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# The Mediterranean Portfolio diet in HIV dyslipidaemia: a pilot randomised controlled trial

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## Introduction

Mediterranean diet reduces the risk of cardiovascular disease, but its effect is unknown in HIV with the additional burdens of infection, inflammation and antiretroviral treatment (ART). This is the first trial to test cholesterol-lowering foods in adults with HIV infection.

## Objective

- To determine feasibility of a definitive trial (not presented here)
- To examine whether a Mediterranean-style diet that incorporates a portfolio of cholesterol - lowering foods reduces cardiovascular risk (CVR) factors in patients with HIV dyslipidaemia.

## Methods

**DESIGN & SETTING:**
- pilot, parallel, randomized controlled trial (ISRCTN32090191)
- 3 HIV centres in UK with ethnically diverse population

**PARTICIPANTS:**
- adults with stable HIV infection on ART >6 months
- LDL-cholesterol (LDL-C) >3mmol/l, not on lipid lowering agents

**RANDOMIZATION:**
- 1 to 1 ratio, independently computer generated allocation sequence with random block sizes, stratified by gender and smoking, concealed in envelopes
- Participants were unaware of the content of the other group's diet

**INTERVENTION**
- Diet1: dietary advice to reduce saturated fat to <10% of energy intake
- Diet2: advice on adopting Mediterranean Diet with supplies of cholesterol-lowering foods (daily: 2g plant stanols, 15g soya protein, 57g nuts, 15g soluble fibre - oats, pearl barley, flaxseed, beans and pulses).

**MEASURES & OUTCOMES** (measured at baseline, month 6 and month 12)
- CVR factors, fasting lipid profile, body composition, arterial stiffness, activity levels
- Food intake: 14-item Mediterranean Diet Score, % Portfolio adherence, 3-day food diaries

**SAMPLE SIZE**
- 80% power to detect 0.5mmol/l (or 10%) difference in LDL-C reduction between groups at 6 months at 5% significance assuming SD 0.6mmol/l (or 10%)

**ANALYSIS**
- Linear regression with adjustment for baseline value of dependent variable to test mean difference in CVR factors between groups
- Intention to treat (ITT) and Complier Average Causal Effect analysis

**TRIAL STATUS:** recruitment is complete
- Ethical approval given by an independent review board (reference 13/ WM/0225)

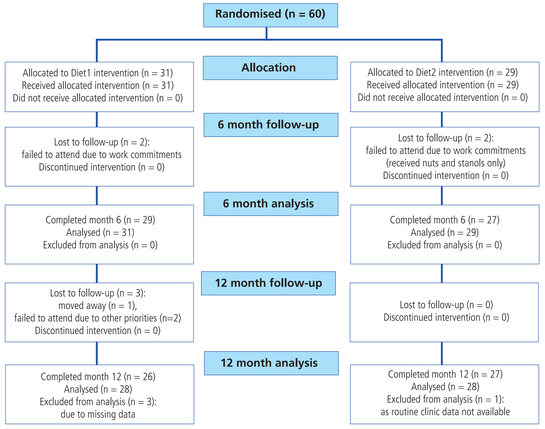
## Results

- 60 adults were randomized and followed up for 1 year (see Figure 1).
- Baseline characteristics were comparable between groups (see Table 1). At 6 months, compared to Diet1, Diet2 group showed significantly greater:
- reduction in LDL-C (Figure 2), total to HDL-cholesterol ratio, systolic BP (Table 2)
- increase in Mediterranean foods: olive oil, fish, legumes (Figure 3)
- Individual adherence varied from 11 to 100% in Portfolio foods (Figure 4).
- Body composition, arterial stiffness, gut function, and levels of physical activity were not significantly different between the groups.
- No evidence of differences in effect by gender or ethnicity (stratified analysis).
- As expected, the estimated treatment effect among compliers to the Mediterranean Diet (LDL-cholesterol -0.87mmol/l, 95%CI -1.79 to 0.05, P = 0.06) and Portfolio cholesterol-lowering foods (-0.76mmol/l, -1.54 to 0.01, P = 0.05) appears larger than that for ITT analysis (-0.38mmol/l -0.68 to -0.09, P = 0.01).

### Table 1: Baseline characteristics of trial participants according to study group (n = 60), expressed as mean (SD) or count (%)

| Characteristic | Diet1 Reduced saturated fat (n = 31) | Diet2 Mediterranean Portfolio (n = 29) | Total (n = 60) |
|---|---|---|---|
| Age, years | 42.8 (7.1) | 42.0 (6.5) | 42.4 (6.8) |
| Women (%) | 17 (55) | 14 (48) | 31 (52) |
| Ethnicity (%)<br>– White European<br>– Black African<br>– Black Caribbean<br>– Asian | <br>13 (42)<br>14 (45)<br>2 (6.5)<br>2 (6.5) | <br>11 (38)<br>16 (55)<br>0 (0)<br>2 (7) | <br>24 (40)<br>30 (50)<br>2 (3)<br>4 (7) |
| Disease duration, years | 6.6 (3.2) | 8.9 (4.5) | 7.7 (4.0) |
| Current CD4, cells/mm³ | 546 (204) | 616 (210) | 580 (209) |
| Duration of treatment, years | 8.2 (3.9) | 7.3 (4.2) | 7.8 (4.0) |
| Antiretroviral class (%)<br>– NNRTI<br>– Boosted Protease inhibitor<br>– Integrase inhibitor | <br>20 (65)<br>11 (35)<br>0 (0) | <br>18 (62)<br>7 (24)<br>4 (14) | <br>38 (63)<br>18 (30)<br>4 (7) |
| Socio-economic class (%)<br>I Managerial & professional<br>II Intermediate<br>III Working | <br>9 (29)<br>5 (16)<br>17 (55) | <br>15 (52)<br>2 (7)<br>12 (41) | <br>24 (40)<br>7 (12)<br>29 (48) |
| Recruitment centre (%)<br>– Heartlands<br>– Queen Elizabeth<br>– Coventry | <br>20 (65)<br>4 (13)<br>7 (22) | <br>20 (69)<br>3 (10)<br>6 (21) | <br>40 (66)<br>7 (12)<br>13 (22) |
| QRISK, % 10 year risk of CVD | 3.1 (2.9) | 2.8 (2.6) | 2.9 (2.7) |
| – Non smoker | 19 (61) | 20 (69) | 39 (65) |
| Systolic blood pressure, mm Hg | 123 (15) | 125 (14) | 124 (14) |
| Diastolic blood pressure, mm Hg | 78 (12) | 78 (9) | 78 (10) |
| Lipid profile, mmol/l<br>– HDL-cholesterol<br>– LDL-cholesterol<br>– Triglycerides | <br>1.5 (0.5)<br>3.9 (0.5)<br>1.2 (0.5) | <br>1.5 (0.6)<br>3.9 (0.6)<br>1.2 (0.5) | <br>1.5 (0.5)<br>3.9 (0.6)<br>1.2 (0.5) |
| Body mass index, kg/m² | 27.9 (5.9) | 28.1 (5.7) | 28.0 (5.7) |

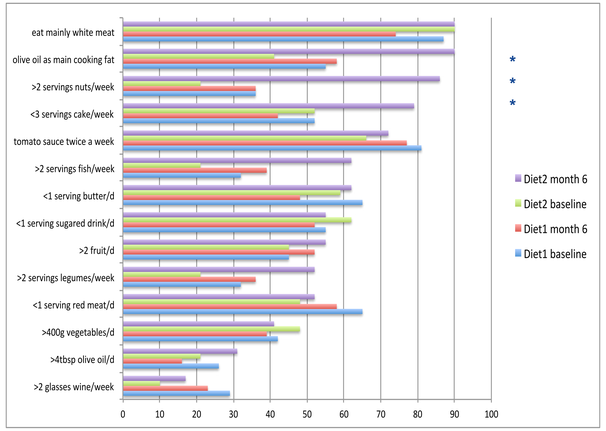
### Figure 1 CONSORT Flow Diagram summarising trial allocation and follow-up




### Table 2: Mean difference between low saturated fat (Diet1) and Mediterranean Portfolio (Diet2) groups at month 6

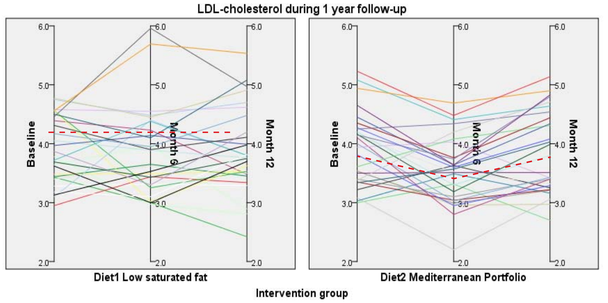
| Endpoint | Time | Diet1 low saturated fat group Mean ±SD (n = 29) | Diet2 Med Portfolio group mean ±SD (n = 31) | Mean difference (MD), adjusted for baseline value (95% CI) | P value | MD, adjusted for baseline value, smoking, gender, socioeconomic status, baseline MDS (95% CI) | P value |
|---|---|---|---|---|---|---|---|
| LDL-cholesterol (mmol/l) | Baseline | 3.9±0.5 | 3.9±0.6 | | | | |
| | Month 6 | 3.9±0.7 | 3.5±0.6 | -0.4 (-0.7 to -0.1) | 0.01 | -0.5 (-0.8 to -0.2) | 0.002 |
| Total to HDL-cholesterol ratio | Baseline | 4.3±0.9 | 4.4±1.4 | | | | |
| | Month 6 | 4.3±1.0 | 4.1±1.2 | -0.3 (-0.6 to -0.1) | 0.01 | -0.4 (-0.6 to -0.1) | 0.004 |
| Systolic BP (mm Hg) | Baseline | 123±15 | 125±14 | | | | |
| | Month 6 | 127±17 | 121±10 | -7 (-2 to -12) | 0.008 | -8 (-13 to -2) | 0.005 |
| Diastolic BP (mm Hg) | Baseline | 78±12 | 78±9 | | | | |
| | Month 6 | 80±10 | 78±8 | -2 (-6 to 2) | 0.3 | -2 (-6 to 2) | 0.2 |
| Mediterranean Diet Score (14-item) | Baseline | 6.8±2.4 | 6.0±2.3 | | | | |
| | Month 6 | 6.6±2.9 | 9.5±2.2 | 3.3 (2.0 to 4.7) | <0.001 | 3.1 (1.6 to 4.5) | <0.001 |
| Saturated fat (g/day) | Baseline | 24.5±13.5 | 25.0±16.5 | | | | |
| | Month 6 | 23.6 ±12.4 | 20.2±10.1 | -3.5 (-10.4 to 3.5) | 0.3 | -2.7 (-11.1 to 5.6) | 0.5 |
| Waist circumference (cm) | Baseline | 93.4 +/-12.7 | 93.9 (11.4) | | | | |
| | Month 6 | 92.7 (14.1) | 92.6 (10.6) | -1.0 (-3.4 to 1.3) | 0.4 | -1.3 (-3.9 to 1.4) | 0.3 |
| Subcutaneous fat (%) | Baseline | 30.8 (12.5) | 30.4 (11.9) | | | | |
| | Month 6 | 28.4 (14.1) | 30.6 (11.2) | 2.0 (-0.8 to 4.7) | 0.2 | 1.4 (-1.5 to 4.3) | 0.3 |

### Figure 3 Mean percentage adherence to dietary components of the Mediterranean Diet Score (%)



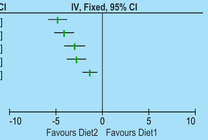

Key: * P<0.05 difference between groups at month 6 determined by Chi square test

### Figure 2: LDL-cholesterol (mmol/l) during 1-year follow-up, by intervention group (mean value represented by red dotted line)




### Figure 4: Adherence to Portfolio food components at month 6 (35-item score)

| Study or Subgroup | Diet1 Low saturated fat Mean | SD | Total | Diet2 Med Portfolio Mean | SD | Total | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Plant stanols | 0.07 | 0.26 | 28 | 4.89 | 2.68 | 27 | -4.82 [-5.84, -3.80] | |
| Nuts | 1.18 | 1.91 | 28 | 5.3 | 2.13 | 27 | -4.12 [-5.19, -3.05] | |
| Soya protein | 0.5 | 1.43 | 28 | 3.48 | 2.65 | 27 | -2.98 [-4.11, -1.85] | |
| Oats & barley | 1.43 | 2.12 | 28 | 4.22 | 1.81 | 27 | -2.79 [-3.83, -1.75] | |
| Beans & oily fish | 1.54 | 1.26 | 28 | 2.89 | 1.74 | 27 | -1.35 [-2.16, -0.54] | |
| Portfolio score | 4.71 | 3.08 | 28 | 20.78 | 7.46 | 27 | | |
| Percentage adherence | 13.43 | 8.71 | 28 | 59.37 | 21.4 | 27 | | |




## Conclusion

Dietetic advice to follow a Mediterranean diet containing nuts, plant stanols and soya protein produced a greater improvement in diet quality, blood pressure, total cholesterol to HDL-cholesterol ratio and a 10% greater reduction in LDL-cholesterol than standard guidelines to reduce saturated fat intake. Analysis assuming full compliance and preserving randomisation suggests a possible doubling of this estimated treatment effect.

This trial has demonstrated potential for efficacy of the Mediterranean Portfolio diet. Future trials are required to demonstrate effectiveness in the HIV population, as data from a recent meta-analysis of non-statin therapy trials suggests that this 0.5mmol/l reduction in LDL-cholesterol could translate to 12% reduction in major vascular events (Silverman et al 2016).

### References:

Stradling C, Thomas GN, Hemming K, et al (2016) Randomised controlled pilot study to assess the feasibility of a Mediterranean Portfolio dietary intervention for cardiovascular risk reduction in HIV dyslipidaemia: a study protocol. BMJ Open 2016;6:e010821

Silverman M, Ference B, Im K, et al (2016) Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA 316(12):1289 :1289

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