabetes risk reduction. The findings from our qualitative work suggest that the successful change experienced by the majority of our participants was related to motivation associated with a sense of control regarding diabetes prevention; however, additional layers of complexity exist in people living with HIV, which

need to be addressed when supporting them to make lifestyle changes. Fear of deliberate weight loss being associated with AIDS-related illness leading to disclosure of HIV status was a common concern and a significant barrier to diet and exercise change, consistent with other reports [7]. By contrast, participants felt happy to disclose their development of diabetes, mirroring findings from a study of people with HIV and tuberculosis coinfection, where participants were open about tuberculosis infection but not HIV [28]. Among our participants of black African origin, HIV stigma and cultural valorization of obesity were cited together as particular barriers to weight loss, which is consistent with previous reports from the USA, the UK and Africa, as well as from non-HIV literature in which heavier body shapes are consistently favoured amongst black women [29]. Our analysis of goal attainment suggests that, taken as a whole, participants can successfully change lifestyle behaviours irrespective of ethnicity. Compared with those of white ethnicity, black and Asian participants were significantly more able to reduce intake of saturated fats, however, there was no difference in attainment of physical activity or weight loss goals.

In the present study, weight loss was associated with a loss of cultural identity for gay men identifying as 'bears', with participants reporting valorization of obesity mirroring that of the participants of black African origin; it is not known if this is specific to HIV-positive gay 'bears'. The health determinants of gay men identifying as 'bears' have not been extensively studied, although such men are recognized to be significantly heavier than gay men who do not identify with this culture [25]. The gay 'bear' participants in this study were white; given they reported similar body shape-related barriers to lifestyle changes to those of the black participants, this may explain, in part, the similar rates of attainment of goals across ethnic groups.

Isolation was a further major barrier to lifestyle change. Those able to seek support tended to achieve more goals during the 6-month intervention. Isolation in this cohort may be linked to two HIV-specific issues: HIV stigma, and the high rates of poor mental health seen in HIV [30]. Addressing isolation is complex, although a potential health-related solution would be to deliver group-based lifestyle change interventions [6].

The strengths and limitations of the present study warrant consideration. The lack of a control arm for comparison of the intervention effect is a limitation and prevents us from quantifying accurately the effect size of the intervention. It is plausible that the participants will have experienced an impact simply through inclusion in the study, which we cannot quantify through our study design. However, our study principally aimed to assess the feasibility and acceptability of the intervention to inform a future definitive trial and the results have gained us an important insight into the participants' experience of the intervention. While the randomized controlled trial design is considered the 'gold standard' for assessing intervention effects, we do recognize there are an increasing number of 'real-world' diabetes

prevention interventions being implemented and evaluated in uncontrolled or non-randomized designs, which have demonstrated meaningful reductions in diabetes risk [5]. We have not collected data to understand the mechanisms of the intervention, for example, ectopic fat, and future investigations might include such measures. We did not power this study to allow subgroup analysis; given the multifactorial nature of increased diabetes risk in this cohort, future studies should allow for a comprehensive analysis including ethnicity and HIV-related factors. A major strength of the present study was our mixed-methods approach, which enabled us to understand the process of behaviour change alongside measures of effectiveness and acceptability. This provides us with a deep insight into the factors that influence the patients' motivations and opportunities for diet and lifestyle change, and offers us the opportunity to better understand how to support patients. The intervention delivered individualized advice to achieve a set of standardized goals, which reflects the approach taken by healthcare practitioners in clinical practice. Finally, although the cohort studied was UK-based, the ethnic diversity of the participants makes the findings relevant to the global HIV pandemic.

In conclusion, increasing rates of obesity and Type 2 diabetes in HIV highlight the urgent need to find effective diabetes prevention measures for this patient group. We have demonstrated that, despite the additional diabetes risk conferred by HIV infection and exposure to antiretroviral agents, an individualized diet and exercise intervention can significantly reduce Type 2 diabetes risk in people living with HIV. Nevertheless, there are significant enablers of and barriers to adopting behaviour change, a number of which are HIV-specific, which should be taken into account when designing interventions for research and clinical practice.

Funding sources

This report was independent research arising from a Research Fellowship fully funded by the UK's National Institute for Health Research (NIHR) and Health Education England (reference CDRF-2012-03-021). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Competing interests

None declared.

Acknowledgements

We thank all the participants in this project. Additionally, we acknowledge the advice given by Dr Abdel Douiri, Senior Statistician at King's College London, UK.

References

- Hadigan C, Kattakuzhy S. Diabetes mellitus type 2 and abnormal glucose metabolism in the setting of human immunodeficiency virus. *Endocrinol Metab Clin North Am* 2014; **43**: 685–696.
- Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, Hirschel B et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis* 2007; **45**: 111–119.
- Duncan AD, Goff LM, Peters BS. Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. *PLoS One* 2018; **13**: e0194199.
- Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. *Implement Sci* 2015; **10**: 172.
- Galaviz KI, Weber MB, Straus A, Haw JS, Narayan KMV, Ali MK. Global Diabetes Prevention Interventions: A Systematic Review and Network Meta-analysis of the Real-World Impact on Incidence, Weight, and Glucose. *Diabetes Care* 2018; **41**: 1526–1534.
- Dunkley AJ, Bodicoat DH, Greaves CJ, Russell C, Yates T, Davies MJ et al. Diabetes Prevention in the Real World: Effectiveness of Pragmatic Lifestyle Interventions for the Prevention of Type 2 Diabetes and of the Impact of Adherence to Guideline Recommendations. A Systematic Review and Meta-analysis. *Diabetes Care* 2014; **37**: 922–933.
- Capili B, Anastasi JK, Chang M, Ogedegbe O. Barriers and facilitators to engagement in lifestyle interventions among individuals with HIV. *J Assoc Nurses AIDS Care* 2014; **25**: 450–457.
- Lindegard B, Hansen T, Hvid T, van Hall G, Plomgaard P, Ditlevsen S et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. *J Clin Endocrinol Metab* 2008; **93**: 3860–3869.
- Woods MN, Wanke CA, Ling P-R, Hendricks KM, Tang AM, Knox TA et al. Effect of a dietary intervention and n-3 fatty acid supplementation on measures of serum lipid and insulin sensitivity in persons with HIV. *Am J Clin Nutr* 2009; **90**: 1566–1578.
- Fitch K, Abbara S, Lee H, Stavrou E, Sacks R, Michel T et al. Effects of lifestyle modification and metformin on atherosclerotic indices among HIV-infected patients with the metabolic syndrome. *AIDS* 2012; **26**: 587–597.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.
- Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344**: 1343–1350.
- Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome - A new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 2006; **23**: 469–480.
- Clayson DJ, Wild DJ, Quarterman P, Duprat-Lomon I, Kubin M, Coons SJ. A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. *Pharmacoeconomics* 2006; **24**: 751–765.
- Craig P, Petticrew M. Developing and evaluating complex interventions: Reflections on the 2008 MRC guidance. *Int J Nurs Stud* 2013; **50**: 585–592.
- Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A et al. Predicting cardiovascular risk in England and Wales: Prospective derivation and validation of QRISK2. *BMJ* 2008; **336**: 1475–1482.
- Surtees PG, Wainwright NWJ. The shackles of misfortune: Social adversity assessment and representation in a chronic-disease epidemiological setting. *Soc Sci Med* 2007; **64**: 95–111.

- 18 Matthews DR, Hosker JP, Rudenski AS. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
- 19 Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care* 2001; **24**: 539–548.
- 20 Hadigan C, Kattakuzhy S. Diabetes mellitus type 2 and abnormal glucose metabolism in the setting of human immunodeficiency virus. *Endocrinol Metab Clin North Am* 2014; **43**: 685–696.
- 21 Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: Current concepts. *Clin Infect Dis* 2015; **60**: 453–462.
- 22 Smith J, Firth J. Qualitative data analysis: the framework approach. *Nurse Res* 2011; **18**: 52–62.
- 23 Hennink MM, Kaiser BN, Marconi VC. Code saturation versus meaning saturation: How many interviews are enough? *Qual Health Res* 2017; **27**: 591–608.
- 24 Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. *BMJ* 2000; **320**: 50–52.
- 25 Moskowitz DA, Turrubiates J, Lozano H, Hajek C. Physical, behavioral, and psychological traits of gay men identifying as bears. *Arch Sex Behav* 2013; **42**: 775–784.
- 26 Appuhamy JA, Kebreab E, Simon M, Yada R, Milligan LP, France J. Effects of diet and exercise interventions on diabetes risk factors in adults without diabetes: meta-analyses of controlled trials. *Diabetol Metab Syndr* 2014; **6**: 127.
- 27 Saumoy M, Alonso-Villaverde C, Navarro A, Olmo M, Vila R, Maria Ramon J et al. Randomized trial of a multidisciplinary lifestyle intervention in HIV-infected patients with moderate-high cardiovascular risk. *Atherosclerosis* 2016; **246**: 301–308.
- 28 Daftary A. HIV and tuberculosis: the construction and management of double stigma. *Soc Sci Med* 2012; **74**: 1512–1519.
- 29 Cohen E, Boetsch G, Palstra FP, Pasquet P. Social valorisation of stoutness as a determinant of obesity in the context of nutritional transition in Cameroon: the Bamileke case. *Soc Sci Med* 2013; **96**: 24–32.
- 30 Blashill AJ, Perry N, Safren SA. Mental health: a focus on stress, coping, and mental illness as it relates to treatment retention, adherence, and other health outcomes. *Curr HIV/AIDS Rep* 2011; **8**: 215–222.