Circulation
Cardiovascular Genetics
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

Contribution of Genome-Wide Significant Single-Nucleotide Polymorphisms and Antiretroviral Therapy to Dyslipidemia in HIV-Infected Individuals : A Longitudinal Study

Margalida Rotger, Cornelia Bayard, Patrick Taffé, Raquel Martinez, Matthias Cavassini, Enos Bernasconi, Manuel Battegay, Bernard Hirschel, Hansjakob Furrer, Andrea Witteck, Rainer Weber, Bruno Ledergerber, Amalio Telenti, Philip E. Tarr and the Swiss HIV Cohort Study

Circ Cardiovasc Genet 2009;2;621-628; originally published online September 18, 2009;
DOI: 10.1161/CIRCGENETICS.109.874412
Circulation: Cardiovascular Genetics is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1942-325X. Online ISSN: 1942-3268

Contribution of Genome-Wide Significant Single-Nucleotide Polymorphisms and Antiretroviral Therapy to Dyslipidemia in HIV-Infected Individuals

A Longitudinal Study

Margalida Rotger, PharmD, PhD; Cornelia Bayard, MD; Patrick Taffé, PhD; Raquel Martinez, BSc; Matthias Cavassini, MD; Enos Bernasconi, MD; Manuel Battegay, MD; Bernard Hirschel, MD; Hansjakob Furrer, MD; Andrea Witteck, MD; Rainer Weber, MD; Bruno Ledergerber, PhD; Amalio Telenti, MD, PhD; Philip E. Tarr, MD; the Swiss HIV Cohort Study

Background—HIV-infected individuals have an increased risk of myocardial infarction. Antiretroviral therapy (ART) is regarded as a major determinant of dyslipidemia in HIV-infected individuals. Previous genetic studies have been limited by the validity of the single-nucleotide polymorphisms (SNPs) interrogated and by cross-sectional design. Recent genome-wide association studies have reliably associated common SNPs to dyslipidemia in the general population.

Methods and Results—We validated the contribution of 42 SNPs (33 identified in genome-wide association studies and 9 previously reported SNPs not included in genome-wide association study chips) and of longitudinally measured key nongenetic variables (ART, underlying conditions, sex, age, ethnicity, and HIV disease parameters) to dyslipidemia in 745 HIV-infected study participants (n=34 565 lipid measurements; median follow-up, 7.6 years). The relative impact of SNPs and ART to lipid variation in the study population and their cumulative influence on sustained dyslipidemia at the level of the individual were calculated. SNPs were associated with lipid changes consistent with genome-wide association study estimates. SNPs explained up to 7.6% (non–high-density lipoprotein cholesterol), 6.2% (high-density lipoprotein cholesterol), and 6.8% (triglycerides) of lipid variation; ART explained 3.9% (non–high-density lipoprotein cholesterol), 1.5% (high-density lipoprotein cholesterol), and 6.2% (triglycerides). An individual with the most dyslipidemic antiretroviral and genetic background had an ≈3- to 5-fold increased risk of sustained dyslipidemia compared with an individual with the least dyslipidemic therapy and genetic background.

Conclusions—In the HIV-infected population treated with ART, the weight of the contribution of common SNPs and ART to dyslipidemia was similar. When selecting an ART regimen, genetic information should be considered in addition to the dyslipidemic effects of ART agents. **(*Circ Cardiovasc Genet*. 2009;2:621-628.)**

Key Words: cardiovascular diseases ■ HIV infection ■ genome-wide analysis ■ genetics ■ hypercholesterolemia

HIV-infected individuals may have accelerated atherogenesis[1], and a major long-term concern is an increased risk of metabolic complications, including myocardial infarction,[2,3] diabetes mellitus,[4,5] stroke, and peripheral vascular disease.[6] A substantial proportion of the myocardial infarction risk in large, observational studies was explained by dyslipidemia.[2,3] The prevalent view is that dyslipidemia in HIV-infected individuals is largely determined by environmental factors such as advanced immunosuppression, uncontrolled HIV viremia,[7,8] and most notably, the dyslipidemic effects of antiretroviral therapy (ART).[9,10] Genetic factors are also likely to be involved.[11–15] However, previous studies investigating common single-nucleotide polymorphisms (SNPs) for their contribution to dyslipidemia in the HIV

Clinical Perspective on p 628

Received April 21, 2009; accepted September 14, 2009.

From the Institute of Microbiology (M.R., C.B., R.M., A.T.), University Hospital and University of Lausanne, Lausanne, Switzerland; Swiss HIV Cohort Study Data Center (P.T.), Lausanne, Switzerland; Infectious Diseases Service (M.C.), Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland; Medical Service, Ospedale Regionale (E.B.), Lugano, Switzerland; Infectious Diseases Service, University Hospital Basel (M.B.), Basel, Switzerland; Infectious Diseases Service, University Hospital Geneva (B.H.), Switzerland; Infectious Diseases Service, University Hospital Bern (H.F.), Switzerland; Infectious Diseases Service, Kantonsspital St. Gallen (A.W.), St. Gallen, Switzerland; Infectious Diseases Service, University Hospital (R.W., B.L.), Zurich, Switzerland; and Infectious Diseases Service, Kantonsspital Bruderholz (P.E.T.), University of Basel, Switzerland.

Drs Rotger, Bayard, and Taffé contributed equally to this work.

The online-only Data Supplement is available at http://circgenetics.ahajournals.org/cgi/content/full/CIRCGENETICS.109.874412.

Correspondence to Philip E. Tarr, MD, Infectious Diseases Service, 4101 Kantonsspital Bruderholz, University of Basel, Basel, Switzerland. E-mail philip.tarr@unibas.ch; Amalio Telenti, MD PhD, Institute of Microbiology, University Hospital Lausanne, 1011 Lausanne-CHUV, Switzerland, E-mail amalio.telenti@chuv.ch

Circ Cardiovasc Genet **is available at http://circgenetics.ahajournals.org** **DOI: 10.1161/CIRCGENETICS.109.874412**

setting were limited by the validity of the SNPs interrogated, the assessment of single or few SNPs only, or by their cross-sectional design.[11–14,16] Recent genome-wide association studies (GWAS) have now afforded a comprehensive, unbiased inventory of common SNPs reproducibly associated with dyslipidemia in the general population.[17–25]

The aim of this study was to evaluate the cumulative impact of SNPs identified in GWAS to dyslipidemia in HIV-infected individuals. A second aim was to longitudinally assess relevant nongenetic factors for their contribution to dyslipidemia. This was done to address the unresolved problem of limited interindividual serum lipid variation explained by GWAS-identified SNPs, despite the expanding number of SNPs known to influence serum lipid levels.[18–20,24,26–29] Genetic data should be assessed in the context of potential environmental modifiers, as previously suggested,[28,30] and dyslipidemia in HIV-infected individuals may represent a paradigmatic setting to calculate the relative contributions of genetic and environmental factors, particularly ART. We therefore aimed to replicate 33 GWAS-identified SNPs and 9 previously reported candidate SNPs not covered by GWAS chips in 745 participants of the Swiss HIV Cohort Study (SHCS) who contributed 34 565 lipid measurements during treatment with varying ART combinations during a median study period of 7.6 years. To date, this is the most comprehensive genetic lipids study undertaken in HIV-infected individuals.

Methods

Participants, Lipids, ART

Study participants were followed up in the SHCS (http://www.shcs.ch) during the study period (January 1, 1999, to October 31, 2008). The SHCS Genetics Project was approved by the ethics committees of all participating centers. Participants gave written informed consent for genetic testing. The study population consisted of 751 SHCS participants, including 426 participants of our previous study on the contribution of 20 candidate SNPs in 13 genes to ART-associated dyslipidemia[11]; 222 randomly selected SHCS Genetics Project participants fulfilling the same inclusion criteria (≥2 years of ART exposure and ≥8 lipid determinations during the study period); and 103 SHCS participants with new-onset diabetes mellitus during longitudinal follow-up after March 1, 2000, who were the subjects of a previous epidemiological study.[4]

As part of routine follow-up, SHCS participants have regular measurements of serum levels of total cholesterol, HDL cholesterol, and triglycerides (TG). Each antiretroviral agent and all cardiovascular (including lipid-lowering) medication are recorded with start and stop dates in the SHCS database. The influence of ART and lipid-lowering agents on lipid levels was assumed to be rapid and reversible.[31] This allowed, at each lipid measurement, to determine the specific ART medications in current use and to "assign" each lipid value to the influence of given ART agents or ART group. If ART was changed or interrupted, subsequent lipid values were thus attributed to the new regimen or to "no ART," respectively. During the follow-up period, each study participant could therefore contribute lipid measurements to >1 ART group. ART agents were distributed into groups defined a priori according to published reports of their lipid effects.[9–11,14,32–35] These ART groups were validated by the results of the regression analysis, which was performed exploiting all 261 408 lipid determinations available in the SHCS database since January 1, 1999. Non-HDL cholesterol was calculated as non-HDL cholesterol=total cholesterol−HDL cholesterol. Non-HDL cholesterol (and not LDL cholesterol) was analyzed to accommodate participants with hypertriglyceridemia and lipid values drawn in the nonfasting state.

Genetic Variants and Genotyping

The genetic variants selected for this study had significant published serum lipid associations, including 33 SNPs from recent GWAS in the general population[18,22–24] and 9 candidate SNPs from the published literature and assessed in previous longitudinal studies of HIV-infected participants followed up in the SHCS[11,12,14,36–41] (supplemental Table I). Of these, 14 SNPs were previously associated with LDL cholesterol, 20 SNPs with HDL cholesterol, and 22 SNPs with TG levels. Following the goal of replication, ie, the use of only previously reported genetic markers, each SNP was only studied for its established association with a particular lipid end point. Genotyping was performed by TaqMan allelic discrimination using TaqMan SNP genotyping assays predesigned by Applied Biosystems, except rs2854117 (home-designed TaqMan assay[11,14]), rs2854116 (restriction fragment length polymorphism analysis[11,14]), and rs1800775 (direct sequencing[11]). The results were entered into the central SHCS genetic database without knowledge of lipid values.

Statistical Analysis

The data were analyzed longitudinally by modeling the individual effects of the different covariables on serum lipid levels, using variance components multivariate regression analysis, as outlined in our previous report.[11] All analyses were adjusted for time-dependent covariables (including ART regimen, age [years], body mass index [BMI; kg/m^2], waist circumference [cm], fasting state, treatment with lipid-lowering agents, smoking status, CD4+ T-cell count [$\log_{10}$], and HIV viral load [$\log_{10}$]) and time-fixed covariables (including sex, presumed mode of HIV transmission, ethnicity, diabetes mellitus status, and the genetic variants). Lipid levels were $\log_{10}$ transformed. On the back-transformed scale, the model was multiplicative and all covariables interacted. Formal gene-gene and gene-drug interaction assessment in our previous study[11] showed that the power of interaction testing in our dataset was limited by the large number of possible interactions and the resulting small number of participants in some resulting strata. Therefore, to avoid overfitting, no formal gene-gene or gene-drug interaction terms were considered here.

We first analyzed the effect of 1 or 2 variant alleles of each SNP on lipid levels separately, adjusted for nongenetic covariables. Then, candidate SNPs with a P value ≤0.2 in the separate analyses were assessed in a multi-SNP model adjusted for all nongenetic covariables. Each SNP was treated as a categorical variable having 3 levels. Model selection[42,43] was performed by backward elimination, as previously described[11] (Taffé and Tarr, unpublished data, 2009), and was based on confounding adjustment, Student t test, Fisher F test, and optimization of the Akaike information criterion.

From the final regression model, and separate for non-HDL cholesterol, HDL cholesterol, and TG, we generated 3 genetic scores that have been used in previous reports[11,18,24] (see supplementary Methods): (1) the first (weighted) genetic score resulted from the weighted sum of the impact of each allele of each SNP on lipid levels, with the estimated coefficients as weights[11] and from considering the most likely mode of inheritance (ie, recessive, additive, or dominant) of each allele to gain statistical power; (2) the second (additive weighted) genetic score assumed an additive (codominant) mode of inheritance and resulted from the weighted sum of the number of alleles of each SNP; and (3) the third (additive unweighted) genetic score also assumed an additive mode of inheritance, but the impact of each SNP was assumed to be the same except for the sign (ie, SNPs with an lipid-increasing effect were added, and SNPs with a lipid-lowering effect were subtracted).[18,20] We calculated the proportion of explained variation in lipid levels[44] for both genetic and nongenetic covariables.[45] All results are first presented using the weighted genetic score and then compared (see supplementary Material) to results using the additive/weighted and the additive/unweighted models when appropriate.

Because the clinical relevance of prolonged dyslipidemia is well documented by studies on genetic causes of dyslipidemia,[46,47] we included all lipid measurements available for each participant and calculated the observed proportions of participants with sustained dyslipidemia during the study period. This was defined, as in our previous reports,[6,11] as more than two thirds of a participant's

Table 1. Characteristics of the Study Participants

Characteristic	Study Participants (n=745)
Baseline age, y, median (interquartile range)	40.1 (35.1 to 48.2)
Men/women, n (% men)	559/186 (75)
Ethnicity, n (%)	
White	656 (88)
Black	51 (6.9)
Hispanic	19 (2.6)
Asian	16 (2.1)
Unknown/other	3 (0.4)
Presumed mode of HIV transmission, n (%)	
Men who had sex with men	309 (41.5)
Heterosexual	265 (35.6)
Injection drug users	144 (19.3)
Unknown/other	27 (3.6)
Follow-up period	
Dropout or death, n (%)	32 (4.3)
CD4+ T-cell count, cells/μL, median (interquartile range)	486 (337 to 680)
HIV viral load (<400 copies/mL), %	84.3
Participants treated with lipid-lowering agents, n (%)	201 (27)
Diabetes mellitus, n (%)	126 (17)

respective lipid measurements being above or below the cutoff level defined by the National Cholesterol Education Program Third Adult Treatment Program (non-HDL cholesterol: >4.1 mmol/L [160 mg/dL]; HDL cholesterol: <1.03 mmol/L [40 mg/dL]; TG: >2.26 mmol/L [200 mg/dL]).[48] The observed proportions of participants with sustained dyslipidemia were then assessed according to ART groups and genetic score, summarized into tertiles (supplemental Tables II through IV). All statistical analyses were conducted using SAS version 9.1 and Stata version 9.2

Results

Characteristics of Participants, ART, and SNPs

Complete genotyping was accomplished for 745 of 751 participants (99.2%). Their characteristics are shown in Table 1. The prevalence of diabetes mellitus was high (17%) because of the inclusion of 103 SHCS participants with incident diabetes mellitus.[4] During the study period, 11 383, 11 410, and 11 772 measurements were made of non-HDL cholesterol, HDL cholesterol, and TG in 743, 742, and 742 participants, respectively. Each participant contributed a median of 15 (interquartile, 13 to 17) lipid measurements and experienced a median of 3 ART modifications (interquartile, 2 to 4) during a median study period of 7.6 (interquartile, 6.9 to 7.8) years. The effect of ART and nongenetic covariables on lipid levels was consistent with published reports (Table 2; Figures 1A, 2A, and 3A). Minor allelic frequencies were similar to previous reports in ethnically similar populations (supplemental Table I). All SNPs were in Hardy-Weinberg equilibrium in the white participants (n=656; $P>0.05$). The genetic effects were similar when nonwhite participants (n=89) were excluded from the analyses, for non-HDL cholesterol, HDL cholesterol, and TG, and in terms of both the magnitude and the direction of the effects (data not shown). Therefore, the following results are all based on the entire study population and are adjusted for ethnicity.

Non-HDL Cholesterol

All 14 interrogated SNPs had an (non-HDL cholesterol–increasing or –lowering) effect compatible with previous estimates (supplemental Table I). In the final, multi-SNP model, adjusted for all nongenetic and genetic covariables, 7 SNPs previously published in GWAS in the general population (rs10402271, rs693, rs562338, rs11206510, rs646776, rs17321515, and rs6511720) and 2 non-GWAS SNPs (rs429358 and rs7412) contributed significantly ($P<0.05$) to non-HDL cholesterol (Figure 1A; supplemental Table I). rs11591147 (*PCSK9*; $P=0.054$; allelic frequency $f=0.01$) was retained in the final model because of its large non-HDL cholesterol-lowering effect in this study and in published reports.[18,46] The final model explained 24.6% of the serum non-HDL cholesterol variation in the study population. Genetic covariables explained 7.6% (weighted score), 6.8% (additive weighted score), and 5.9% (additive unweighted score), respectively. ART explained 3.9%, the CD4+ count

Table 2. Antiretroviral Regimens Grouped According to Their Impact on Serum Lipid Levels

Serum Lipid Analyzed	Group 1	Group 2	Group 3
Non-HDL cholesterol	No ART	PI (except ATV/r)	NA
	NRTI only	NNRTI	
	Atazanavir boosted with ritonavir (ATV/r)		
HDL cholesterol	No antiretroviral therapy	PI	NNRTI
	NRTI only		
Triglycerides	No antiretroviral therapy	Single PI-containing ART (without ritonavir)	Ritonavir-containing ART (except ATV/r)
	NRTI only	ATV/r	
	Nevirapine-containing ART without a PI	Efavirenz	
	Atazanavir unboosted		

Because <0.5% of lipid determinations were made during raltegravir, etravirine, or T20 exposure, these agents were not considered in the analysis. NA indicates not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

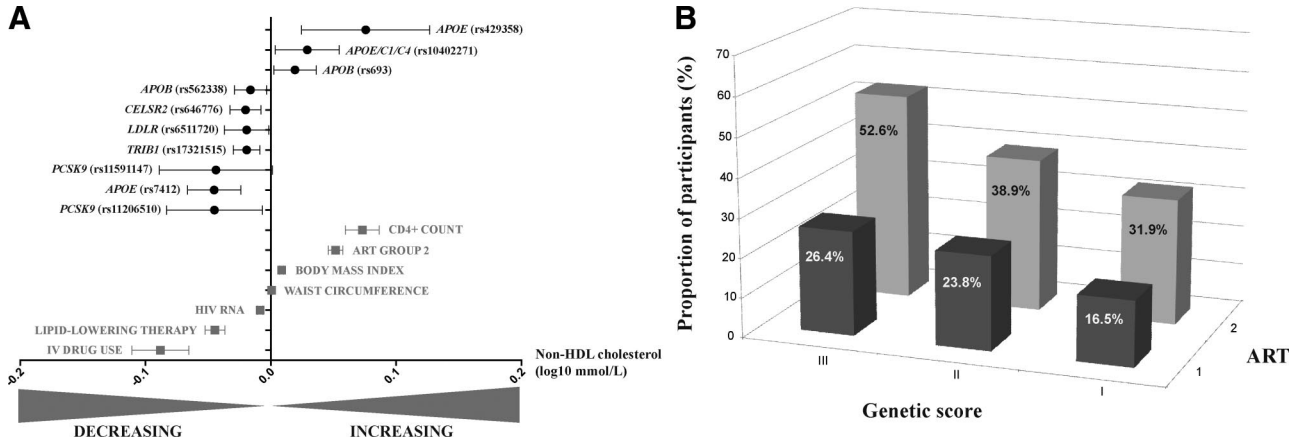


Figure 1. A, Impact of genetic and key nongenetic variables on non-HDL cholesterol level in the final, multivariable analysis. Results of the weighted model represented as the estimated effect and 95% CI on non-HDL cholesterol (log_{10} mmol/L) are shown for ART, body mass index (impact on non-HDL cholesterol per 1 kg/m^2 increase), CD4+ count (impact per 1 log_{10} increase), HIV viral load (impact per 1-log_{10} increase), and waist circumference (impact per 1-cm increase). The reference for the regression model represents the non-HDL cholesterol level (4.12 mmol/L; 95% CI, 3.84 to 4.42 mmol/L) for a virtual 39-year-old white woman: heterosexual HIV acquisition, not fasting, body mass index of 23 kg/m^2, nonsmoker, not diabetic, not treated with ART or lipid-lowering agents, with a CD4+ count of 500 cells/μL, HIV viral load <40 copies/mL, and common alleles at all tested genetic loci. B, Participants with sustained high non-HDL cholesterol levels according to genetic score and ART group. Results of the weighted model representing the proportion of participants with sustained high non-HDL cholesterol levels above the National Cholesterol Education Program Third Adult Treatment Program cutoff value (4.1 mmol/L). Sustained high non-HDL cholesterol levels were observed in 28 of 170 (16.5%; 95% CI, 11.2% to 22.9%) participants with a favorable genetic plus favorable ART profile (ie, category I genetic score and treatment with group 1 ART) compared with 143 of 272 (52.6%; 95% CI, 46.5% to 58.6%) with an unfavorable genetic + unfavorable ART profile (ie, genotype score III and treatment with group 2 ART). For further detail, refer to supplemental Figure IB and IC.

explained 1%, and the serum HIV RNA level explained 0.3% of serum non-HDL cholesterol variation.

Group 2 ART (Table 2) was in use at 66.9% of the 11 383 non-HDL cholesterol measurements and was associated with higher observed, median non-HDL cholesterol levels (4.11 mmol/L) than group 1 ART (3.5 mmol/L, $P<0.001$), given at 33.1% of non-HDL cholesterol measurements. Within each ART group, participants with higher genetic scores more frequently had sustained high non-HDL cholesterol levels (Figure 1B; supplemental Table II). For example,

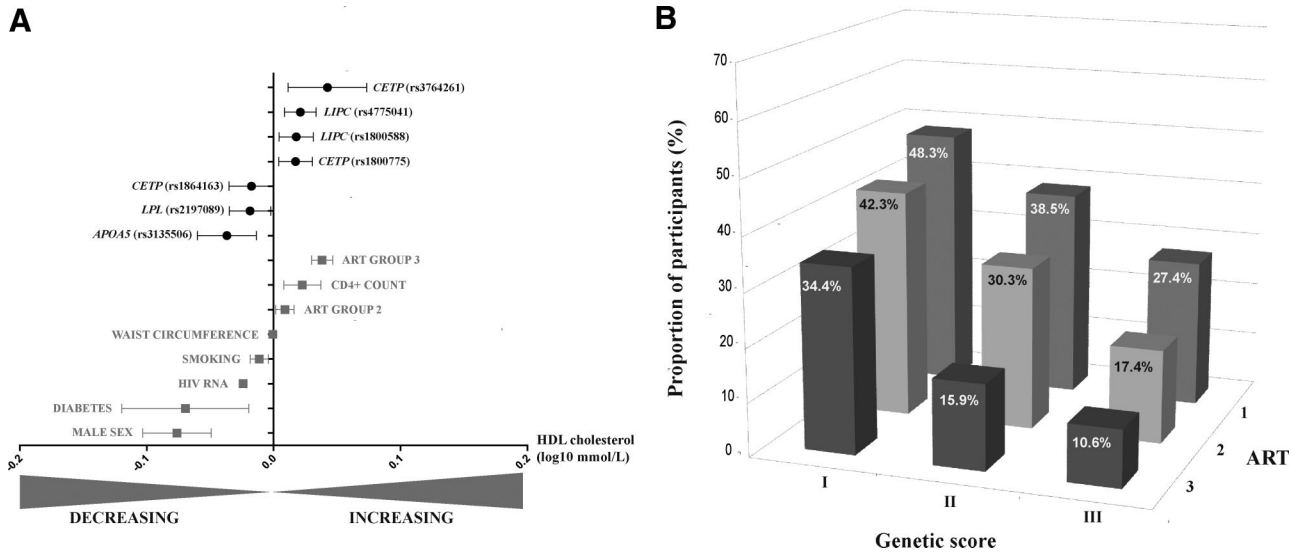


Figure 2. A, Impact of genetic and key nongenetic variants on HDL cholesterol level in the final, multivariable analysis. Results of the weighted model represented as the estimated effect and 95% CI on HDL cholesterol (log_{10} mmol/L) are shown for ART, body mass index (impact on HDL cholesterol per 1-kg/m^2 increase), CD4+ count (impact per 1-log_{10} increase), HIV viral load (impact per 1-log_{10} increase), and waist circumference (impact per 1-cm increase). The reference for the regression model represents the HDL cholesterol level (1.42 mmol/L, 95% CI, 1.32 to 1.55 mmol/L) for a virtual person, calculated as outlined for non-HDL cholesterol in the footnote to Figure 1A. B, Participants with sustained low HDL cholesterol level according to genetic score and ART group. Results of the weighted model representing the proportion of participants with sustained low HDL cholesterol levels below the National Cholesterol Education Program Third Adult Treatment Program cutoff value (1.04 mmol/L). Sustained low HDL cholesterol levels were observed in 13 of 123 (10.6%; 95% CI, 5.7% to 17.4%) participants with a favorable genetic plus favorable ART profile (ie, category III genetic score and group 3 ART) compared with 71 of 147 (48.3%; 95% CI, 40.0% to 56.7%) with an unfavorable genetic and unfavorable ART profile (ie, genotype score I and group 1 ART). For further detail, refer to supplemental Figure IIB and IIC.

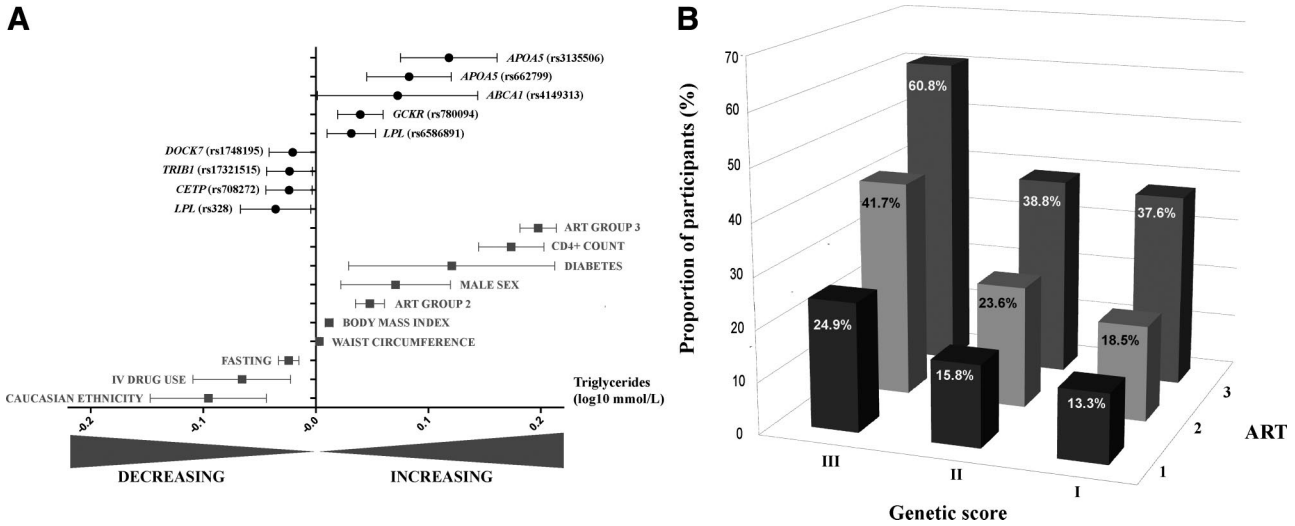


Figure 3. A, Effect of genetic and key nongenetic variants on TG level in the final, multivariable analysis. Results of the weighted model represented as the estimated effect and 95% CI on TG (log_{10} mmol/L) are shown for ART, body mass index (impact on non-HDL cholesterol per 1-kg/m^2 increase), CD4+ count (impact per 1-log_{10} increase), HIV viral load (impact per 1 log_{10} increase), and waist circumference (impact per 1-cm increase). The reference for the regression model represents the TG level for a virtual person (1.72 mmol/L, 95% CI, 1.50 to 1.97 mmol/L), calculated as outlined for non-HDL cholesterol in the footnote to Figure 1A. B, Participants with sustained hypertriglyceridemia according to genetic score and ART group. Results of the weighted model representing the proportion of participants with sustained high hypertriglyceridemia above the National Cholesterol Education Program Third Adult Treatment Program cutoff value (2.25 mmol/L). Reading example: sustained hypertriglyceridemia was observed in 22 of 166 (13.3%; 95% CI, 5% to 19.4%) participants with the favorable genetic ART profile (ie, category I genetic score and group 1 ART) compared with 65 of 107 (60.8%; 95% CI, 50.1% to 70.0%) with an unfavorable genetic ART profile (ie, genotype score III and group 3 ART). For further detail, refer to supplemental Figures IIIB and IIIC.

among protease inhibitor– or non-nucleoside reverse transcriptase inhibitor–treated participants (ART group 2), sustained non-HDL cholesterol was observed in 68 of 213 (31.9%) participants with the favorable genetic score I and in 143 of 272 (52.6%) participants with the unfavorable genetic score III ($P<0.001$). Irrespective of the genetic model used, there was a ≈3-fold difference in the proportion of participants with sustained high non-HDL cholesterol values when comparing the most unfavorable and the most favorable genetic ART profile (supplemental Figure I).

HDL Cholesterol

Nineteen of the 20 interrogated SNPs had an effect compatible with previous estimates (supplemental Table I). In the final, multi-SNP model, 7 SNPs previously published in GWAS contributed significantly to HDL cholesterol (Figure 2A; supplemental Table I). The 7 SNPs retained in the final model were rs1800775, rs3764261, rs1864163, rs2197089, rs1800588, rs3135506, and rs4775041. The final model explained 22.2% of the serum HDL cholesterol variation in the study population. Genetic covariables explained 6.2% (weighted score), 5.6% (additive weighted score), and 5.2% (additive unweighted score). ART explained 1.5%, the CD4+ count explained 0.1%, and the serum HIV RNA level explained 3.1% of serum HDL cholesterol variation.

Group 2 and group 3 ART were in use at 47.6% and 26.3%, respectively, of the 11 410 HDL cholesterol measurements and were associated with higher observed, median HDL cholesterol levels (1.18 mmol/L, $P<0.001$; and 1.28 mmol/L, $P<0.001$, respectively) than group 1 ART (1.1 mmol/L; given at 26.1% of HDL cholesterol measurements). Within each ART group, participants with higher genetic scores less frequently had sustained low HDL cholesterol levels (Figure 2B; supplemental Table III). For example, among protease inhibitor–treated participants (ART group 2), sustained low HDL cholesterol was observed in 34 of 196 (17.4%) participants with the favorable genetic score III and in 82 of 194 (42.3%) participants with the unfavorable genetic score I ($P<0.001$). Irrespective of the genetic model used, there was a ≈5-fold difference in the proportion of participants with sustained low HDL cholesterol values when comparing the most unfavorable and the most favorable genetic ART profile (supplemental Figure II).

TG

Twenty of the 22 interrogated SNPs had an effect compatible with previous estimates (supplemental Table I). In the final, multi-SNP model, 9 SNPs contributed significantly to TG levels, of which 6 were previously published in GWAS (rs780094, rs328, rs6586891, rs17321515, rs3135506, and rs1748195), and of which 3 were non-GWAS SNPs (rs708272, rs4149313, and rs662799; Figure 3A; supplemental Table I).The final model explained 25.2% of the serum TG variation in the study population. Genetic covariables explained 6.8% (weighted score), 6.4% (additive weighted score), and 5.0% (additive unweighted score). ART explained 6.2%, the CD4+ count explained 1%, and the serum HIV RNA level explained 0.03% of serum TG variation.

Group 2 and group 3 ART were in use at 45.2% and 21.4%, respectively, of the 11 772 TG measurements and were associated with higher observed, median TG levels (1.82 mmol/L, $P<0.001$; 2.5 mmol/L, $P<0.001$, respectively) than group 1 ART (1.6 mmol/L), given at 26.1% of TG measurements. Within each ART group, participants with higher genetic scores more frequently had sustained hyper-

triglyceridemia (Figure 3B; supplemental Table IV). For example, among participants treated with ATV/r or efavirenz (ART group 2), sustained hypertriglyceridemia was observed in 37 of 200 (18.5%) participants with the favorable genetic score I and in 78 of 187 (41.7%) participants with the unfavorable genetic score III ($P<0.001$). Irrespective of the genetic model used, there was an ≈4- to 5-fold difference in the proportion of participants with sustained high TG values when comparing the most unfavorable and the most favorable genetic ART profile (supplemental Figure III).

Discussion

This longitudinal study validated all SNPs that have consistently been associated with dyslipidemia in GWAS in the general population, as of February 2008,[26–28,30] as influencing serum lipid levels in HIV-infected individuals. Genetic data alone explained up to 7.6% of the interindividual lipid variation. This is similar to published GWAS estimates and similar to the contribution of ART alone, which in isolation explained up to 6.2% of the variation.

Recent GWAS have recorded a limited contribution of common SNPs to explaining interindividual variation in serum lipid levels, diabetes mellitus, and myocardial infarction in the general population.[19,20,26–28] This is perceived as disappointing as regards the genetic prediction of common metabolic disorders. In this study of HIV-infected individuals, however, SNPs associated with dyslipidemia, when considered in the context of key nongenetic influences, most notably antiretroviral drugs and HIV disease parameters, afforded significant prediction of sustained dyslipidemia at the level of the individual. An individual with the most dyslipidemic treatment and genetic background had an approximately 3-fold, 5-fold, and 4- to 5-fold increased risk of sustained high non-HDL cholesterol, low HDL cholesterol, or hypertriglyceridemia, respectively compared with an individual with the least dyslipidemic therapy and genetic background. In aggregate, these observations argue against the interpretation of complex genetic trait data in isolation, without consideration of all clinically relevant environmental factors. The contribution of genetic background to dyslipidemia was similar or greater in magnitude than the contribution of ART. This suggests that clinicians should consider genetic information as well as the dyslipidemic effects of ART agents when selecting an antiretroviral regimen, if our findings are independently confirmed.

Strengths of this study include SNP selection based on GWAS and longitudinal study design. Thus, our results are likely to have increased validity compared with previous genetic-dyslipidemia association studies in the HIV setting reported by us[11,14] and others,[12,13,16] which were limited by the restriction to single or few SNPs with limited validity, small sample size, lipids measured at a single time point, patients treated with protease inhibitors only, and male sex. This study exploited data collected prospectively over >7 years and representing >34 000 lipid measurements from >700 individuals. Given the interruptions and changes of ART made over time, participants were exposed to a median of 4 different antiretroviral regimens, and thereby served as their own controls. The study was thus capable of assessing the genetic effects on the background of this powerful shifting environmental influence. Although GWAS have capitalized on data from thousands of individuals, most have been cross-sectional in design and therefore incompletely able to account for changing environmental factors that modify SNP-lipid associations.[28] This may be an important reason why in GWAS of, eg, diabetes mellitus[19,20] and cardiovascular events,[29] in which serum lipids and other key environmental variables were determined at a single time point, SNPs improved the prediction of the trait only marginally.

The best method for summarizing the effects of multiple SNPs into a single, clinically useful genetic "score" is currently being debated.[29,49,50] We tested both additive scores,[18,23,24] in which each allele was assumed to have the same lipid impact, and scores weighted for the magnitude of the SNP effect.[19,20] These different scoring methods performed similarly in identifying participants with sustained dyslipidemia. However, the combination of any of the genetic scores with antiretroviral treatment information provided the best risk prediction at the individual level.

Limitations of this study include the relatively small number of women and nonwhite persons because our study participants were 75% men and 88% white. In addition, although the "direction" of SNP effects (lipid lowering or increasing) was the same as estimated in GWAS, not all reported SNPs were brought over to the final model. This reflects the small effect estimates associated with some of the genetic variants as well as the fact that some SNPs—originating from different publications—were in strong linkage disequilibrium (eg, SNPs located within the *APOA5/A4/C3/A1* cluster), and their effect was appropriately captured by 1 single genetic marker. On the other hand, the TG effect of rs4149313 (an *ABCA1* SNP not covered by GWAS chips)[11] needs to be independently validated before it can be considered a true finding.

In conclusion, this study represents one of the first attempts at integrating genetic, environmental (ART), disease parameters (HIV), and demographic variables in the evaluation of dyslipidemia at the population and the individual level. Importantly, the comprehensive consideration of GWAS-established SNPs and nongenetic covariables assessed longitudinally had the capacity to predict high non-HDL cholesterol levels, the lipid disorder most closely linked to cardiovascular events. We have recently initiated an international, multicohort study to explore genetic associations with acute coronary artery disease events in HIV-infected individuals.

Acknowledgements

The members of the Swiss HIV Cohort Study are M. Battegay, E. Bernasconi, J. Böni, H.C. Bucher, Ph. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the Swiss HIV Cohort Study, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), H. Hirsch, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother and Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, A. Telenti, A. Trkola, P. Vernazza, R. Weber, and S. Yerly.

Sources of Funding

The Swiss HIV Cohort Study, which is financed by the Swiss National Science Foundation, funded this study.

Disclosures

None.

References

1. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, Schouten JT, Smieja M. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation*. 2008;118:e29–e35.
2. DAD Study Group; Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiébaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735.
3. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007; 92:2506–2512.
4. Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, Hirschel B, Cavassini M, Bernasconi E, Schmid P, Egger M, Weber R. 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.
5. Worm SW, De Wit S, Weber R, Sabin CA, Reiss P, El-Sadr W, Monforte AD, Kirk O, Fontas E, Dabis F, Law MG, Lundgren JD, Friis-Moller N. Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human immunodeficiency virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study). *Circulation*. 2009;119:805–811.
6. Periard D, Cavassini M, Taffe P, Chevalley M, Senn L, Chapuis-Taillard C, de Valliere S, Hayoz D, Tarr PE; Swiss HIV Cohort Study. High prevalence of peripheral arterial disease in HIV-infected persons. *Clin Infect Dis*. 2008;46:761–767.
7. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med*. 1989;86:27–31.
8. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289:2978–2982.
9. Fontas E, van Leth F, Sabin CA, Friis-Møller N, Rickenbach M, d'Arminio Monforte A, Kirk O, Dupon M, Morfeldt L, Mateu S, Petoumenos K, El-Sadr W, de Wit S, Lundgren JD, Pradier C, Reiss P; D:A:D Study Group. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis*. 2004;189:1056–1074.
10. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, Tarr PE, Vernazza P, Battegay M, Bucher HC. Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study. *Antivir Ther*. 2005;10:585–591.
11. Arnedo M, Taffe P, Sahli R, Furrer H, Hirschel B, Elzi L, Weber R, Vernazza P, Bernasconi E, Darioli R, Bergmann S, Beckmann JS, Telenti A, Tarr PE; Swiss HIV Cohort Study. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. *Pharmacogenet Genomics*. 2007;17:755–764.
12. Fauvel J, Bonnet E, Ruidavets JB, Ferrieres J, Toffoletti A, Massip P, Chap H, Perret B. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. *AIDS*. 2001;15:2397–2406.
13. Foulkes AS, Wohl DA, Frank I, Puleo E, Restine S, Wolfe ML, Dube MP, Tebas P, Reilly MP. Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. *PLoS Med.* 2006;3:e52.
14. Tarr PE, Taffe P, Bleiber G, Furrer H, Rotger M, Martinez R, Hirschel B, Battegay M, Weber R, Vernazza P, Bernasconi E, Darioli R, Rickenbach M, Ledergerber B, Telenti A. Modeling the influence of APOC3, APOE, and TNF polymorphisms on the risk of antiretroviral therapy-associated lipid disorders. *J Infect Dis*. 2005;191:1419–1426.
15. Tarr PE, Telenti A. Toxicogenetics of antiretroviral therapy: genetic factors that contribute to metabolic complications. *Antivir Ther*. 2007;12: 999–1013.
16. Chang SY, Ko WS, Kao JT, Chang LY, Sun HY, Chen MY, Hsieh SM, Sheng WH, Chang SF, Liu WC, Wu CH, Hsu HJ, Kao CL, Lee CN, Hung CC, Chang SC. Association of single-nucleotide polymorphism 3 and c.553G>T of APOA5 with hypertriglyceridemia after treatment with highly active antiretroviral therapy containing protease inhibitors in hiv-infected individuals in Taiwan. *Clin Infect Dis*. 2009;48:832–835.
17. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447:661–678.
18. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen MR, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet*. 2008;40:189–197.
19. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, Berglund G, Altshuler D, Nilsson P, Groop L. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med*. 2008; 359:2220–2232.
20. Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med*. 2008;359:2208–2219.
21. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007;357:443–453.
22. Sandhu MS, Waterworth DM, Debenham SL, Wheeler E, Papadakis K, Zhao JH, Song K, Yuan X, Johnson T, Ashford S, Inouye M, Luben R, Sims M, Hadley D, McArdle W, Barter P, Kesaniemi YA, Mahley RW, McPherson R, Grundy SM, Bingham SA, Khaw KT, Loos RJ, Waeber G, Barroso I, Strachan DP, Deloukas P, Vollenweider P, Wareham NJ, Mooser V. LDL-cholesterol concentrations: a genome-wide association study. *Lancet*. 2008;371:483–491.
23. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson BK, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjogren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science*. 2007;316:1331–1336.
24. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Heath SC, Timpson NJ, Najjar SS, Stringham HM, Strait J, Duren WL, Maschio A, Busonero F, Mulas A, Albai G, Swift AJ, Morken MA, Narisu N, Bennett D, Parish S, Shen H, Galan P, Meneton P, Hercberg S, Zelenika D, Chen WM, Li Y, Scott LJ, Scheet PA, Sundvall J, Watanabe RM, Nagaraja R, Ebrahim S, Lawlor DA, Ben-Shlomo Y, vey-Smith G, Shuldiner AR, Collins R, Bergman RN, Uda M, Tuomilehto J, Cao A, Collins FS, Lakatta E, Lathrop GM, Boehnke M, Schlessinger D, Mohlke KL, Abecasis GR. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet*. 2008;40:161–169.
25. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Bostrom KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jorgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvelle AF, Meisinger C, Midthjell K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Pettersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjogren M, Steinthorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M, Altshuler D.

Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet*. 2008; 40:638–645.
26. Aulchenko YS, Ripatti S, Lindqvist I, Boomsma D, Heid IM, Pramstaller PP, Penninx BW, Janssens AC, Wilson JF, Spector T, Martin NG, Pedersen NL, Kyvik KO, Kaprio J, Hofman A, Freimer NB, Jarvelin MR, Gyllensten U, Campbell H, Rudan I, Johansson A, Marroni F, Hayward C, Vitart V, Jonasson I, Pattaro C, Wright A, Hastie N, Pichler I, Hicks AA, Falchi M, Willemsen G, Hottenga JJ, de Geus EJ, Montgomery GW, Whitfield J, Magnusson P, Saharinen J, Perola M, Silander K, Isaacs A, Sijbrands EJ, Uitterlinden AG, Witteman JC, Oostra BA, Elliott P, Ruokonen A, Sabatti C, Gieger C, Meitinger T, Kronenberg F, Doring A, Wichmann HE, Smit JH, McCarthy MI, van Duijn CM, Peltonen L. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. *Nat Genet*. 2009;41:47–55.
27. Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, Kaplan L, Bennett D, Li Y, Tanaka T, Voight BF, Bonnycastle LL, Jackson AU, Crawford G, Surti A, Guiducci C, Burtt NP, Parish S, Clarke R, Zelenika D, Kubalanza KA, Morken MA, Scott LJ, Stringham HM, Galan P, Swift AJ, Kuusisto J, Bergman RN, Sundvall J, Laakso M, Ferrucci L, Scheet P, Sanna S, Uda M, Yang Q, Lunetta KL, Dupuis J, de Bakker PI, O'Donnell CJ, Chambers JC, Kooner JS, Hercberg S, Meneton P, Lakatta EG, Scuteri A, Schlessinger D, Tuomilehto J, Collins FS, Groop L, Altshuler D, Collins R, Lathrop GM, Melander O, Salomaa V, Peltonen L, Orho-Melander M, Ordovas JM, Boehnke M, Abecasis GR, Mohlke KL, Cupples LA. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet*. 2009;41:56–65.
28. Manolio TA. Cohort studies and the genetics of complex disease. *Nat Genet*. 2009;41:5–6.
29. Kathiresan S, Melander O, Anevski D, Guiducci C, Burtt NP, Roos C, Hirschhorn JN, Berglund G, Hedblad B, Groop L, Altshuler DM, Newton-Cheh C, Orho-Melander M. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med*. 2008;358:1240–1249.
30. Sabatti C, Service SK, Hartikainen AL, Pouta A, Ripatti S, Brodsky J, Jones CG, Zaitlen NA, Varilo T, Kaakinen M, Sovio U, Ruokonen A, Laitinen J, Jakkula E, Coin L, Hoggart C, Collins A, Turunen H, Gabriel S, Elliot P, McCarthy MI, Daly MJ, Jarvelin MR, Freimer NB, Peltonen L. Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. *Nat Genet*. 2009;41:35–46.
31. Purnell JQ, Zambon A, Knopp RH, Pizzuti DJ, Achari R, Leonard JM, Locke C, Brunzell JD. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS*. 2000;14:51–57.
32. Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, Lichtenstein K, Rightmire A, Sankoh S, Wilber R. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS*. 2005;19:153–162.
33. Martínez E, Arnaiz JA, Podzamczer D, Dalmau D, Ribera E, Domingo P, Knobel H, Riera M, Pedrol E, Force L, Llibre JM, Segura F, Richart C, Cortés C, Javaloyas M, Aranda M, Cruceta A, de Lazzari E, Gatell JM; Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med*. 2003;349:1036–1046.
34. Periard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, Marcovina SM, Glauser MP, Nicod P, Darioli R, Mooser V. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. *Circulation*. 1999;100:700–705.
35. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998;12:F51–F58.
36. Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de Faire U, Danesh J. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA*. 2007;298:1300–1311.
37. Dallongeville J, Lussier-Cacan S, Davignon J. Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis. *J Lipid Res*. 1992;33:447–454.
38. Kuivenhoven JA, Jukema JW, Zwinderman AH, de Knijff P, McPherson R, Bruschke AV, Lie KI, Kastelein JJ. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. The Regression Growth Evaluation Statin Study Group. *N Engl J Med*. 1998;338:86–93.
39. Lee KW, Ayyobi AF, Frohlich JJ, Hill JS. APOA5 gene polymorphism modulates levels of triglyceride, HDL cholesterol and FERHDL but is not a risk factor for coronary artery disease. *Atherosclerosis*. 2004;176:165–172.
40. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, Krauss RM, Rubin EM. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. *Science*. 2001; 294:169–173.
41. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. *Hum Mol Genet*. 2002;11:3031–3038.
42. Murtaugh P. Methods of variable selection in regression modeling. *Comm Stat Simulat Comput*. 1998;27:711–734.
43. Zucchini W. An introduction to model selection. *J Math Psychol*. 2000; 44:41–61.
44. Schemper M. Predictive accuracy and explained variation. *Stat Med*. 2003;22:2299–2308.
45. Xu R. Measuring explained variation in linear mixed effects models. *Stat Med*. 2003;22:3527–3541.
46. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272.
47. Hoeg JM, Feuerstein IM, Tucker EE. Detection and quantitation of calcific atherosclerosis by ultrafast computed tomography in children and young adults with homozygous familial hypercholesterolemia. *Arterioscler Thromb*. 1994;14:1066–1074.
48. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
49. Tiret L, Tregouet DA, Cambien F. Cholesterol gene polymorphisms and cardiovascular events. *N Engl J Med*. 2008;359:92–93.
50. Vergeer M, El-Harchaoui K, Stroes ES. Cholesterol gene polymorphisms and cardiovascular events. *N Engl J Med*. 2008;359:92.

CLINICAL PERSPECTIVE

HIV-infected individuals have an increased risk of myocardial infarction. This risk is in part attributable to dyslipidemia, which may result from the use of antiretroviral therapy (ART). A genetic predisposition to ART-associated dyslipidemia has long been suspected because dyslipidemia develops in some but not in all patients, despite similar antiretroviral treatment and comparable demographic and HIV-related characteristics. Recent genome-wide association studies have now convincingly associated common single-nucleotide polymorphisms to variation in serum lipid levels in the general population. In this study, we reassessed the contribution of genome-wide association study–identified single-nucleotide polymorphisms, ART, and other relevant factors (eg, age, sex, ethnicity, CD4+ count, HIV RNA, lipid-lowering therapy) to serum lipid levels. We evaluated >34 000 lipid measurements provided by 745 HIV-infected Swiss HIV Cohort Study participants followed up longitudinally for a median of 7.6 years. Single-nucleotide polymorphisms and ART explained similar proportions of lipid variation in the study sample. Individuals with unfavorable genetic background more often had significantly sustained elevation of non–high-density lipoprotein cholesterol and greater risk of having low high-density lipoprotein cholesterol or hypertriglyceridemia. Our findings suggest that when selecting an ART regimen, both the dyslipidemic effects of ART agents and genetic information should be considered.

Supplemental Material (for online publication only)

Supplementary Methods: Comparison of the 3 genetic scores

1) Weighted genetic score

$$\log_{10}(lipid) = \alpha_0 + \underbrace{\alpha_1 age + \alpha_2 gender + ...}_{demographic\ factors\ and\ ART} + \underbrace{\beta_1 SNP1_{cat2} + \beta_2 SNP1_{cat3} + \gamma_1 SNP2_{cat2} + \gamma_2 SNP2_{cat3} + ...}_{genetic\ score}$$

α_0 represents the reference category, i.e. the lipid level for a virtual 39-year-old, caucasian woman, with heterosexual HIV acquisition, not fasting, body mass index of 23 kg/m2, non-smoker, not diabetic, not treated with ART or lipid-lowering agents, with a CD4+ T cell count of 500 cells/µl and undetectable viral load, and common alleles (i.e. category 1) at all tested polymorphic markers. $SNP1_{cat2}$ takes value 1 if only one allele variant is present and 0 otherwise. $SNP1_{cat3}$ takes value 1 if only two copies of the allele variant are present and 0 otherwise.

In this model the effect of each allele of each SNP on serum lipid levels is freely assessed.

2) Additive, weighted genetic score

$$\log_{10}(lipid) = \alpha_0 + \underbrace{\alpha_1 age + \alpha_2 gender + ...}_{demographic\ factors\ and\ ART} + \underbrace{\beta_1 SNP1_{cat2} + 2\beta_1 SNP1_{cat3} + \gamma_1 SNP2_{cat2} + 2\gamma_1 SNP2_{cat3} + ...}_{genetic\ score}$$

In this model the effect of each allele of each SNP on lipid level is assumed to be additive, while allowing the impact of each SNP to be freely assessed.

3) Additive, unweighted genetic score

$$\log_{10}(lipid) = \alpha_0 + \underbrace{\alpha_1 age + \alpha_2 gender + ...}_{demographic\ factors\ and\ ART} + \underbrace{\beta SNP1_{cat2} + 2\beta SNP1_{cat3} - \beta SNP2_{cat2} - 2\beta SNP2_{cat3} + ...}_{genetic\ score}$$

In this model the effect of each allele of each SNP on serum lipid levels is assumed to be additive, and the impact of each SNP is assumed to be the same except for the sign. In this example, SNP1 increases the lipid level, while SNP2 decreases it.

Supplementary Table 1: Multivariate Analysis of the contribution of SNPs to dyslipidemia.

NON-HDL-CHOLESTEROL							SNP by SNP analysis	Multi-SNP model		
SNP[1]	**Nearest gene**	**SNP type**	**Chromosome**	**Allele[2]**	**Minor Allele Frequency**	**Published non-HDL effect of rare allele (Ref.)**	**Separate effect of one and two variant alleles (p-values) on NHC[3] (n=743)**	**SNP effect in final, fully adjusted model[3] (n=743), *additive, unweighted* genetic model[5]**	**SNP effect in final, fully adjusted model[3] (n=743), *additive, weighted* genetic model**	**SNP effect in final, fully adjusted model[3] (n=743), *weighted* genetic model**
rs429358	*APOE*	exon	19	T>C	0.11	↑ [1,2]	0.002 (p=0.82); 0.081 (p=0.003)[4]	0.017 0.034	0.015 0.030 (p=0.075)	0 0.076 (p=0.004)
rs7412	*APOE*	exon	19	C>T	0.07	↓ [1,2]	-0.054 (p<0.0001); -0.074 (p=0.32)[4]	-0.017 -0.034	-0.043 -0.086 (p<0.0001)	-0.045 -0.045 (p<0.001)
rs10402271	*APOE/C1/C4*	inter-genic	19	T>G	0.31	↑ [3]	0.011 (p=0.19); 0.044 (p=0.002)[4]	0.017 0.034	0.015 0.030 (p= 0.015)	0 0.029 (p=0.026)
rs693	*APOB*	Exon	2	G>A	0.44	↑ [3-5]	0.026 (p=0.005); 0.025 (p=0.031)[4]	0.017 0.034	0.009 0.018 (p=0.125)	0.019 0.019 (p=0.026)
rs562338	*APOB*	inter-genic	2	G>A	0.22	↓ [3]	-0.023 (p=0.009); -0.044 (p=0.008)[4]	-0.017 -0.034	-0.018 -0.036 (p=0.007)	-0.016 -0.032 (p=0.013)
rs754523	*APOB*	inter-genic	2	A>G	0.27	↑ [3]	0.016 (p=0.053); 0.018 (p=0.24)	NA	NA	NA
rs2000813	*LIPG*	exon	18	C>T	0.29	↑ [6]	-0.0003 (p=0.97); 0.017 (p=0.23)	NA	NA	NA
rs11591147	*PCSK9*	exon	1	G>T	0.01	↓ [4,7]	-0.047 (p=0.054)[4]	-0.017	-0.036 (p=0.122)	-0.044 (p=0.058)
rs11206510	*PCSK9*	inter-genic	1	T>C	0.19	↓ [3]	-0.003 (p=0.74); -0.058 (p=0.005)[4]	-0.017 -0.034	-0.008 -0.016 (p=0.225)	0 -0.045 (p=0.021)
rs646776	*CELSR2, PSRC1, SORT1*	3' down-stream	1	T>C	0.24	↓ [4]	-0.019 (p=0.024); -0.059 (p=0.0005)[4]	-0.017 -0.034	-0.022 -0.044 (p=0.0006)	-0.020 -0.040 (p=0.001)
rs16996148	*CILP2*	3' down-stream	19	G>T	0.09	↓ [3,4]	-0.008 (p=0.47); -0.042 (p=0.24)	NA	NA	NA

rs17321515	*TRIB1*	3' down-stream	8	A>G	0.47	↓ [4]	-0.013 (p=0.18); -0.041 (p=0.0003)[4]	-0.017 -0.034	-0.019 -0.038 (p=0.0005)	-0.019 -0.038 (p<0.001)
rs12654264	*HMGCR*	intron	5	A>T	0.37	↑ [10]	-0.001 (p=0.87); 0.031 (p=0.02)[4]	NA	NA	NA
rs6511720	*LDLR*	intron	19	G>T	0.12	↓[3,4]	-0.022 (p=0.026); -0.029 (p=0.33)[4]	-0.017	-0.018 (p=0.03)	-0.019 -0.019 (p=0.033)

Significant non-genetic variables in the final model were HIV transmission via intravenous drug use (-0.089; p<0.001), lipid lowering therapy (-0.045; p<0.001), HIV RNA (-0.009; p<0.001), waist circumference (0.001; p=0.002), Body Mass Index (0.01; p<0.001), treatment with a regimen from ART group 2 (0.052; p<0.001) and CD4+ count (0.073; p<0.001).

HDL-CHOLESTEROL							**SNP by SNP analysis**	**Multi-SNP model**		
SNP[1]	**Nearest gene**	**SNP type**	**Chromosome**	**Allele**[2]	**Minor Allele Frequency**	**Published HDL-Cholesterol effect of rare allele (Ref.)**	**Separate effect of one and two variant alleles (p-values) on HDL-C**[3] **(n=742)**	**SNP effect in final, fully adjusted model**[3] **(n=742),** ***additive unweighted*** **genetic model**[5]	**SNP effect in final, fully adjusted model**[3] **(n=742),** ***additive, weighted*** **genetic model**	**SNP effect in final, fully adjusted model**[3] **(n=742),** ***weighted*** **genetic model**
rs1800775	*CETP*	5'upstream	16	C>A	0.48	↑[4,5]	0.03 (p=0.002) 0.062 (p<0.0001)[4]	0.015 0.030*	0.016 0.032 (p=0.04)	0.017 0.034 (p=0.011)
rs3764261	*CETP*	5'upstream	16	C>A	0.29	↑[3]	0.023 (p=0.006) 0.083 (p<0.0001)[4]	0.015 0.030	0.015 0.030(p=0.07)	0 0.042 (p=0.008)
rs1864163	*CETP*	intron	16	G>A	0.27	↓[3]	-0.034 (p<0.0001) -0.051 (p=0.0008)[4]	-0.015 -0.030	-0.012 -0.024 (p=0.103)	-0.018 -0.018 (p=0.055)
rs9989419	*CETP*	intergenic	16	G>A	0.42	↓[3]	-0.023 (p=0.013) -0.039 (p=0.001)[4]	NA	NA	NA
rs12596776	*SLC12A3/ CETP*	intron	16	C>G	0.08	↑[3]	0.015 (p=0.21) 0.019 (p=0.68)	NA	NA	NA
rs1566439	*NLRC5/ CETP*	intron	16	T>C	0.39	↑[3]	0.013 (p=0.14) 0.019 (p=0.15)	NA	NA	NA
rs328	*LPL*	exon	8	C>G	0.11	↑[4]	0.021 (p=0.048) -0.004 (p=0.90)	NA	NA	NA
rs2197089	*LPL*	3' downstream	8	A>G	0.43	↓[3]	-0.027 (p=0.004) -0.018 (p=0.13)[4]	-0.015 -0.030	-0.009 -0.018 (p=0.111)	-0.019 -0.019 (p=0.027)
rs6586891	*LPL*	intergenic	8	A>C	0.32	↓[3]	-0.006 (p=0.52) -0.002 (p=0.9)	NA	NA	NA
rs1800588	*LIPC*	5'upstream	15	C>T	0.25	↑[4]	0.053 (p=0.006) 0.01 (p=0.22)[4]	0.015 0.030	0.017 0.034 (p=0.013)	0.018 0.036 (p=0.01)
rs4775041	*LIPC*	intergenic	15	G>C	0.24	↑[3]	0.024 (p=0.008) 0.037 (p=0.02)[4]	0.015 0.030	0.021 0.042 (p=0.0009)	0.021 0.042 (p=0.001)
rs3135506*	*APOA5*	exon	11	G>C	0.07	↓	-0.037 (p=0.003) -0.023 (p=0.73)[4]	-0.015 -0.030	-0.034 -0.068 (p=0.003)	-0.037 -0.037 (p=0.002)
rs662799	*APOA5*	5'upstream	11	A>G	0.08	↓[8]	-0.012 (p=0.3) 0.038 (p=0.5)	NA	NA	NA
rs4846914	*GALNT2*	intron	1	A>G	0.44	↓[3,4]	-0.002 (p=0.87) -0.012 (p=0.34)	NA	NA	NA
rs17145738	*TBL2*	3' downstream	7	C>T	0.11	↑[4]	0.006 (p=0.56) -0.021 (p=0.56)	NA	NA	NA

rs17321515	*TRIB1*	3' downstream	8	A>G	0.47	↑ [4]	0.014 (p= 0.15) -0.006 (p=0.59)	NA	NA	NA
rs3890182	*ABCA1*	intron	9	G>A	0.13	↓ [4]	-0.007 (p=0.47) -0.021 (p=0.54)	NA	NA	NA
rs4149268	*ABCA1*	intron	9	C>T	0.42	↓ [3]	-0.005 (p= 0.57) -0.005 (p=0.67)	NA	NA	NA
rs2156552	*LIPG, ACAA2*	intergenic	18	T>A	0.14	↓ [3,4]	-0.002 (p=0.82) -0.038 (p= 0.24)	NA	NA	NA
rs2338104	*KCTD10 (MVK/MMAB*	intron	12	G>C	0.42	↑ [3]	-0.002 (p= 0.87) 0.005 (p=0.68)	NA	NA	NA

Significant non-genetic variables in the final model were male sex (co-efficient: -0.076; p<0.001), diabetes mellitus (-0.070; p=0.007), HIV RNA (-0.024; p<0.001), smoking (-0.011; p=0.002), waist circumference (-0.001; p=0.005), treatment with a regimen from ART group 2 (0.009; p=0.017), CD4+ count (0.023; p=0.002), and treatment with a regimen from ART group 3 (0.038; p<0.001).

*** rs3135506 was associated with HDL-cholesterol and TG in our previous report[6]. Although rs3135506 is not covered by GWAS chips, it is in strong linkage disequilibrium (r^2= 0.98) with a SNP associated in GWAS with HDL-cholesterol and TG levels [rs28927680][4]**

TRIGLYCERIDES							**SNP by SNP analysis**	**Multi-SNP model**		
SNP[1]	**Nearest gene**	**SNP type**	**Chromo some**	**Allele**[2]	**Minor Allele Fre-quency**	**Published tri-glyceride effect of rare allele (Ref.)**	**Separate effect of one and two variant alleles (p-values) on TG**[3] **(n=742)**	**SNP effect in final, fully adjusted model**[3] **(n=742),** ***additive unweighted*** **genetic model**[5]	**SNP effect in final, fully adjusted model**[3] **(n=742),** ***additive, weighted*** **genetic model**	**SNP effect in final, fully adjusted model**[3] **(n=742),** ***weighted*** **genetic model**
rs2854117	*APOC3*	5'upstream	11	C>T	0.30	↑ [9]	0.027 (p=0.097) -0.019 (p=0.52)	NA	NA	NA
rs2854116	*APOC3*	5'upstream	11	T>C	0.40	↑ [9]	0.026 (p=0.12) 0.015 (p=0.51)	NA	NA	NA
rs780094	*GCKR*	intron	2	C>T	0.44	↑ [3-5]	0.035 (p=0.046) 0.063 (p=0.004)[4]	0.033 0.066	0.04 0.08 (p=0.0001)	0.04 0.08 (p=0.0001)
rs429358	*APOE*	exon	19	T>C	0.11	↑ [2]	0.003 (p=0.86) 0.10 (p= 0.06)	NA	NA	NA
rs7412	*APOE*	exon	19	C>T	0.07	↓ [2]	0.006 (p=0.76) 0.257 (p=0.08)	NA	NA	NA
rs693	*APOB*	exon	2	G>A	0.44	↑ [3,4]	-0.001 (p=0.94) -0.008 (p=0.70)	NA	NA	NA
rs708272	*CETP*	intron	16	G>A	0.39	↓ [10]	-0.025 (p= 0.14) -0.047 (p= 0.045) [4]	0.033 0.066	-0.026 -0.052 (p=0.016)	-0.024 -0.048 (p=0.024)
rs328	*LPL*	exon	8	C>G	0.11	↓ [4]	-0.027 (p=0.16) -0.133 (p=0.02) [4]	0.033 0.066	-0.037 -0.074 (p=0.022)	-0.036 -0.072 (p=0.025)
rs2197089	*LPL*	3' downstream	8	A>G	0.43	↑ [3]	0.013 (p=0.45) 0.003 (p=0.90)	NA	NA	NA
rs6586891	*LPL*	intergenic	8	A>C	0.32	↑ [3]	0.036 (p=0.026) 0.064 (p= 0.01) [4]	0.033 0.066	0.03 0.06 (p=0.007)	0.031 0.062 (p=0.004)
rs4775041	*LIPC*	intergenic	15	G>C	0.24	↑ [3]	0.011 (p=0.50) 0.004 (p=0.88)	NA	NA	NA
rs5128	*APOC3*	3' downstream	11	C>G	0.10	↑ [9]	0.044 (p= 0.021) 0.073 (p=0.44)	NA	NA	NA
rs3135506 *****	*APOA5*	exon	11	G>C	0.07	↑	0.114 (p<0.0001) -0.190 (p=0.11) [4]	0.033 0.066	0.101 0.202 (p<0.0001)	0.118 0.118 (p<0.0001)
rs662799	*APOA5*	5'upstream	11	A>G	0.08	↑ [8,11]	0.076 (p=0.0003) 0.270 (p=0.02) [4]	0.033 0.066	0.084 0.168 (p<0.0001)	0.083 0.166 (p<0.0001)
rs16996148	*CILP2*	3'	19	G>T	0.09	↓ [3,4]	-0.018 (p=0.38)	NA	NA	NA

		downstream					-0.022 (p=0.75)			
rs4846914	*GALNT2*	intron	1	A>G	0.44	↑ [4]	0.021 (p=0.23) 0.024 (p=0.30)	NA	NA	NA
rs17145738	*TBL2*	3' downstream	7	C>T	0.11	↓ [3,4]	-0.020 (p= 0.31) -0.013 (p=0.85)	NA	NA	NA
rs17321515	*TRIB1*	3' downstream	8	A>G	0.47	↓ [3,4]	-0.019 (p=0.30) -0.051 (p=0.02)	0.033 0.066	-0.023 -0.046 (p=0.027)	-0.023 -0.046 (p=0.024)
rs12130333	*ANGPTL 3, DOCK7, ATG4C*	intergenic	1	C>T	0.19	↓ [4]	-0.023 (p=0.17) 0.034 (p=0.39)	NA	NA	NA
rs1748195	*DOCK7, ANGPTL 3*	intron	1	C>G	0.33	↓ [3]	-0.028 (p=0.085) -0.059 (p=0.02) [4]		-0.020 -0.040 (p=0.057)	-0.021 -0.042 (p=0.053)
rs481843	*APOA5*	intergenic	11	C>T	0.09	↑ [5]	0.008 (p=0.71) 0.11 (p=0.30)	NA	NA	NA
rs4149313	*ABCA1*	exon	9	T>C	0.16	↑ [6]	0.019 (p=0.307) 0.073 (p=0.060) [4]	0.033 0.066	0.030 0.060 (p=0.031)	0 0.073 (p=0.046)

Significant non-genetic variables in the final model were Caucasian ethnicity (-0.096, p<0.001), HIV transmission via intravenous drug use (-0.066; p=0.003), fasting state (-0.024; p<0.001), waist circumference (0.003; p<0.001), Body Mass Index (0.012; p<0.001), treatment with a regimen from ART group 2 (0.048; p<0.001), male sex (0.07; p=0.004), diabetes mellitus (0.121; p=0.01), CD4+ count (0.174; p<0.001), and treatment with a regimen from ART group 3 (0.198; p<0.001).

*** rs3135506 was associated with HDL-cholesterol and TG in our previous report [6]. Although rs3135506 is not included in current GWAS chips, it is in strong linkage disequilibrium (r^2= 0.98) with a SNP associated in GWAS with HDL-cholesterol and TG levels [rs28927680][4].**

[1]rs number included in dbSNP build 129.

[2](+) strand relative to the human reference sequence.

[3]The co-efficient represents the impact of the SNP on plasma lipid levels compared with the reference value of the regression model which represents the lipid level for a virtual 39-year-old, Caucasian woman, heterosexual HIV acquisition, not fasting, body mass index of 23 kg/m2, non-smoker, not diabetic, not treated with ART or lipid-lowering agents, with a CD4+ T cell count of 500 cells/µl, undetectable HIV viremia, and common alleles at all tested genetic loci.

[4]Global T-test significant at the 5% level.

[5]The global p-value for the unweighted additive genetic score is <0.001

Supplementary Table 2A Generation of *weighted* non-HDL cholesterol genetic scores

Genetic score=0.07355*rs429358_d3-0.04547*rs7412_d2_3+0.02782*rs10402271_d3 +0.01941*rs693_d2_3-0.01632*nrs562338-0.04091*rs11591147_d2-0.04715*rs11206510_d3-0.01962*nrs646776-0.03010*rs17321515_d3-0.01986*rs6511720_d2_3

where nrs… indicates the number of variant alleles. rs…_d2_d3, dominant mode of inheritance. rs…_d3, recessive mode.

rs11591147_d2 is observed with only one variant.

Weighted cumulative effect of alleles, with NHC-increasing effect (added) and NHC-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-0.16731<=genetic score<=-0.03055	240	**Genetic Score = I** • n=240 participants • 32.2 % of study population • contributed 3541 NHC determinations • median NHC level 3.5 mmol/L
-0.03055<genetic score<=-0.0045	212	**Genetic Score = II** • n=212 participants • 28.5 % of study population • contributed 3272 NHC determinations • median NHC level 3.9 mmol/L
genetic score>-0.0045	293	**Genetic Score = III** • n=293 participants • 39.3 % of study population • contributed 4570 NHC determinations • median NHC level, 4.2 mmol/L
TOTAL	**745**	**11383 NHC determinations;** **median NHC level, 3.9 mmol/L**

Supplementary Table 2B: Generation of *additive weighted* non-HDL cholesterol genetic scores

Genetic score=0.01487*nrs429358-0.04276*nrs7412+0.01452*nrs10402271+0.008923*nrs693
-0.01804*nrs562338-0.03611*nrs11591147-0.00829*nrs11206510-0.02189*nrs646776
-0.01913*nrs17321515-0.01764*nrs6511720

nrs… indicates the number of variant alleles.

Weighted cumulative effect of alleles, with NHC-increasing effect (added) and NHC-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-0.17792<=genetic score<=-0.04230	247	**Genetic Score = I** • n=247 participants • 33.2 % of study population • contributed 3702 NHC determinations • median NHC level 3.6 mmol/L
-0.04230<genetic score<=-0.01411	244	**Genetic Score = II** • n=244 participants • 32.8 % of study population • contributed 3708 NHC determinations • median NHC level 3.9 mmol/L
genetic score>-0.01411	254	**Genetic Score = III** • n=254 participants • 34.0 % of study population • contributed 3973 NHC determinations • median NHC level, 4.2 mmol/L
TOTAL	**745**	**11383 NHC determinations;** **median NHC level, 3.9 mmol/L**

Supplementary Table 2C: Generation of *additive unweighted* non-HDL cholesterol genetic scores

Genetic score=nrs429358-nrs7412+nrs10402271+nrs693-nrs562338-nrs11591147-nrs11206510-nrs646776-nrs17321515-nrs6511720

nrs… indicates the number of variant alleles.

Cumulative number of alleles with NHC-increasing effect (added) and NHC-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-8	1	**Genetic Score = I** • n=267 participants • 35.8 % of study population • contributed 3935 NHC determinations • median NHC level, 3.67mmol/L
-7	3	
-6	6	
-5	19	
-4	43	
-3	70	
-2	125	
-1	176	**Genetic Score = II** • n=310 participants • 41.6 % of study population • contributed 4827 NHC determinations • median NHC level, 3.89mmol/L
0	134	
1	96	**Genetic Score = III** • n=168 participants • 22.6 % of study population • contributed 2621 NHC determinations • median NHC level, 4.3mmol/L
2	55	
3	13	
4	3	
6	1	
TOTAL	**745**	**11383 NHC determinations;** **median NHC level, 3.9mmol/L**

Supplementary Table 3A: Generation of *weighted* HDL-cholesterol genetic scores

Genetic score=0.01725*nrs1800775+0.04240*rs3764261_d3-0.01751*rs1864163_d2_3
-0.01865*rs2197089_d2_3+0.01779*nrs1800588+0.02109*nrs4775041-0.03691*rs3135506_d2_3

nrs… indicates the number of variant alleles. rs…_d2_d3, dominant mode of inheritance. rs…_d3, recessive mode.

Weighted cumulative effect of alleles, with HDL-C-increasing effect (added) and HDL-C-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-0.07307<=genetic score<=-0.00112	255	**Genetic Score = I** • n=255 participants • 34.2 % of study population • contributed 3874 HDL-C determinations • median HDL-C level 1.1 mmol/L
-0.00112<genetic score<=0.02023	230	**Genetic Score = II** • n=230 participants • 30.9 % of study population • contributed 3530 HDL-C determinations • median HDL-C level 1.2 mmol/L
genetic score>0.02023	260	**Genetic Score = III** • n=260 participants • 34.9 % of study population • contributed 4006 HDL-C determinations • median HDL-C level, 1.3 mmol/L
TOTAL	**745**	**11410 HDL-C determinations;** **median HDL-C level, 1.2 mmol/L**

Supplementary Table 3B: Generation of *additive weighted* HDL-cholesterol genetic scores

Genetic score=0.01608*nrs1800775+0.01526*nrs3764261-0.01192*nrs1864163
-0.00890*nrs2197089+0.01712*nrs1800588+0.02142*nrs4775041-0.03446*nrs3135506

nrs… indicates the number of variant alleles.

Weighted cumulative effect of alleles, with HDL-C-increasing effect (added) and HDL-C-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-0.08454<=genetic score<=0.0101	246	**Genetic Score = I** • n=246 participants • 33.0 % of study population • contributed 3731 HDL-C determinations • median HDL-C level 1.1 mmol/L
0.0101<genetic score<=0.03906	240	**Genetic Score = II** • n=240 participants • 32.2 % of study population • contributed 3704 HDL-C determinations • median HDL-C level 1.2 mmol/L
genetic score>0.03906	259	**Genetic Score = III** • n=259 participants • 34.8 % of study population • contributed 3975 HDL-C determinations • median HDL-C level, 1.3 mmol/L
TOTAL	**745**	**11410 HDL-C determinations;** **median HDL-C level, 1.2 mmol/L**

Supplementary Table 3C: Generation of *additive unweighted* HDL-cholesterol genetic scores

Genetic score=nrs1800775+nrs3764261-nrs1864163-nrs2197089+nrs1800588+nrs4775041-nrs3135506

nrs… indicates the number of variant alleles

Cumulative number of alleles with HDL-C-increasing effect (added) and HDL-C-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-4	7	**Genetic Score = I** • n=178 participants • 23.9 % of study population • contributed 2713 HDL-C determinations • median HDL-C level, 1.1mmol/L
-3	23	
-2	61	
-1	87	
0	129	**Genetic Score = II** • n=264 participants • 35.4 % of study population • contributed 4053 HDL-C determinations • median HDL-C level, 1.2mmol/L
1	135	
2	125	**Genetic Score = III** • n=303 participants • 40.7 % of study population • contributed 4644 HDL-C determinations • median HDL-C level, 1.3mmol/L
3	91	
4	55	
5	19	
6	10	
7	3	
TOTAL	**745**	**11410 HDL-C determinations;** **median HDL-C level, 1.2mmol/L**

Supplementary Table 4A: Generation of *weighted* triglyceride genetic scores

Genetic score=0.03951*nrs780094-0.02503*nrs708272-0.02811*nrs328
+0.03097*nrs6586891+0.1157*rs3135506_d2_3+0.08260*nrs662799-0.02364*nrs17321515
-0.01964*nrs1748195+0.07328*rs4149313_d3

nrs… indicates the number of variant alleles, rs…_d2_d3 means dominant mode of inheritance, and rs…_d3 recessive mode.

Weighted cumulative effect of alleles, with TG-increasing effect (added) and TG-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-0.24192<=genetic score<=-0.01224	245	**Genetic Score = I** • n=245 participants • 32.9 % of study population • contributed 3935 TG determinations • median TG level 1.7mmol/L
-0.01224<genetic score<=0.04545	246	**Genetic Score = II** • n=246 participants • 33.0 % of study population • contributed 3756 TG determinations • median TG level 1.8 mmol/L
genetic score>0.04545	254	**Genetic Score = III** • n=254 participants • 34.1 % of study population • contributed 4081 TG determinations • median TG level, 2.2 mmol/L
TOTAL	**745**	**11772 TG determinations;** **median TG level, 1.9mmol/L**

Supplementary Table 4B: Generation of *additive weighted* triglyceride genetic scores

Genetic score=0.03971*nrs780094-0.02552*nrs708272-0.03666*nrs328+0.02998*nrs6586891
+0.1013*nrs3135506+0.08355*nrs662799-0.02297*nrs17321515-0.02035*nrs1748195
+0.02963*nrs4149313

nrs… indicates the number of variant alleles.

Weighted cumulative effect of alleles, with TG-increasing effect (added) and TG-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-0.18137<=genetic score<=-0.00668	246	**Genetic Score = I** • n=246 participants • 33.0 % of study population • contributed 3946 TG determinations • median TG level 1.7mmol/L
-0.00668<genetic score<=0.05118	245	**Genetic Score = II** • n=245 participants • 32.9 % of study population • contributed 3743 TG determinations • median TG level 1.8 mmol/L
genetic score>0.05118	254	**Genetic Score = III** • n=254 participants • 34.1 % of study population • contributed 4083 TG determinations • median TG level, 2.2 mmol/L
TOTAL	**745**	**11772 TG determinations;** **median TG level, 1.9mmol/L**

Supplementary Table 4C: Generation of *additive unweighted* triglyceride genetic scores

Genetic score=nrs780094-nrs708272-nrs328+nrs6586891+nrs3135506+nrs662799-nrs17321515-nrs1748195+nrs4149313

nrs… indicates the number of variant alleles.

Cumulative number of alleles with TG-increasing effect (added) and TG-lowering effect (subtracted) in final model	**Number of Participants**	**Genetic Score**
-7	1	**Genetic Score = I** • n=204 participants • 27.4 % of study population • contributed 3289 TG determinations • median TG level, 1.7 mmol/L
-6	1	
-5	6	
-4	26	
-3	69	
-2	101	
-1	149	**Genetic Score = II** • n=319 participants • 42.8 % of study population • contributed 4970 TG determinations • median TG level, 1.8 mmol/L
0	170	
1	126	**Genetic Score = III** • n=222 participants • 29.8 % of study population • contributed 3513 TG determinations • median TG level, 2.2 mmol/L
2	61	
3	32	
4	3	
TOTAL	**745**	**11772 TG determinations;** **median TG level, 1.9mmol/L**

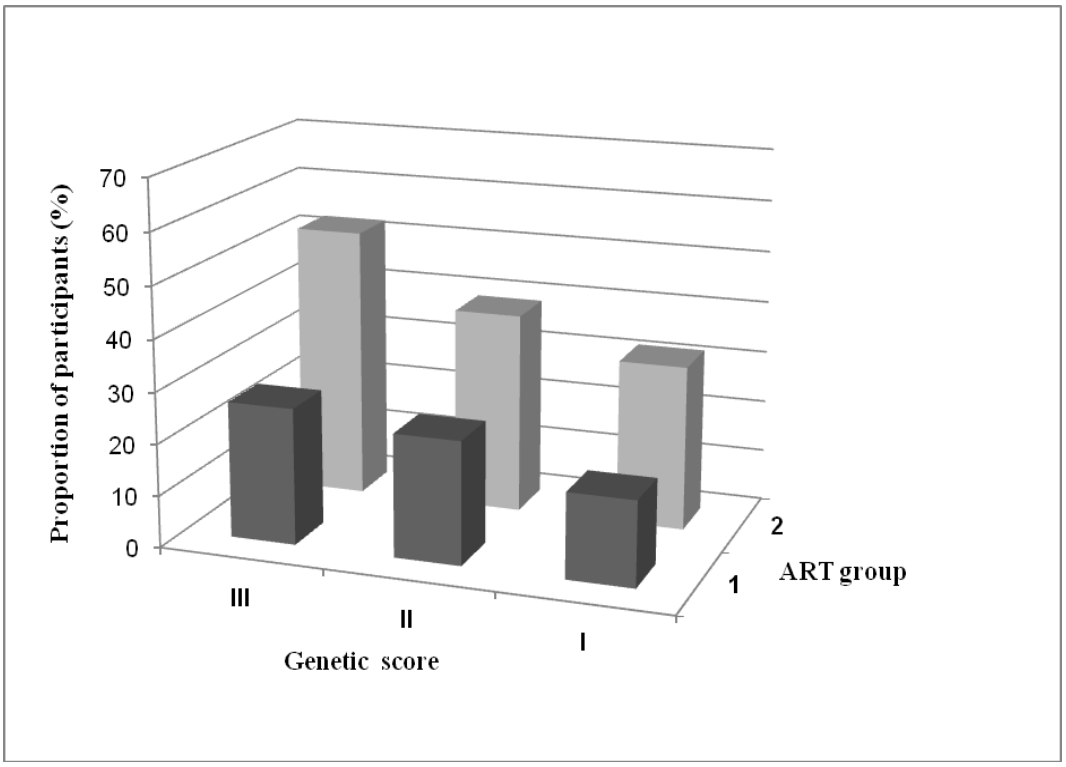
Supplementary Figures 1: non-HDL cholesterol

Using the *weighted* genetic scoring system (**Figure 1B**), sustained high non-HDL cholesterol levels were observed in 28 of 170 (16.5%; 95% confidence interval (CI), 11.2-22.9%) participants with a favorable genetic-ART profile (i.e. category I genetic score and treatment with group 1 ART), compared to 143 of 272 (52.6 %; 95%CI, 46.5-58.6%) for participants with an unfavorable genetic-ART profile (i.e. Genetic Score III and treatment with group 2 ART).

Using the *additive weighted* genetic score, the corresponding figures were 28 of 173 (16.2 %; 95% CI, 11.0-22.5%) vs. 121 of 234 (51.7 %; 95%CI, 45.1-58.3%).

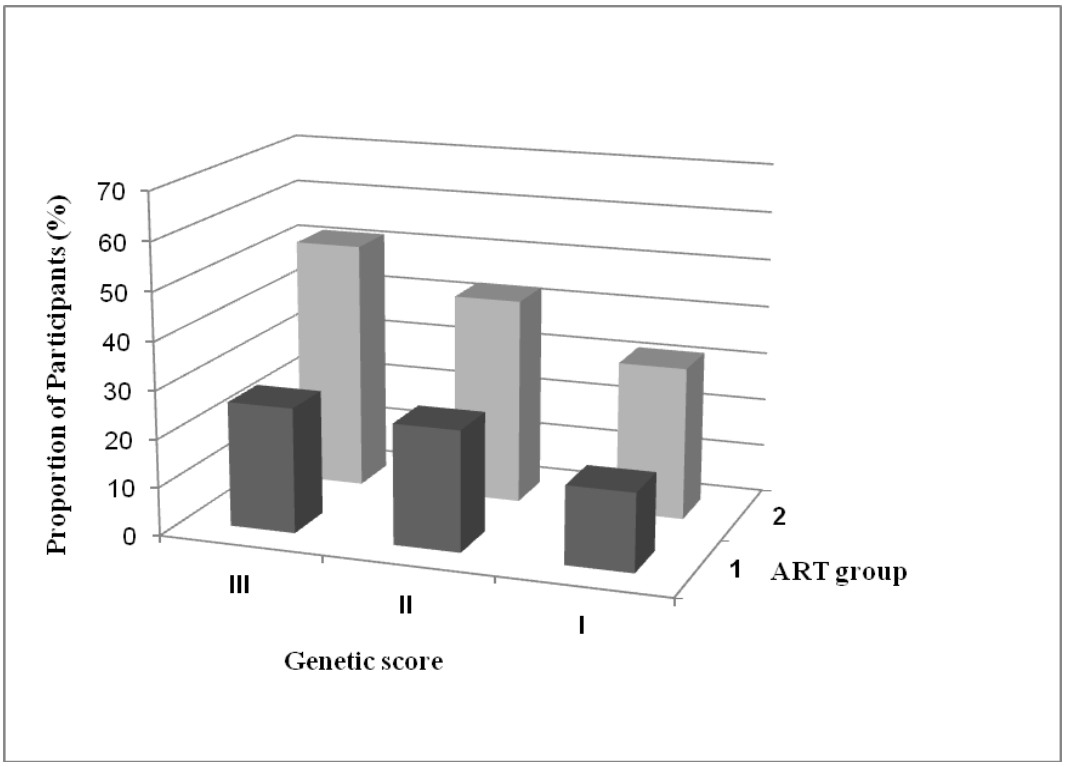
Using the *additive unweighted* genetic score, the corresponding figures were 38 of 188 (20.2 %; 95% CI, 14.7-26.7%) vs. 86 of 158 (54.4 %; 95% CI, 46.2-52.3%).

Fig. S1A: Observed proportion of participants with sustained high non-HDL cholesterol levels above the NCEP-ATPIII cutoff value (4.1 mmol/L) according to genetic score and ART groups (***weighted*** genetic model)



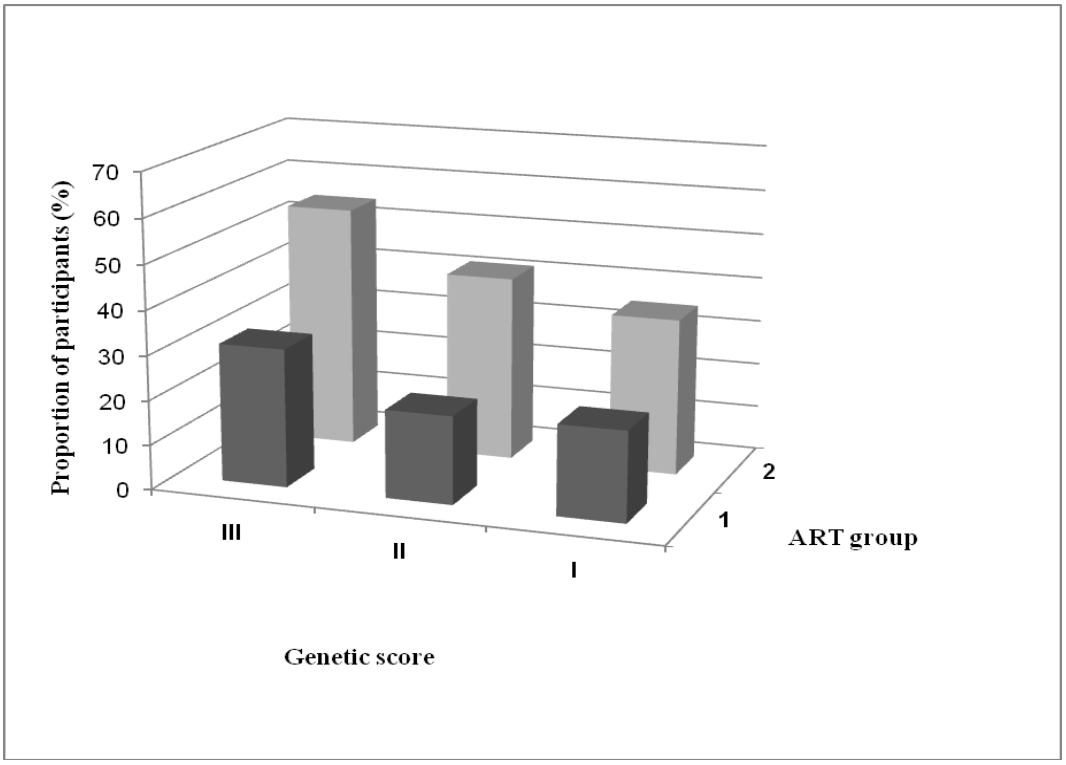
	Genetic Score		
ART Group	**III**	**II**	**I**
1 (no ART, NRTI only or ATVr)	52 of 197 (26.4%)	35 of 147 (23.8%)	28 of 170 (16.5%)
2 (NNRTI or PI, except ATVr containing ART)	143 of 272 (52.6%)	75 of 193 (38.9%)	68 of 213 (31.9%)

Fig. S1B: Observed proportion of participants with sustained high non-HDL cholesterol levels above the NCEP-ATPIII cutoff value (4.1. mmol/L) according to genetic score and ART groups (***additive weighted*** genetic model)



	Genetic Score		
ART Group	**III**	**II**	**I**
1 (no ART, NRTI only or ATVr)	44 of 169 (26%)	43 of 172 (25%)	28 of 173 (16.2%)
2 (NNRTI or PI, except ATVr containing ART)	121 of 234 (51.7%)	94 of 220 (42.8%)	71 of 224 (31.7%)

Fig. S1C: Observed proportion of participants with sustained high non-HDL cholesterol levels above the NCEP-ATPIII cutoff value (4.1 mmol/L) according to genetic score and ART groups (***additive unweighted*** genetic model)



	Genetic Score		
ART Group	**III**	**II**	**I**
1 (no ART, NRTI only or ATVr)	35 of 113 (31%)	42 of 213 (19.7%)	38 of 188 (20.2%)
2 (NNRTI or PI, except ATVr containing ART)	86 of 158 (54.4%)	115 of 278 (41.4%)	85 of 242 (35.1%)

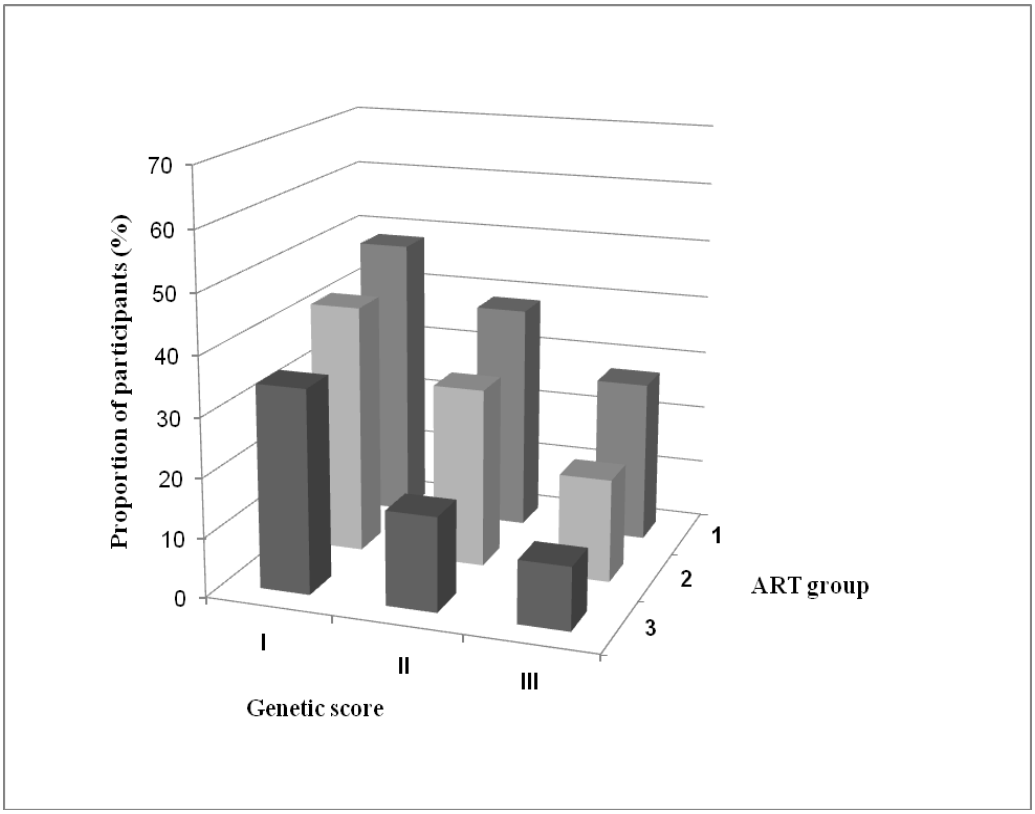
Supplementary Figures 2: HDL-Cholesterol

Using the *weighted* genotype scoring system, sustained low HDL-C levels were observed in 13 of 123 (10.6 %; 95%CI, 5.7-17.4%) participants with a favorable genetic-ART profile (i.e. category III genetic score, and treatment with group 3 ART), compared to 71 of 147 (48.3 %; 95% CI, 40.0-56.7%) with an unfavorable genetic-ART profile (i.e. Genetic Score I and treatment with group 1 ART) (**Fig. 2B**).

Using the *additive weighted* genetic score, the corresponding figures were 12 of 119 (10.1 %; 95%CI, 5.3-17.0%) vs. 68 of 149 (45.6 %; 95%CI, 37.5-54.0%).

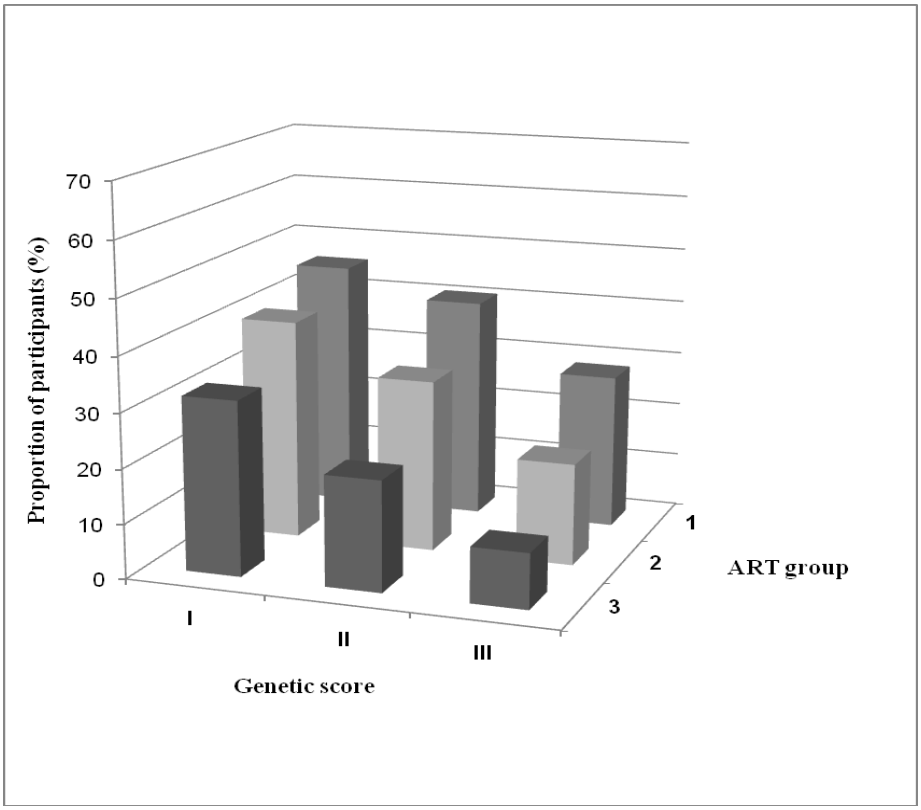
Using the *additive unweighted* genetic score, the corresponding figures were 14 of 145 (9.7 %; 95%CI, 5.4-15.7%) vs. 50 of 102 (49.0 %; 95%CI, 39.0-59.1%).

Fig. S2A: Observed proportion of with sustained low HDL-C levels below the NCEP-ATPIII cutoff value(1.03 mmol/L) according to genetic Score and ART groups (***weighted*** genetic model)



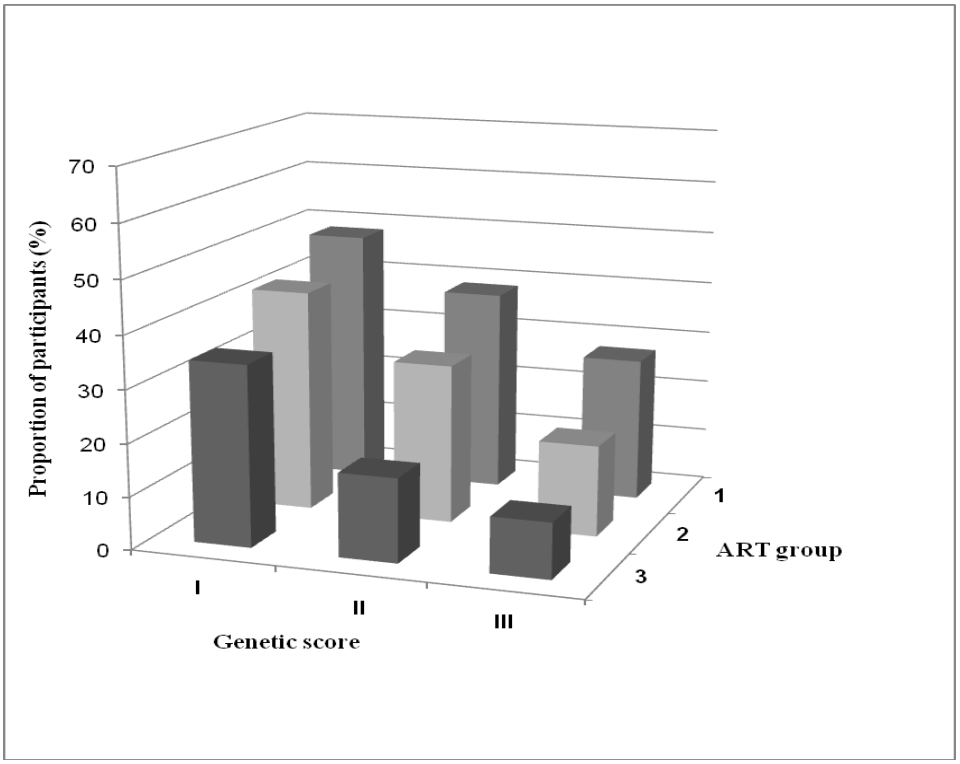
	Genetic Score		
ART Group	**I**	**II**	**III**
3 (NNRTI containing ART)	43 of 125 (34.4 %)	18 of 113 (15.9 %)	13 of 123 (10.6 %)
2 (PI containing ART)	82 of 194 (42.3 %)	53 of 175 (30.3 %)	34 of 196 (17.4 %)
1 (no ART or NRTI only)	71 of 147 (48.3 %)	52 of 135 (38.5 %)	45 of 164 (27.4 %)

Fig. S2B: Observed proportion of with sustained low HDL-C levels below the NCEP-ATPIII cutoff value(1.03 mmol/L) according to genetic Score and ART groups (***additive weighted*** genetic model)



	Genetic Score		
ART Group	**I**	**II**	**III**
3 (NNRTI containing ART)	36 of 113 (31.9%)	26 of 129 (20.2%)	12 of 119 (10.1%)
2 (PI containing ART)	77 of 191 (40.3%)	55 of 175 (31.4%)	37 of 199 (18.6%)
1 (no ART or NRTI only)	68 of 149 (45.6%)	52 of 128 (40.6%)	48 of 169 (28.4%)

Fig. S2C: Observed proportion of with sustained low HDL-C levels below the NCEP-ATPIII cutoff value(1.03 mmol/L) according to genetic Score and ART groups (***additive unweighted*** genetic model)



	Genetic Score		
ART Group	**I**	**II**	**III**
3 (NNRTI containing ART)	28 of 84 (33.3 %)	32 of 132 (24.2 %)	14 of 145 (9.7 %)
2 (PI containing ART)	63 of 141 (44.7 %)	61 of 191 (31.9 %)	45 of 233 (19.3 %)
1 (no ART or NRTI only)	50 of 102 (49.0 %)	63 of 150 (42.0 %)	55 of 194 (28.4 %)

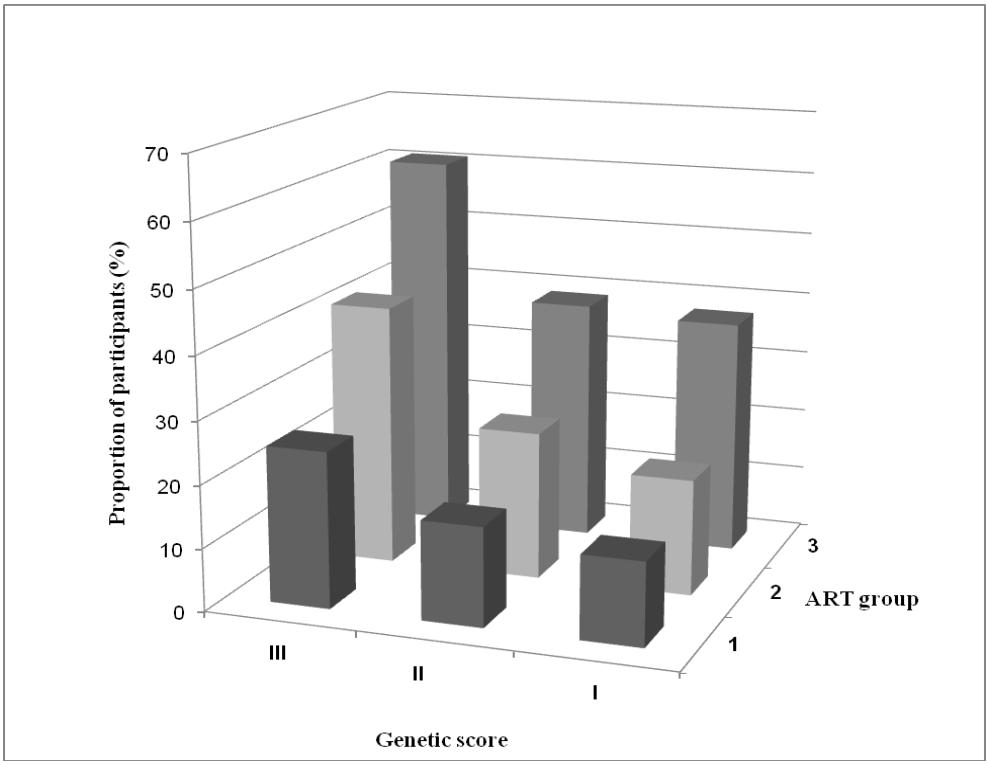
Supplementary Figures 3: Triglycerides

Using the *weighted* genotype scoring system, sustained hypertriglyceridemia was observed in 22 of 166 (13.3 %; 95%CI8., 5-19.4%) participants with the a favorable genetic-ART profile (i.e. category I genetic score, and treatment with group 1 ART), compared to 65 of 107 (60.8 %; 95%CI, 50.1-70.0%) with an unfavorable genetic-ART profile (i.e. Genetic Score III and treatment with group 3 ART (**Fig. 3B**).

Using the *additive weighted* genetic score, the corresponding figures were 21 of 166 (12.7 %; 95%CI, 8.0-18.7%) vs. 68 of 114 (59.7 %; 95%CI, 50.0-68.7%).

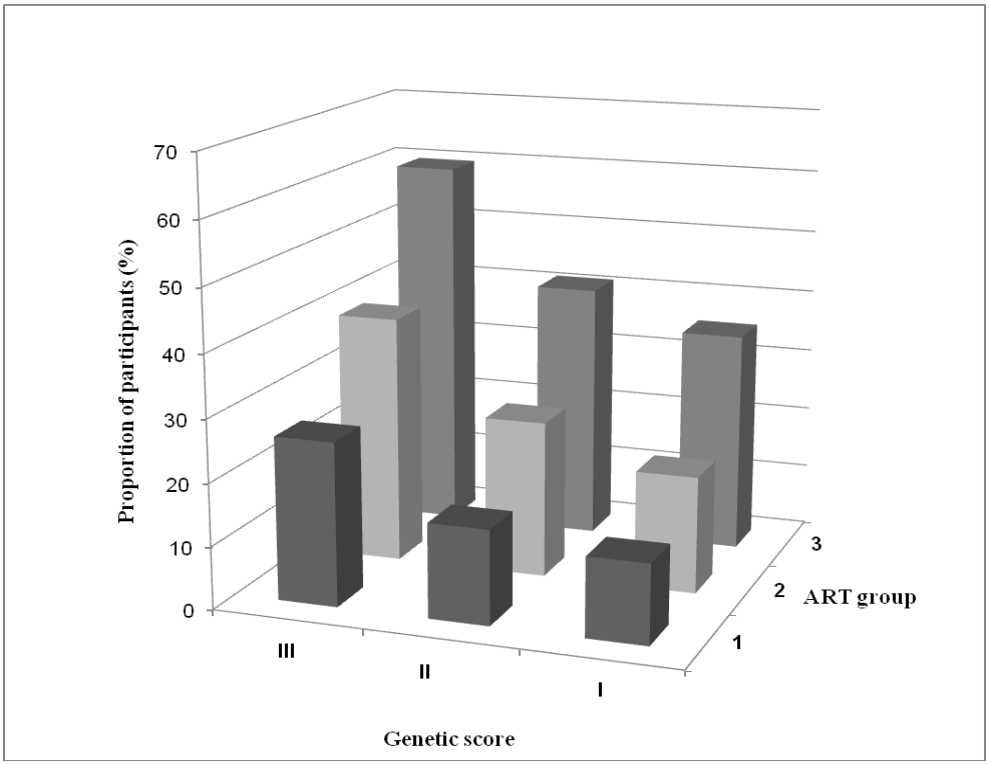
Using the *additive unweighted* genetic score, the corresponding figures were 22 of 138 (15.9%; 95% CI, 10.3-23.1%) vs. 55 of 97 (56.7 %; 95%CI, 46.3-66.7%).

Fig. S3A: Observed proportion of with sustained high TG levels above the NCEP-ATPIII cutoff value (2.26 mmol/L) according to genetic score and ART groups (***weighted*** genetic model)



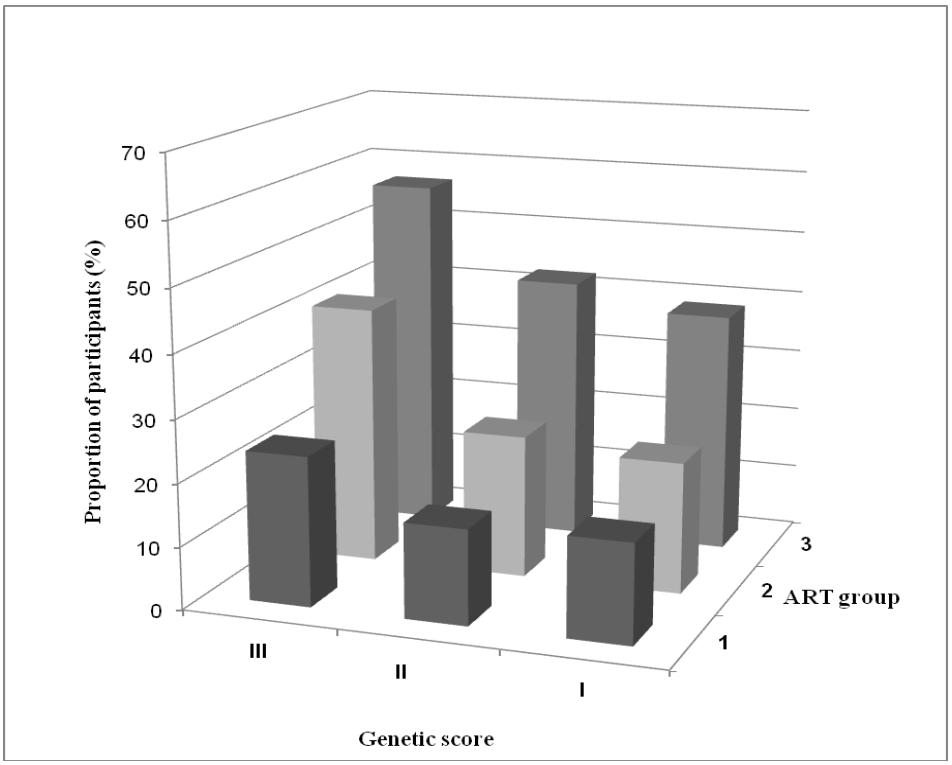
	Genetic Score		
ART Group	**III**	**II**	**I**
1 (No ART, NRTI, NVP)	44 of 177 (24.9 %)	26 of 165 (15.8 %)	22 of 166 (13.3 %)
2 (ATV/r, EFV; PI containing ART but without RTV)	78 of 187 (41.7 %)	47 of 199 (23.6 %)	37 of 200 (18.5 %)
3 (Ritonavir-containing ART without ATV/r)	65 of 107 (60.8 %)	45 of 116 (38.8 %)	44 of 117 (37.6 %)

Fig. S3B: Observed proportion of with sustained high TG levels above the NCEP-ATPIII cutoff value (2.26 mmol/L) according to genetic score and ART groups (***additive weighted*** genetic model)



	Genetic Score		
ART Group	**III**	**II**	**I**
1 (No ART, NRTI, NVP)	46 of 176 (26.1%)	25 of 166 (15.1%)	21 of 166 (12.7%)
2 (ATV/r, EFV; PI containing ART but without RTV)	76 of 192 (39.6%)	49 of 196 (25%)	37 of 198 (18.7%)
3 (Ritonavir-containing ART without ATV/r)	68 of 114 (59.7%)	44 of 107 (41.1%)	42 of 119 (35.3%)

Fig. S3C: Observed proportion of with sustained high TG levels above the NCEP-ATPIII cutoff value (2.26 mmol/L) according to genetic score and ART groups (***additive unweighted*** genetic model)



	Genetic Score		
ART Group	**III**	**II**	**I**
1 (No ART, NRTI, NVP)	38 of 159 (23.9 %)	32 of 211 (15.2 %)	22 of 138 (15.9 %)
2 (ATV/r, EFV; PI containing ART but without RTV)	70 of 170 (41.2 %)	58 of 254 (22.8 %)	34 of 162 (21 %)
3 (Ritonavir-containing ART without ATV/r)	55 of 97 (56.7 %)	60 of 142 (42.3 %)	39 of 101 (38.6 %)

Reference List

1. Bennet AM, Di AE, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de FU, Danesh J. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA*. 2007; 298:1300-1311.

2. Dallongeville J, Lussier-Cacan S, Davignon J. Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis. *J Lipid Res*. 1992; 33:447-454.

3. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Heath SC, Timpson NJ, Najjar SS, Stringham HM, Strait J, Duren WL, Maschio A, Busonero F, Mulas A, Albai G, Swift AJ, Morken MA, Narisu N, Bennett D, Parish S, Shen H, Galan P, Meneton P, Hercberg S, Zelenika D, Chen WM, Li Y, Scott LJ, Scheet PA, Sundvall J, Watanabe RM, Nagaraja R, Ebrahim S, Lawlor DA, Ben-Shlomo Y, vey-Smith G, Shuldiner AR, Collins R, Bergman RN, Uda M, Tuomilehto J, Cao A, Collins FS, Lakatta E, Lathrop GM, Boehnke M, Schlessinger D, Mohlke KL, Abecasis GR. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet*. 2008; 40:161-169.

4. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen MR, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet*. 2008; 40:189-197.

5. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson BK, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjogren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science*. 2007; 316:1331-1336.

6. Arnedo M, Taffe P, Sahli R, Furrer H, Hirschel B, Elzi L, Weber R, Vernazza P, Bernasconi E, Darioli R, Bergmann S, Beckmann JS, Telenti A, Tarr PE. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. *Pharmacogenet Genomics*. 2007; 17:755-764.

7. Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006; 354:1264-1272.

8. Lee KW, Ayyobi AF, Frohlich JJ, Hill JS. APOA5 gene polymorphism modulates levels of triglyceride, HDL cholesterol and FERHDL but is not a risk factor for coronary artery disease. *Atherosclerosis*. 2004; 176:165-172.

9. Fauvel J, Bonnet E, Ruidavets JB, Ferrieres J, Toffoletti A, Massip P, Chap H, Perret B. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. *AIDS*. 2001; 15:2397-2406.

10. Kuivenhoven JA, Jukema JW, Zwinderman AH, de KP, McPherson R, Bruschke AV, Lie KI, Kastelein JJ. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. The Regression Growth Evaluation Statin Study Group. *N Engl J Med*. 1998; 338:86-93.

11. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, Krauss RM, Rubin EM. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. *Science*. 2001; 294:169-173.