
UNIVERSITE DE LAUSANNE – FACULTE DE BIOLOGIE ET DE MEDECINE

Département de pathologie et médecine de laboratoire

Institut de Microbiologie

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

THESE

préparée sous la direction du Professeur Amalio Telenti
avec la collaboration du Docteur Philip E. Tarr
et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Rapport de synthèse

Les individus HIV-positifs constituent une population à risque pour les maladies cardiovasculaires telles que l'infarctus cardiaque ou cérébrale. Celles-ci découlent d'une formation accélérée d'athérosclérose. Ces pathologies s'expliquent en grande partie par une dyslipidémie observée au sein de cette population et qui sont dues à des facteurs externes tels que : l'immunosuppression avancée, la virémie non-contrôlée, et les effets de la thérapie antirétrovirale. Récemment, des polymorphismes nucléotidiques simples (SNP) associés à la dyslipidémie ont été mis en évidence d'une manière globale par des Genome-Wide Association Studies (GWAS). Le but principal de cette étude est d'évaluer et de valider l'effet cumulatif des SNP identifiés dans ces GWAS pour la dyslipidémie chez des patients HIV-positifs. De plus, l'identification des facteurs non-génétiques qui contribuent à la dyslipidémie démontrent l'importance des facteurs externes, tels que mentionnés ci-dessus, et en particulier à ceux de la thérapie antirétrovirale.

Les participants de l'étude proviennent de trois groupes : 426 personnes sélectionnées pour une étude précédente, 222 personnes sélectionnées de façon arbitraire dans la « Cohorte HIV Suisse » et 103 personnes sélectionnées avec un « New-Onset Diabetes mellitus » identifiées lors d'études précédentes. Ces individus ont contribué à plus de 34'000 mesures de lipides sur une durée moyenne supérieure à 7 ans. Pour l'étude, 33 SNP identifiés dans des GWAS et 9 SNP identifiés dans d'autres études publiées dans la littérature non-couverte par des GWAS ont été repris. Le génotypage a été complété pour 745 (99.2%) des 751 participants.

Pour les analyses statistiques, les thérapies antirétrovirales ont été divisées en trois groupes (favorisant peu, moyennement et fortement la dyslipidémie), et trois scores génétiques ont été créés (profil favorable, moyennement favorable, non favorable/favorisant la dyslipidémie). Dans un premier temps, l'effet sur la valeur des lipides d'un ou deux allèles variants a été analysé au moyen d'un modèle de régression pour chaque SNP en ajustant le modèle pour les variables non-génétiques. Dans un deuxième temps, les SNP ayant une valeur $p \leq 0.2$ ont été repris dans un model Multi-SNP, ce modèle est également ajusté pour les variables non-génétiques. Puisque cette étude se base sur des SNP précédemment identifiés, celle-ci évalue uniquement l'association établie entre chaque SNP et les critères qui ont été établis au préalable, tels que : Cholestérol totale, HDL Cholestérol, non-HDL Cholestérol ou Triglycérides. Les résultats trouvés lors de l'étude confirment les résultats de la littérature.

Cette étude montre que les SNP associés à la dyslipidémie doivent être analysés dans le contexte d'une thérapie antirétrovirale en tenant compte de la démographie et en considérant les valeurs du HIV (CD4+, virémie). Ces SNP montrent une tendance à prédire une dyslipidémie prolongée chez l'individu. En effet, un patient avec une thérapie antirétrovirale favorisant la dyslipidémie et un patrimoine génétique non-favorable a un risque qui est 3-fois plus important d'avoir un Non-HDL-Cholestérol élevé, 5-fois plus important d'avoir un HDL-Cholestérol abaissé, et 4 à 5-fois plus important d'avoir une hypertriglycémie qu'un patient qui suit une thérapie antirétrovirale favorisant peu la dyslipidémie qui a un patrimoine génétique favorable. Vu la corrélation entre les SNP et la thérapie antirétrovirale, les cliniciens devraient intégrer les informations génétiques afin de choisir une thérapie antirétrovirale en fonction du patrimoine génétique.

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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

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

A Longitudinal Study

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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 atherogenesis¹, 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 environ-

mental 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

Clinical Perspective on p 628

investigating common single-nucleotide polymorphisms (SNPs) for their contribution to dyslipidemia in the HIV

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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 dyslipidemia¹¹; 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 sequencing¹¹). 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/m²], waist circumference [cm], fasting state, treatment with lipid-lowering agents, smoking status, CD4+ T-cell count [log₁₀], and HIV viral load [log₁₀]) and time-fixed covariables (including sex, presumed mode of HIV transmission, ethnicity, diabetes mellitus status, and the genetic variants). Lipid levels were log₁₀ 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 study¹¹ 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 described¹¹ (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 weights¹¹ 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 levels⁴⁴ 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/ μ L, 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 NRTI only Atazanavir boosted with ritonavir (ATV/r)	PI (except ATV/r) NNRTI	NA
HDL cholesterol	No antiretroviral therapy NRTI only	PI	NNRTI
Triglycerides	No antiretroviral therapy NRTI only Nevirapine-containing ART without a PI Atazanavir unboosted	Single PI-containing ART (without ritonavir) ATV/r Efavirenz	Ritonavir-containing ART (except ATV/r)

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.

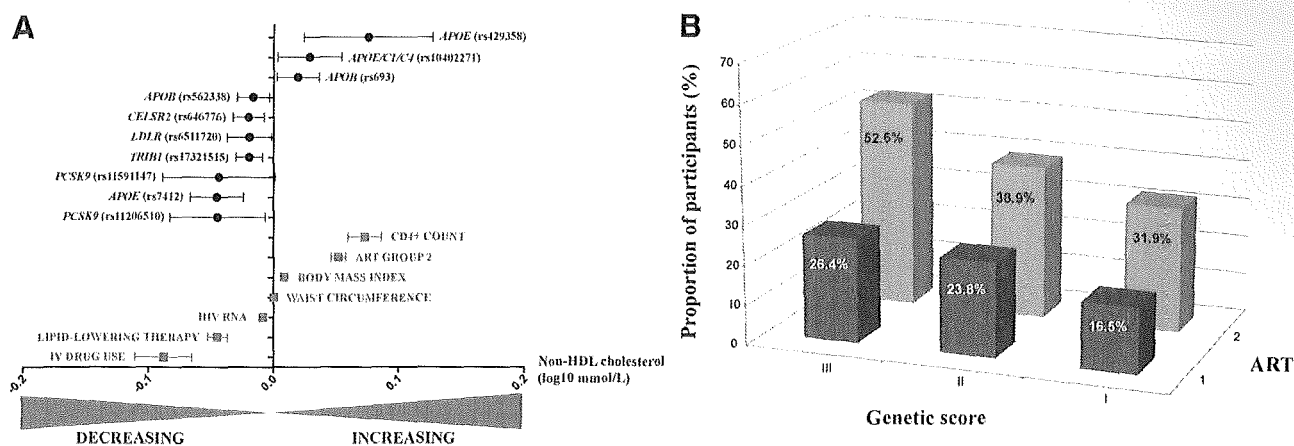


Figure 1. A, Impact of genetic and key nongenetic variables on non-HDL cholesterol level in the final, multivariable analysis. Results of the weighted model represented as the estimated effect and 95% CI on non-HDL cholesterol (\log_{10} mmol/L) are shown for ART, body mass index (impact on non-HDL cholesterol 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 1B and 1C.

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,

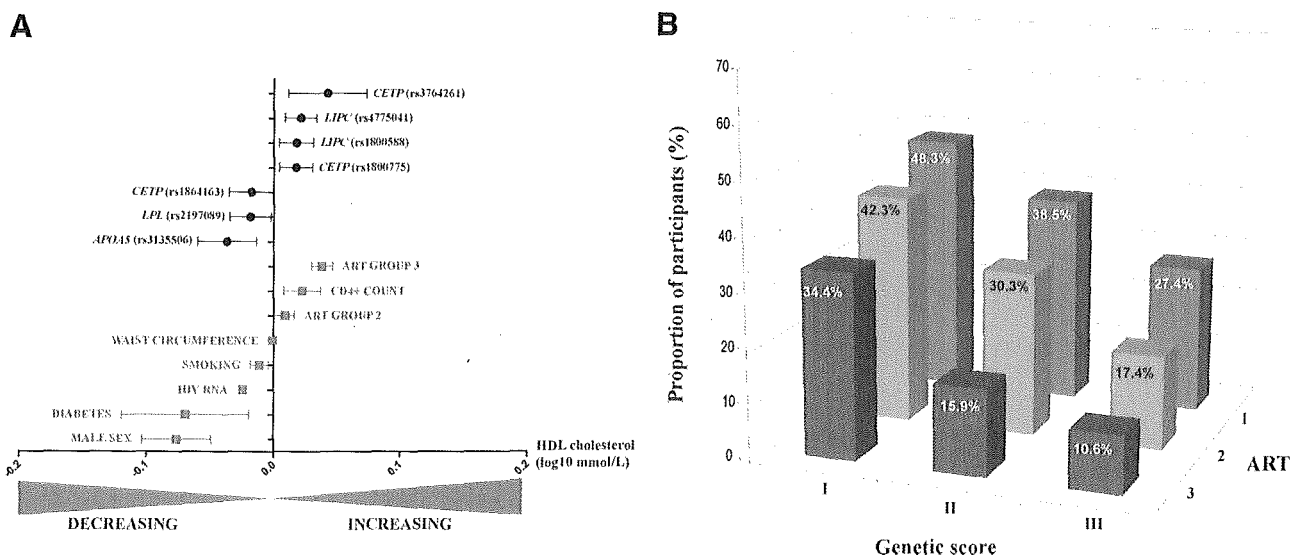


Figure 2. A, Impact of genetic and key nongenetic variants on HDL cholesterol level in the final, multivariable analysis. Results of the weighted model represented as the estimated effect and 95% CI on HDL cholesterol (\log_{10} mmol/L) are shown for ART, body mass index (impact on HDL cholesterol per 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 2B and 2C.

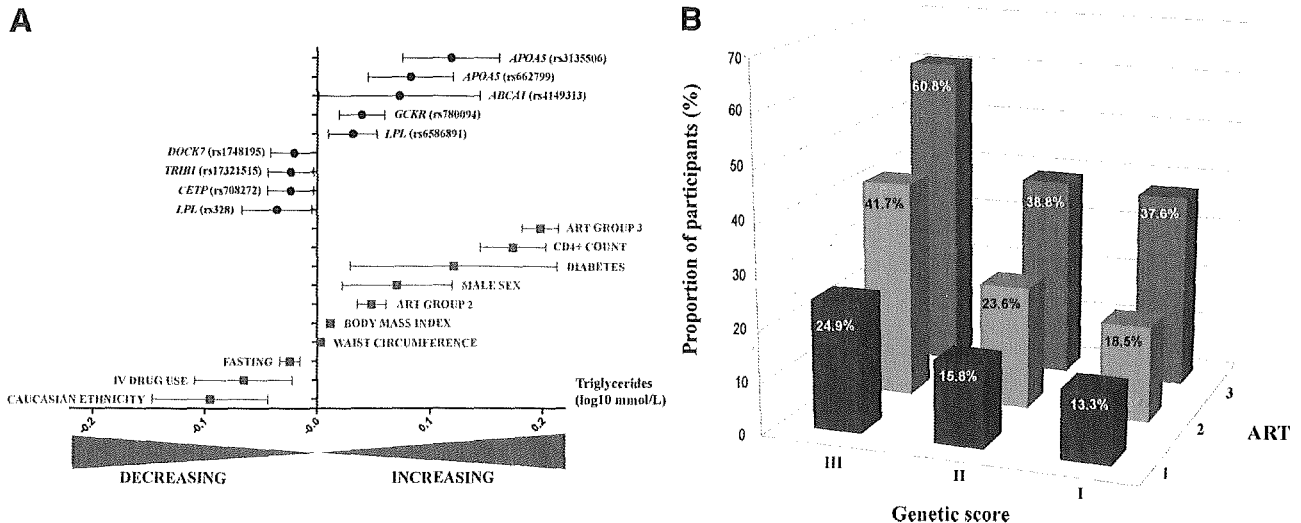


Figure 3. A, Effect of genetic and key nongenetic variants on TG level in the final, multivariable analysis. Results of the weighted model represented as the estimated effect and 95% CI on TG (log₁₀ mmol/L) are shown for ART, body mass index (impact on non-HDL cholesterol per 1-kg/m² increase), CD4+ count (impact per 1-log₁₀ increase), HIV viral load (impact per 1 log₁₀ 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.

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Disclosures

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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.