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## **Cardiovascular Risk Evaluation and Anti-retroviral Therapy Effects in an HIV cohort: implications for clinical management: The CREATE 1 study**

Michael Aboud, Ali Elgalib, Laura Pomeroy, George Panayiotakopoulos, Elias Skopelitis, Alastair Duncan, Ranjababu Kulasegaram, Caroline Dimian, Fiona Lampe, Anthony S Wierzbicki, et al.

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**Cardiovascular Risk Evaluation and Anti-retroviral Therapy  
Effects in an HIV cohort: implications for clinical  
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3 **Cardiovascular Risk Evaluation and Anti-retroviral Therapy Effects in an HIV cohort:**  
4 **implications for clinical management: The CREATE 1 study**  
5  
6

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53 **Conflict of Interest:** BSP has sat as a consultant on advisory boards for Abbott,  
54 GlaxoSmithKline, and Tibotec Pharmaceuticals. ASW has received grant support, lecture  
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56 GlaxoSmithKline, Merck kGA, Merck-Sharp & Dohme, Roche, Pfizer, Sanofi-Aventis and  
57 Takeda pharmaceuticals.  
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4 **Abstract - 247 words (max 250)**  
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8 **Aims:** To determine the cardiovascular disease (CVD) risk profile of a large UK HIV cohort  
9 and how highly active antiretroviral therapy (HAART) affects this.  
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12 **Methods:** A cross-sectional study within a large inner city Hospital and neighbouring district  
13 hospital. 1021 HIV positive outpatients representative of the complete cohort; 990 who had  
14 no previous CVD were included in CVD risk analysis. We recorded demographics, highly  
15 active antiretroviral therapy (HAART) history and CVD risk factors. CVD and coronary heart  
16 disease (CHD) risks were calculated using the Framingham (1991) algorithm adjusted for  
17 family history.  
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26 **Results:** The non-CVD cohort (n=990) was 74% male, 51% Caucasian and 73.1% were on  
27 HAART. Mean age was 41±9 years, systolic blood pressure 120±14mmHg, total cholesterol  
28 4.70±1.05mmol/L, HDL-C 1.32±0.48 mmol/L and 37% smoked. Median CVD risk was 4 (0-  
29 56)% in men and 1.4(0-37) % in women; CHD risks were 3.5(0-36)% and 0.6(0-16)%.  
30  
31 CVD risk was >20% in 6% of men and 1% of women and >10% in 12% of men and 4% of  
32 women. CVD risk was higher in Caucasians than other ethnicities; the risk factor contributing  
33 most was raised cholesterol. For patients on their first HAART, increased CHD risk (26.2%  
34 vs. 6.5%; odds ratio 4.03, p<0.001) was strongly related to duration of therapy.  
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46 **Conclusions:** Modifiable risk factors, especially cholesterol, and also duration of HAART,  
47 were key determinants of CVD risk.  
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50 **Discussion:** Regular CHD and/or CVD risk assessment should be performed on patients with  
51 HIV, especially during HAART therapy. The effect of different HAART regimens on CHD  
52 risk should be considered when selecting therapy.  
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57 Clinical Trials.gov identifier: NCT0105092  
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### **What is known about this topic?**

There is a higher incidence of observed cardiovascular disease in HIV patients, and this is increased with HIV therapy. Much of the increase has been ascribed to smoking within patients with high risk lifestyle, and the contribution of therapy and its duration to increasing cholesterol is uncertain.

### **What does this article add?**

This paper demonstrates that cholesterol, rather than smoking, is the most important contributor to increased predicted CV/CHD risk in our HIV cohort. It also shows that duration of HAART is key, and hence has important implications for the screening and management of patients with HIV infection.

### **Paper: 3270 words**

### **Introduction**

Anti-retroviral therapy (HAART) has reduced traditional HIV-associated disease and death[1]. Cardiovascular disease (CVD) has emerged as a major cause of morbidity and mortality in HIV following initial reports of dyslipidaemia[2 3 4], probably as a result of the combination of the pro-inflammatory effects of HIV infection, an increased prevalence of traditional risk factors (RFs), and the effects of HAART[5 6 7 8].

Cardiovascular disease risk screening is an increasing priority in national health care strategies[9]. Risk is calculated using tools derived from epidemiological studies including the USA Framingham study [10], UK primary care databases (QRISK)[11] and European prospective cohort studies (SCORE)[12]. In all these calculators, CVD or CHD risk is calculated using age, gender, smoking, systolic blood pressure (SBP), and total cholesterol: high-density lipoprotein cholesterol (TC: HDL-C) ratio[13]. *Ad hoc* adjustments can be made to CVD risk factor profiles to add the effects of family history of premature CHD, ethnicity and obesity[13]. HIV cohorts in the UK, and most of the developed world, are an “aging

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3 population”, and hence there is an increasing need to focus on CVD. Traditional CVD RFs  
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5 are increased in HIV populations [14 15], and seem to predict risk in a similar fashion to  
6  
7 uninfected populations [16].  
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10 This study was designed to describe the CVD RF burden in a large HIV cohort and to  
11  
12 apply these findings to recommendations for clinical practice.  
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## 15 **Methods**

### 16 **Setting**

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20 CREATE (cardiovascular risk evaluation and antiretroviral therapy) is a cross-sectional study  
21  
22 looking at estimated 10-year CVD and CHD risk, and the metabolic syndrome in HIV, and  
23  
24 this study, CREATE 1, concentrates on the former aspects. Recruitment was from a large  
25  
26 inner London teaching hospital with a large HIV cohort (exceeding 2500), and a medium-  
27  
28 sized local district hospital with a more affluent demographic.  
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### 33 **Study population**

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36 Patients at both hospitals are from a diverse ethnic and socioeconomic group. The  
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38 study recruited from June 2005 to September 2006. The protocol was approved by the St  
39  
40 Thomas’ Hospital Ethics Committee. In order to minimise selection bias, all HIV-infected  
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42 outpatients were eligible providing they were regular attendees for their general HIV care and  
43  
44 were not pregnant. Patients were not recruited from specialist clinics, such as the  
45  
46 lipodystrophy or hepatitis co-infection clinics, to avoid unfair weighting of patients with  
47  
48 metabolic issues. These patients were still open to study entry from their general HIV clinic  
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50 attendance. The research staff identified clinics for inclusion, and all such patients were  
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52 offered entry.  
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### 57 **Data Collection**

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3 A structured proforma was used to collect data on demographics, basic anthropometry,  
4 HIV and HAART history, current CD4 cell counts, HIV viral loads and details of co-  
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6 infections.  
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10 Ethnicity was self reported and categorised as: Afro-Caribbean, black African, white  
11 (Caucasian), Asian, and other. Details of HAART were recorded, including the date of  
12 commencement, protease inhibitor use, and the current regimen.  
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15 Anthropometric, physiological and biochemical parameters required to define  
16 cardiovascular risk and the metabolic syndrome were collected. The use of anti-atheroma  
17 therapies, including anti-thrombotic, antihypertensive, lipid-lowering and hypoglycaemic  
18 drugs, was collected, and the use of recreational drugs recorded. Weight, height, waist  
19 circumference and blood pressure, were measured by trained experienced research nurses or  
20 doctors using standard criteria. Blood pressure was measured in the sitting position after 5  
21 minutes rest with an Omron 320 automated system calibrated to British Hypertension Society  
22 standards. Blood lipids were measured fasting when possible, and assayed on a Roche Hitachi  
23 platform by standard techniques of CHOD-PAP for cholesterol and a non-ionic precipitation  
24 method for HDL-cholesterol. Data were entered directly onto the proforma during clinic  
25 attendance. Missing information on the database was checked with the source data, clinical  
26 notes, on scheduled review. The database was regularly cross-checked with the source data.  
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45 The estimated risk of CVD and CHD was calculated using the Framingham  
46 (1991)[10] equation recommended for UK use by both the Joint British Societies Guidelines  
47 (2005)[17] and the National Institute for Health and Clinical Excellence (NICE) guidelines  
48 (2008)[18]. No adjustment was made for ethnicity as the population was of diverse origin and  
49 no specific correction factors exist for West Africans. CHD risk relates to the development of  
50 coronary heart disease (MI, CHD death, angina, coronary insufficiency). CVD additionally  
51 includes stroke, congestive heart failure and peripheral vascular disease.  
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3 To assess CVD risk in a control population, data was compared with the  
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5 QRESEARCH database[19], which is derived from a UK general practice population, a self-  
6  
7 referred CVD risk programme in the UK (HEART-UK/Unilever CVD risk assessment  
8  
9 study)[20] and with the combined DAD cohort studies of cardiovascular risk in HIV[15 21]  
10  
11 Table 1a-c. The DAD study (Data Collection on Adverse Events of Anti-HIV Drugs) is a  
12  
13 collaboration of eleven prospective cohorts of HIV-infected individuals from across Europe,  
14  
15 Australia, and the US, totalling over 30,000 participants.  
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### 21 **Statistical Analysis**

22  
23 Statistical analysis was performed with SPSS. This analysis included only patients free  
24  
25 of pre-existing CHD diagnoses. Estimated 10-y CHD/CVD risk was summarised using  
26  
27 medians and the proportion with values >10% and >20% per decade. Subgroups were  
28  
29 compared using Chi-squared or Fishers exact test for categorical variables and Mann-Whitney  
30  
31 tests for continuous variables. Logistic regression was used to assess the association of  
32  
33 HAART use with 10-y CHD risk >10% and to investigate the extent to which this association  
34  
35 was independent of traditional CHD risk factors. The association of duration of HAART use  
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37 with 10-y CHD risk was examined in a subgroup of patients on first line HAART.  
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### 44 **Results**

#### 45 **Patient Characteristics**

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47 1021 patients were recruited, of which 990 were free of pre-existing CVD (table 1).  
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49 For the purposes of data presentation and analysis (table 1 a & 1b) the total numbers in  
50  
51 CREATE1 were 990 and exclude patients with established CVD. For purposes of comparison  
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53 with the DAD study cohorts, which included CVD, data from the complete cohort of 1021  
54  
55 was used (table 1c).  
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3 The majority, 74%, were male, 50.8% were white, 6.9% Afro-Caribbean, 33.3%  
4 African (various), 1.9% Asian, and 6.9 % from other ethnic groups. Men who have sex with  
5 men (MSM) comprised 43.9%, and 41% were heterosexual. Intravenous drug abuse was  
6 reported by 1.65%. The median HIV viral load was 50 copies/ml and CD4 count 406  
7 cells/mm<sup>3</sup>, and 73.1% were on HAART. CVD was present in 3% of both men and women,  
8 and diabetes in 3% and 2% respectively. The mean ( $\pm$ SD) age was 41 $\pm$ 9 years (48.6 %  $\geq$ 40  
9 years). Current or recent smoking (within 5 years) was reported by 37% and was commoner  
10 in whites (51% vs. 23%;  $p=0.02$ ) than black Africans. The systolic blood pressure (SBP) was  
11 120 $\pm$ 14 mmHg and 11% had a SBP >140mmHg. The total cholesterol was 4.70 $\pm$ 1.05 mmol/L  
12 and HDL-C was 1.32 $\pm$ 0.48mmol/L. An elevated total cholesterol (>5 mmol/L) was present in  
13 35.6%. HDL-C <1mmol/L in men or <1.2mmol/L in women was found in 33%. An elevated  
14 TC: HDL ratio > 5 was present in 18.7% and > 6 in 7.6%. Lipid-lowering drugs had been  
15 prescribed in 10.8%.

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36 The male population in CREATE 1 was younger (41 vs. 52 yrs), contained more  
37 smokers (45 vs.13%), had lower SBP (121 vs. 140 mmHg), slightly lower total cholesterol  
38 (4.7 vs. 5.1 mmol/L) and less established CHD than those self-referring for CVD risk  
39 screening in the HEART-UK/Unilever study. Similarly women recruited to CREATE 1 were  
40 younger (39 vs. 52 yrs), had lower SBP (118 vs. 134mmHg) and cholesterol (4.7 vs. 5.2  
41 mmol/L) and less CHD (3 vs. 9 %) but more smoked (16 vs.13%). HEART-UK/Unilever  
42 participants were markedly different in ethnic origin (92% were non-Caucasian) and were  
43 more centrally obese (64 vs. 40%). The population was similar to that recruited to the DAD  
44 study cohorts (table 1c) except for marginally lower total cholesterol (4.7 vs. 5.0 mmol/l),  
45 higher HDL-C (1.23 vs. 1.1 mmol/l) and BMI (24.7 vs. 23 kg/m<sup>2</sup>) and a lower prevalence of  
46 current smoking (37 vs. 51%).  
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## Cardiovascular and coronary Heart Disease Risk

The median CVD risk was 4 (0-56)%/decade in men and 1.4 (0-37) %/decade in women while CHD risks were 3.5 (0-36) %/decade and 0.6(0-16)%/decade respectively. CVD risk was >20% in 6% of men and 1% of women and >10% in 12% of men and 4% of women while CHD risk exceeded 10% in 13% of men and 2% of women and was >20% in 2% of men but no women. CVD risk was lower in all decade cohorts than the HEART-UK/Unilever study, although our patients were significantly younger and had a higher prevalence of smoking (table 1a & 1b). There was suggestion of increased CHD risk among males in our cohort compared to general population seen by general practitioners [19] In this study for men aged 45-55years, CHD risk >15% was present in 14.7% compared with 7.76% in the control group.. There was insufficient data to make meaningful comparisons for females.

Analyses were performed to investigate the associations of gender, ethnicity (Caucasians vs. non-Caucasians), risk group (MSM vs. heterosexuals) and use of HAART with CVD and CHD risk. The median CVD and CHD risks was 4.4% and 2% for men and 1.4% and 1% for women ( $p<0.001$ ). The proportions with CVD risk > 10% were 21.8% vs. 3.8% ( $p<0.001$ ) and for CHD risk  $\geq 10\%$  16.4% vs. 0.4% ( $p<0.001$ ) respectively. Statistically significant differences in CHD risk were also seen for those in older age groups, and groups stratified by total cholesterol above or below 5mmol/L, SBP above or below 140mmHg and smokers vs. non-smokers. (data not shown)

Compared to non-Caucasians, Caucasians had greater CVD and CHD risks, and approximately a 3-fold increase in the prevalence of CHD risk >10% or CVD risk >20%. These differences could partly be attributed to more males among our Caucasians (96% vs. 53%;  $p<0.001$ ) hence more MSM individuals (73% vs. 13%;  $p<0.001$ ), higher viral load (2.63

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3 vs. 2.33;  $p < 0.001$ ), but also higher median CD4 count (432 vs. 381;  $p < 0.001$ ), more smoking  
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5 (50% vs. 22%;  $p < 0.001$ ) and lower HDL-C (1.22 vs. 1.42 mmol/L;  $p < 0.001$ ). No significant  
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7 differences in CVD or CHD risk were observed in MSM compared to male heterosexuals,  
8  
9 despite significant differences in age (40 vs. 42 years;  $p < 0.001$ ), smoking (50% vs. 37%;  
10  
11  $p < 0.001$ ) and prevalence of drug-treated hypertension (5% vs. 11%;  $p = 0.003$ ) and higher viral  
12  
13 loads (2.66 vs. 2.33;  $p < 0.001$ ) and CD4 counts (434 vs. 381;  $p < 0.001$ ).  
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### 16 17 18 **HAART use**

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22 705 patients out of 973 were on HAART; 245 were on their first line regimen, of  
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24 whom 44.1% had used HAART for  $< 1$  yr, and about a third and a quarter used HAART for 1-  
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26 3yrs and  $> 3$ yrs respectively.  
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29 Patients on HAART had significantly raised median CVD risk (3.57% vs. 2.34%;  
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31  $p = 0.01$ ) and CHD (0.64% vs. 0.38 %;  $p < 0.001$ ) risk, associated with increased age (42 vs. 37  
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33 years,  $p < 0.001$ ), higher total cholesterol (4.86 vs. 4.24 mmol/L;  $p < 0.001$ ) but also lower viral  
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35 load (1.96 vs. 4.02;  $p < 0.001$ ), and higher HDL-C (1.39 vs. 1.12 mmol/L;  $p < 0.001$ ).  
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39 The duration of HAART was associated with CVD and CHD risk. For this analysis,  
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41 only the 245 participants on first line therapy were included in order to avoid confounding  
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43 from previous HAART use. The proportions with 10 year CVD and CHD risk  $> 20\%$  for  
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45 those on HAART  $< 1$ yr were 4.3% and 0.8% and for  $\geq 3$ yrs exposure 11% and 4.8%  
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47 respectively ( $p = 0.01$ ). These differences were statistically significant for both Caucasians and  
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49 non-Caucasians. A further analysis was performed to define variables within this group  
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51 associated with increased CVD risk with duration of HAART. Age  $\geq 40$ yrs, total cholesterol  
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53  $\geq 5$ mmol/L, and SBP  $\geq 140$ mmHg were all more common in the group who had been on  
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55 HAART the longest. Conversely, there were fewer persons with low HDL-C in the  $\geq 3$  year  
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57 compared with  $< 1$ yr HAART groups and the TC/HDL ratio did not vary with length of time  
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3 on HAART (Table 3b). Smoking was not a factor that contributed to a higher CHD risk for  
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5 those on HAART for longer periods (as a group), as there were similar proportions of  
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7 smokers in each group regardless of the duration on HAART.  
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10 The contribution that each Framingham equation variable made to estimated  
11  
12 CVD/CHD risk in patients on HAART was investigated. The unadjusted odds ratio for high  
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14 CVD risk was 1.36 (0.92, 2.00) for HAART users vs. non- users. Adjusting for age and sex,  
15  
16 the odds ratio fell to 1.13(0.72, 1.80). Similarly the unadjusted odds ratio for high CHD risk  
17  
18 was 1.59 (0.99, 2.57) for HAART users vs. non- users and after adjustment for age and sex,  
19  
20 the odds ratio fell to 1.02 (0.57, 1.85). This excess risk was accounted for after adjustment for  
21  
22 SBP, smoking and total cholesterol; the biggest fall in odds ratio was observed after  
23  
24 correction for cholesterol alone (0.63 (0.34- 1.20)).  
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29 A similar analysis was performed for 245 patients on first-time HAART according to  
30  
31 duration of HAART (<1 year, 1-3 years,  $\geq 3$  years) (figure 1). The unadjusted odds ratio for  
32  
33 high CHD risk were 1.24 for 1-3 years and 5.13 for  $\geq 3$ years groups, compared to the <1 year  
34  
35 group (Figure 3). Again the greatest contribution to the excess risk in both the 1-3 years and  $\geq$   
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37 3 years groups was total cholesterol, as indicated by the comparatively large fall in odds ratio  
38  
39 after adjustment for total cholesterol.  
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## 45 **Discussion**

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48 The increased frequency of observed CHD in HIV-infected versus uninfected patients  
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50 has focused attention on appropriate strategies to prevent cardiovascular disease in this  
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52 population. Observational cohort studies have shown an increase in observed CVD events  
53  
54 with the use of HAART, particularly with protease inhibitors [15 21]. Some of the protease  
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56 inhibitor effect can be attributed to drug-associated dyslipidaemia [21].  
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3 Among our UK-based cohort in CREATE1, levels of CVD and CHD risk appeared  
4 high compared to similar age groups in the general population, with a higher prevalence of  
5 smoking and hypercholesterolaemia. The average CVD and CHD risks in our cohort were  
6 6.0% and 4.15% respectively. The CHD risk was much lower than the 7-7.4% CHD risk seen  
7 in the Italian SIMONE cohort of HIV infected patients [22 23], where the prevalence of  
8 elevated CVD risk >10% was 17% and CHD risk>10% was 10%. CVD risk >20% was  
9 present in 4.9% and CHD risk >20% in 1.6%. Other cohort studies of HIV-infected patients  
10 have shown higher prevalence of CHD risk >10% of 23% and >20% in 8% [24] or 11% [14].  
11 In the DAD study the same version of the Framingham risk scoring tool used in our study  
12 determined that the CHD risk was 2.4% [25]. Thus the population recruited to CREATE 1 is  
13 at intermediate risk for CVD compared to other HIV cohort studies. The CHD risk in the  
14 CREATE 1 cohort was elevated compared to a similar cohort of the general population from  
15 the QRESEARCH database and the proportions with elevated CVD risk were similar to sex-  
16 matched age cohorts from the self-selected general population recruited for the HEART-  
17 UK/Unilever Study[20].

18  
19 We found in CREATE 1 that caucasians were much more likely to have a CVD or  
20 CHD risk  $\geq 10\%$  than non-Caucasians. Even amongst the non-Caucasians, the proportion with  
21 raised CVD or CHD risk increased with the duration of HAART (from 3.5% with <1 year use  
22 to 17.9% with >3 years use; n=245 first line users only). While many guidelines recommend  
23 adjustment of the Framingham risk for additional risk factors, this remains controversial. The  
24 Framingham risk calculator was derived from data on a mainly white working class  
25 population, and predicted the correct proportion at risk in patients with HIV in DAD cohort  
26 study [25]. Aside from Caucasians, the largest ethnic sub-group in CREATE 1 was African  
27 and diverse with respect to country of origin. Secondary adjustment for ethnicity is possible  
28 and tends to reduce CVD and CHD risk in African-derived populations compared to Asian or

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3 Caucasian populations in the UK [26] but is limited and is mostly based on West Africans.  
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5 The degree of adjustment required for other African populations has not been determined but  
6  
7 CVD risk is elevated in urban or migrant populations[27 28]. In this study as CVD and CHD  
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9 risks had already been adjusted for family history further adjustment was not performed[17].  
10  
11 In Afro-Caribbean general population the age-adjusted prevalence of CVD is 0.61 but there is  
12  
13 no data on patients with HIV with this ethnic background in the UK.  
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16  
17 In our study, the increased predicted CVD and CHD risk among Caucasians is at  
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19 variance with a large prospective HIV cohort study of observed acute myocardial infarctions  
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21 from the USA [29], where African-American race was a significant predictor of acute  
22  
23 myocardial infarction, with a relative risk 1.43 compared to non-African-Americans. This  
24  
25 may well reflect differences in underlying risk factors between the 2 cohorts, such as  
26  
27 proportions of smokers, differences in BMI and dysglycaemia and effects of social  
28  
29 deprivation. Similar discrepancies were found between our cohort and the same US cohort in  
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31 respect of gender as among our female patients there were very few with even a moderately  
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33 high predicted CVD or CHD risk. There was a marked increase in the relative rate of  
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35 females with observed acute myocardial infarctions in the same US HIV cohort, with a  
36  
37 relative risk of 2.98, compared to the control population [29].  
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44 In this study smoking was less frequent than in the DAD cohort (37 vs. 52%) and  
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46 showed pronounced ethnic and gender differences. Smoking was most associated with CVD  
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48 risk in males and was commoner in Caucasians. In females the prevalence of smoking was  
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50 slightly increased compared to the general population. A large proportion of the cohort was  
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52 heterosexual black African, where smoking was less prevalent than among Caucasians (23%  
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54 vs. 51%). Therefore, the relative contribution of smoking to CVD risk in this population is  
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56 likely to be lower than in other studies.  
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3 The greatest population-attributable risk in the INTERHEART study was  
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5  
6 dyslipidaemia. Dyslipidaemia is frequent in HIV [25]. Dyslipidaemia related to the duration  
7  
8 of HAART therapy contributed most to an increased predicted CVD and CHD risk amongst  
9  
10 our cohort. The duration of first line HAART use was associated with a CHD risk  $\geq 10\%$ , with  
11  
12 a relative risk  $> 5$  for those on HAART for over 3 years compared to those who on HAART  
13  
14 for under one year. This finding replicates those of the DAD study recruited from 1999-2003  
15  
16 [21] and shows that despite the availability of newer protease inhibitors that do not  
17  
18 significantly affect lipid concentrations, most patients were still receiving HAART regimens  
19  
20 that induced dyslipidaemia and increased CHD risk.  
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24 These findings provide a rationale for specific policies for the management of cardiovascular  
25  
26 risk in people with HIV, using adaptations of standard guidelines from the Joint British  
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28 Societies [17] or NICE [18]. This study demonstrates that management of CVD risk in HIV  
29  
30 patients should consider length of exposure to HAART as well as ethnicity and gender. Risk  
31  
32 calculators give only broad estimates of risk [30] and additional risk stratification may be  
33  
34 required in intermediate (10-20%) risk patients [31 32]. Patients at 10-20% risk should be  
35  
36 prioritised for intensive lifestyle interventions. Modifiable risk factors should be actively  
37  
38 managed, including the use of anti-hypertensives and lipid-lowering agents where lifestyle  
39  
40 changes such as diet and exercise do not suffice. It is important for the individual and the  
41  
42 patient cohort to reduce rates of smoking, and to attain optimum body weight [5 6]. If these  
43  
44 intervention strategies are not successful in reducing CHD risk, then changing HAART  
45  
46 regimens should be considered [33 34 35]. The observation that duration of first line HAART  
47  
48 correlated strongly with CHD risk, has clinical implications for management. It is important  
49  
50 that CHD is assessed before and after treatment, to ascertain the extent to which the HAART  
51  
52 might be contributing to increased CHD risk. There are a number of antiretroviral agents that  
53  
54 do not affect lipids to the extent of other current therapies. These include the newer generation  
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3 protease inhibitors, such as atazanavir[36], although this advantage is mitigated in part by the  
4  
5 concomitant use of ritonavir as a pharmacological enhancer[37]. Other agents that have a  
6  
7 favourable lipid profile include raltegravir, an integrase inhibitor[38], as well as some of the  
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9 agents that have been available for many years, such as nevirapine[34 35].  
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4 **List of Abbreviations**  
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6 CREATE 1- Cardiovascular Risk Evaluation and Antiretroviral Therapy Effects (Study  
7 name).  
8

9  
10 BMI= body mass index.  
11

12  
13 CHD = coronary heart disease risk  
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15  
16 CVD= cardiovascular disease risk.  
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18  
19 CVR= cardiovascular risk.  
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21  
22 HDL= high-density lipoprotein.  
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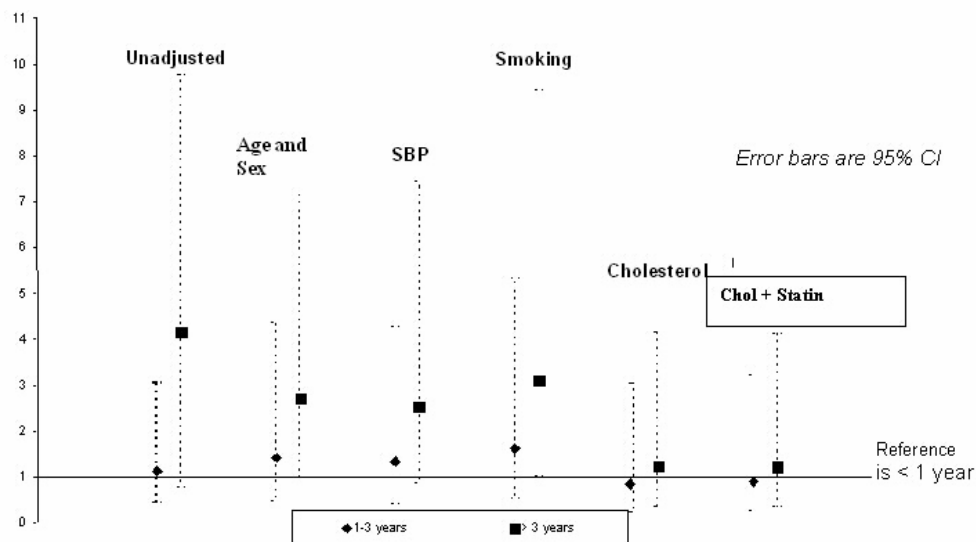
24  
25 IHD= ischaemic heart disease.  
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27  
28 MSM= men who have sex with men.  
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31 (s)BP= (systolic) blood pressure.  
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TC= total cholesterol.

Figure 1. Comparison of CHD risk with length of treatment with HAART before and after adjustment for CHD risk factors.



**Contribution of CV risk factors to Odds Ratio (OR) for 10 year CHD risk>10% by length of time on HAART.**  
**N=243 first line HAART users only (Odds Ratio Y-axis). 1<sup>st</sup> adjustment for age/sex; then sequentially for sBP, Smoking and Total Chol. The degree of OR drop reflects the contribution of that factor to risk in the first place. Biggest OR drop seen when TC corrected for.**

Table 1a-c: Clinical characteristics of male and female patients attending a HIV service in the UK compared with a general cardiovascular risk screening group in the UK and the DAD cohort study.

1a – HIV positive males in CREATE 1 compared to a HEART UK population

	Cohort without CVD (male; n=737)	HEART-UK (male; n= 27,776)
Age	41.2± 9.2	51.5± 16.2*
Caucasian(%)	65	Not available
Smoking (%)	45*	13.4
Systolic Blood Pressure (mmHg)	121± 14	140± 17*
Hypertension (%)	12	13
Total Cholesterol (mmol/L)	4.70± 1.05	5.10± 1.00*
HDL-cholesterol (mmol/L)	1.25± 0.44	1.20± 0.40
Diabetes (%)	2	4
CHD (+) (%)	NA	11
BMI (kg/m <sup>2</sup> )	24.6± 3.8	-
Waist > 102 cm (%)	24	25

1b – HIV positive females in CREATE 1 compared to a HEART UK population

	Cohort without CVD (female; n=253)	HEART-UK (female; n=43,261)
Age	38.8± 8.8	52.1± 15.4*
Caucasian(%)	9	Not available
Smoking (%)	16*	12.7
Systolic Blood Pressure (mmHg)	118±14	134± 19*
Hypertension (%)	9	13
Total Cholesterol (mmol/L)	4.74± 1.04	5.20±1.00*
HDL-cholesterol (mmol/L)	1.54± 0.54	1.50± 0.40
Diabetes (%)	2	3
IHD (+) (%)	NA	8.7*
BMI (kg/m <sup>2</sup> )	27.8± 6.1	-
Waist > 88 cm (%)	64*	40.1

1c - Complete cohort in CREATE 1 compared to subjects in the DAD study	Complete CREATE 1 cohort , including CVD (N=1022)	DAD (N=23,468)
Age	40 (35-46)	39 (34-47)
Caucasian(%)	51	-
Male (%)	76	75
MSM	44	45
Smoking (%)	37*	51
Systolic Blood Pressure (mmHg)	120 (110-130)	120 (110-130)
Hypertension (%)	12*	8.5
Total Cholesterol (mmol/L)	4.7 (3.9-5.3)	5.0 (4.2-6.0)
HDL-cholesterol (mmol/L)	1.23 (1.00-1.53)	1.1 (0.9- 1.4)
Diabetes (%)	3	2.5
IHD (+) (%)	3	1.4
CD4 count (mm <sup>3</sup> /L)	406( 289-562)	418( 255-612)
Viral Load (log)	<1.70 (<1.70-3.54)	<2.7 (<2.7-6.9)
BMI (kg/m <sup>2</sup> )	24.7 (22.3-27.7)	23( 21-25)
Waist > 102 cm (%)	24	-
Family history early CHD (%)	13	11.7

**Table 2. Association of factors with current HAART use**

n/N (%)	Using HAART	Not using HAART	p value
	N=705	N=258	(Chi-squared/Fishers Exact test)
Male	509/705 (72.2)	204/258 (79.1)	p=0.031
Age >40 yrs	388/705 (55.0)	83/258 (32.2)	p<0.001
Caucasian	330/690 (47.8)	149/253 (58.9)	p=0.003
MSM	279/705 (39.6)	144/258 (55.8)	p<0.001
Chol >5 mmol/l	296/705 (42.0)	47/258 (18.2)	p<0.001
Lipid lowering drug use	88/705 (12.5)	6/258 (2.3)	p<0.001
HDL <1 mmol/l	134/705 (19.0)	95/258 (36.8)	p<0.001
TC/HDL ratio >4.5	192/705 (27.2)	88/258 (34.1)	p=0.037
Sys BP >140 mmHg	77/705 (10.9)	29/258 (11.2)	p=0.89
Smoker	250/705 (35.5)	107/258 (41.5)	p=0.087

Table 3 a &amp; b: Mean lipid values according to HAART use

## a) Mean Total cholesterol, HDL cholesterol and Total/HDL ratio by current HAART use

HAART now		Total Cholesterol	HDL-Cholesterol	TC: HDL ratio
No	Mean	4.28	1.14	4.05
	N	258	258	258
	Std. Deviation	0.89	0.34	1.32
Yes	Mean	4.88	1.40	3.84
	N	705	705	705
	Std. Deviation	1.06	0.51	1.34
Total	Mean	4.72	1.33	3.90
	N	963	963	963
	Std. Deviation	1.05	0.49	1.34

## b) Mean Total cholesterol, HDL cholesterol and Total/HDL ratio by years on first line

Yrs 1 <sup>st</sup> Line		Total Cholesterol	HDL-cholesterol	TC: HDL ratio
<1	Mean	4.50	1.23	3.98
	N	108	108	108
	Std. Deviation	0.97	0.42	1.27
1-3	Mean	4.81	1.41	3.75
	N	76	76	76
	Std. Deviation	0.96	0.50	1.33
≥3	Mean	5.31	1.49	3.91
	N	61	61	61
	Std. Deviation	0.86	0.49	1.39
Total	Mean	4.80	1.35	3.89
	N	245	245	245
	Std. Deviation	0.99	0.48	1.32

**Contributions of authors:**

BSP is senior author and conceived, designed and managed the clinical trial and wrote the manuscript. MA, ES, LP, GP, CD, RK, AD & A E helped with study design and recruitment and manuscript writing. FL and AW helped with study design, manuscript writing and statistical analysis. All authors have seen all the key drafts, including final submission.

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