Effect of SLCO1B1 c.521T>C polymorphism on the lipid response to statins in people living with HIV on a boosted protease inhibitor-containing regimen

Marzolini, Catia; Cavassini, Matthias; Braun, Dominique L.; Hachfeld, Anna; Bernasconi, Enos; Calmy, Alexandra; Schmid, Patrick; Battegay, Manuel; Elzi, Luigia

Collaborators: Martinez De Tejada Weber, Begona; Kaiser, Laurent; Keiser, Olivia; Yerly Ferrillo, Sabine

How to cite

MARZOLINI, Catia et al. Effect of SLCO1B1 c.521T>C polymorphism on the lipid response to statins in people living with HIV on a boosted protease inhibitor-containing regimen. In: British journal of clinical pharmacology, 2023, vol. 89, n° 9, p. 2739–2746. doi: 10.1111/bcp.15754

This publication URL: https://archive-ouverte.unige.ch/unige:172934

Publication DOI: 10.1111/bcp.15754

Received: 15 March 2023 | Revised: 21 April 2023 | Accepted: 22 April 2023

DOI: 10.1111/bcp.15754

ORIGINAL ARTICLE

Effect of SLCO1B1 c.521T>C polymorphism on the lipid response to statins in people living with HIV on a boosted protease inhibitor-containing regimen

Catia Marzolini[1] | Matthias Cavassini[2] | Dominique L. Braun[3] | Anna Hachfeld[4] | Enos Bernasconi[5] | Alexandra Calmy[6] | Patrick Schmid[7] | Manuel Battegay[1] | Luigia Elzi[8] | the Swiss HIV Cohort Study

[1]Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

[2]Service of Infectious Diseases, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland

[3]Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland

[4]Department of Infectious Diseases, University Hospital Bern, University of Bern, Bern, Switzerland

[5]Division of Infectious Diseases, Ente Ospedaliero Cantonale Lugano, University of Geneva and University of Southern Switzerland, Lugano, Switzerland

[6]Division of Infectious Diseases, University Hospital Geneva, University of Geneva, Geneva, Switzerland

[7]Department of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[8]Division of Infectious Diseases, Regional Hospital Bellinzona, Bellinzona, Switzerland

Correspondence
Catia Marzolini, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, Basel, Switzerland.
Email: catia.marzolini@usb.ch

Funding information
Swiss National Science Foundation, Grant/Award Number: 201369

Aims: We previously observed that some individuals on HIV boosted protease inhibitor-containing regimen do not achieve their lipid targets despite elevated statin concentrations. This study evaluated whether the common single polymorphism c.521T>C in *SLCO1B1*, associated with reduced statin uptake in the liver, could explain this observation.

Methods: People living with HIV in the Swiss HIV Cohort Study were eligible if they were on a boosted protease inhibitor concomitantly with a statin for at least 6 months and if their *SLCO1B1* genotype was available. Furthermore, their lipids had to be documented before and after the introduction of the statin. The statin efficacy was defined as % change in total cholesterol, low-density lipoprotein–cholesterol, high-density lipoprotein–cholesterol and triglycerides levels after statin initiation compared to pretreatment levels. Lipid response was adjusted for differences in potency and dose between statins.

Results: In total, 88 people living with HIV were included, of whom 58, 28 and 2 carried the *SLCO1B1* TT, TC and CC genotypes, respectively. The change in lipid levels after statin initiation tended to be lower in carriers of the polymorphism although the difference was not statistically significant (TT *vs*. TC/CC: total cholesterol: −11.7 *vs*. −4.8%; low-density lipoprotein− cholesterol: −20.6 *vs*. −7.4%; high-density lipoprotein–cholesterol: 1.6 *vs*. 0%; triglycerides: −11.5 *vs*. −7.9%). In the multiple linear regression, change in total cholesterol was inversely correlated with the total cholesterol level prestatin treatment (coefficient −6.60, 95% confidence interval: −9.63 to −3.56, $P < .001$).

Conclusion: The lipid-lowering effect of statins tended to be attenuated by *SLCO1B1* polymorphism and progressively declined as total cholesterol under the boosted protease inhibitor treatment decreased.

Members of the Swiss HIV Cohort Study are listed in the Acknowledgements section.

KEYWORDS
lipid-lowering response, polymorphism, protease inhibitor, SLCO1B1, statin

1 | INTRODUCTION

Lipid abnormalities are highly prevalent, particularly in people living with HIV (PLWH) as a result of HIV infection itself, side effects of certain antiretroviral drugs (notably boosted protease inhibitors) and aging of the HIV population.[1–3] Statins are the most commonly used medications for the treatment of dyslipidaemia in PLWH because of their proven efficacy for lowering low-density lipoprotein (LDL) cholesterol and for reducing the risk of cardiovascular diseases.[4]

The lipid-lowering effect of statins occurs through the inhibition of the hepatic β-hydroxy β-methylglutaryl-CoA reductase and therefore relies on their ability to access the liver. Statins are actively transported in the liver by members of the organic anion transporting polypeptide (OATP) family, notably OATP1B1.[5] This hepatic transporter is encoded by the *SLCO1B1*, a gene displaying a large number of single nucleotide polymorphisms (SNPs).[6] Among them, the common SNP rs4149056, characterized by a nucleotide change from T to C in position 521 in the coding region of *SLCO1B1*, has been associated with a reduced transport activity of OATP1B1,[7] resulting in increased plasma concentrations of several statins.[8–10] As *SLCO1B1* c.521T>C reduces the entry of statins in the liver, the site of metabolic elimination and action, carriers of this variant are more likely to experience adverse effects (due to high plasma concentrations of the statin) while the lipid-lowering effect may be attenuated (due to lower concentrations of the statin in the liver). The consideration related to the increased risk of adverse effects comes from a genome wide case–control study, which analysed >300 000 genetic variations and found that the SNP rs4149056 was significantly associated with an increased risk of simvastatin induced myopathy.[11] The consideration related to the lipid-lowering effect comes from the PROSPER study (PROspective Study of Pravastatin in the Elderly at Risk), which found that the SNP rs4149056 was associated with significantly less LDL cholesterol- lowering response to pravastatin (TT genotype: −37%; TC genotype: −36%; CC genotype: −31.8%, $P = 0.003$).[12] Another study showed an attenuated total cholesterol-lowering effect to statins in carriers of the variant (TT genotype −22%; CC genotype: −16.5%).[13] Finally, a large cohort study reported that carriers of the *SLCO1B1* CC genotype were less likely to achieve the lipid target goals.[14] Of interest, an analysis of the Swiss HIV Cohort Study (SHCS) showed that some PLWH on a boosted protease inhibitor-containing regimen did not achieve the lipid target despite elevated statin concentrations.[15] This observation has been attributed to the inhibition of OATP1B1 by boosted protease inhibitors, which prevents the entry of statins into the liver leading consequently to less inhibition of β-hydroxy β-methylglutaryl-CoA reductase. However, considering that the *SLCO1B1* rs4149056 polymorphism was shown to increase the exposure of boosted protease inhibitors,[16,17] this pharmacokinetic/pharmacodynamic interaction could be genetically determined.

What is already known about this subject

- We previously observed that some individuals on boosted protease inhibitor-containing regimen do not achieve their lipid target despite elevated statin concentrations.
- The common single polymorphism c.521T>C in *SLCO1B1* gene encoding OATP1B1 has been associated with reduced statin uptake in the liver and reduced lipid-lowering effect in some studies.

What this study adds

- After statin initiation, the reduction in lipid levels tended to be lower in individuals on a boosted protease inhibitor carrying the polymorphism although the difference was not statistically significant.
- Absolute reduction in total cholesterol was correlated to prestatin cholesterol levels with elevated pretreatment cholesterol levels being associated with higher reduction.

We postulated that PLWH on boosted protease inhibitor treatment and carrying the *SLCO1B1* 521CC or 521TC genotype could have a lower lipid-lowering response while having a higher risk of developing statin related muscle toxicity compared to carriers of the 521TT genotype. Thus, this study aimed to assess the effect of the SNP rs4149056 on the change in lipids and muscle toxicity after initiating a statin in PLWH on a boosted protease inhibitor regimen.

2 | METHODS

2.1 | Study population and study design

PLWH enrolled in the SHCS were eligible if they had received a protease inhibitor-containing regimen concomitantly with 1 of the commonly prescribed statins (e.g. rosuvastatin, atorvastatin or pravastatin) for at least 6 months and if their *SLCO1B1* genotype status was available in the SHCS database. In addition, their lipid values had to be documented before (at least 1 set of values) and after the initiation of the statin (at least 2 consecutive sets of values 3–6 months apart). The study was approved by the local ethics committees. All participants provided informed consent including for genetic testing.

2.2 | Effect of SLCO1B1 genotype on the lipid response and adverse effects

The response to statins was defined as the percentage change in total-, LDL-, high-density lipoprotein–cholesterol and triglycerides levels measured for the most part 1 year after the initiation of the statin compared to levels under treatment with the boosted protease inhibitor. Lipid values are coded in the SHCS database as obtained in a *fasting* or *nonfasting* state. However, since this information is not always reliable, total cholesterol was chosen as primary endpoint for the response to lipid-lowering therapy and exploratory analyses were performed for the other lipid parameters using the values coded as *fasting*. Furthermore, the response was adjusted for differences in dose and potency between statins.[18]

Muscle toxicity was evaluated considering incident clinical and laboratory adverse effects. Adverse clinical events were defined as hospitalizations for rhabdomyolysis, myositis, myopathy and liver failure. Adverse laboratory events were defined as grade 3 or 4 elevations above the upper limit of normal of any of the following parameters: alanine aminotransferase, aspartate aminotransferase, total bilirubin and creatinine kinase. Individuals with elevated creatinine kinase values following a myocardial infarction were excluded from the study.

The socio-demographic characteristics, the clinical and HIV-related parameters, the treatment as well as the laboratory values before and after the introduction of the statin were extracted from the SHCS database. The values of creatinine kinase are not collected routinely in the SHCS database and therefore were obtained from the physician in charge of the patient.

2.3 | SLCO1B1 genotype

Genotyping data for *SLCO1B1* rs4149056 were obtained from a previous project of the SHCS which aimed at evaluating the effect of several genetic variants on lopinavir/ritonavir (LPV/r) pharmacokinetics.[19] Thus, for the current project, we used the same dataset and selected PLWH on an LPV/r-containing regimen who were also receiving a statin.

2.4 | Statistical analysis

Descriptive analyses are presented as median and interquartile range (IQR) for continuous variables and as percentages for categorical variables. The χ^2 test was used to compare participants' characteristics based on *SLCO1B1* genotype (TT *vs*. TC/CC). The mean change in lipid levels was compared for *SLCO1B1* TT and TC/CC genotypes using the Mann–Whitney test. Univariable and multivariable linear regressions were used to identify factors associated with the mean change in total cholesterol after initiation of the statin. The model was adjusted for age, sex, obesity, arterial hypertension, history of cardiovascular disease, smoking, hepatitis C virus coinfection, CD4 cell count and viral suppression at statin initiation, duration of antiretroviral treatment, total cholesterol at baseline, the concurrent use of ezetimibe or fenofibrate and the dose of the statin. Overall *P* values <.05 were considered statistically significant. Statistical analyses were conducted using STATA (StataCorp, version 13 for Windows College Station, TX, USA).

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/2020.[20]

3 | RESULTS

3.1 | Study population

Overall, 88 Caucasian PLWH were included in the analysis; of those, 58, 28 and 2 carried the *SLCO1B1* TT, TC and CC genotypes, respectively, representing an allele frequency of 18.2% (C allele). Given the small number of CC genotype, the TC and CC genotypes were grouped for the subsequent analyses. Table 1 describes the characteristics of the study population according to *SLCO1B1* genotype. Overall, the participants were mostly male ($n = 69$, 78%), virologically suppressed (HIV RNA <50 copies/mL; $n = 72$, 82%) under a LPV/r-containing regimen and were mostly treated with pravastatin ($n = 68$, 78%) for the dyslipidaemia. The median daily pravastatin dose was 40 mg in carriers of the *SLCO1B1* TC/CC genotypes and 20 mg in those with the TT genotype. There were no significant differences among the *SLCO1B1* genotype groups in terms of age, HIV-related factors, prevalence of selected comorbidities or median lipid values at baseline (before statin initiation).

3.2 | Effect of SLCO1B1 genotype on the lipid response

Upon initiation of LPV/r treatment, all lipid values increased compared to baseline values, no significant differences in terms of percentage change in lipids were observed between the *SLCO1B1* TT genotype group compared to the TC/CC genotypes. Initiation of a statin reduced the total cholesterol value by 11.7% in individuals homozygous for the T allele and by 4.8% in those heterozygous/homozygous for the C (i.e. allele associated with a reduced transport function; Table 2). The LDL-cholesterol, high-density lipoprotein–cholesterol and triglycerides were reduced by 20.6, 1.6 and 11.5% in TT *vs*. 7.4, 0 and 7.9% in TC/CC, respectively. Although the *SLCO1B1* TC/CC group had a reduced lipid-lowering response to statin treatment compared to the TT group, the difference did not reach statistical significance for any of the lipid parameters (*P* values

TABLE 1 Baseline characteristics of the study population according to the presence of *SLCO1B1* c.521T>C polymorphism.

Variable		Genotype TC/CC $n = 30$		Genotype TT $n = 58$		*P*
Median age, years (IQR)		49	(44–55)	46	(40–52)	.124
Male, *n* (%)		24	(80.0)	45	(77.6)	.794
Prior AIDS-defining condition, *n* (%)		16	(53.3)	23	(39.7)	.221
Median CD4 cell count at cART initiation, cells/μL (IQR)		319	(263–489)	371	(267–517)	.360
Median HIV RNA at cART initiation, log10 copies/mL (IQR)		5.1	(4.9–5.7)	5.2	(3.7–5-9)	.551
Median CD4 cell count at statin initiation, cells/μL (IQR)		439	(280–584)	463	(293–596)	.686
Viral suppression <50 copies/mL at statin initiation, n (%)		25	(83.3)	47	(81.0)	.791
HCV co-infection (HCV antibodies), *n* (%)		6	(20.0)	9	(15.5)	.401
HBV co-infection (HBsAg- positive), *n* (%)		3	(10.0)	2	(3.5)	.216
Smoking, *n* (%)		13	(43.3)	28	(48.3)	.660
Arterial hypertension, *n* (%)		2	(6.7)	5	(8.6)	.543
Diabetes mellitus, *n* (%)		3	(10.0)	5	(8.6)	.556
Obesity (BMI > 30 kg/m^2), (%)		3	(10.0)	4	(6.9)	.180
Familial history of cardiovascular diseases, *n* (%)		3	(10.0)	14	(24.1)	.093
Prior cardiovascular disease, *n* (%)		5	(16.7)	9	(15.5)	.557
Median years of cART (IQR)		6.6	(3.3–8.6)	7.5	(5.3–10.2)	.254
Median total cholesterol at baseline, mmol/L (IQR)		5.5	(4.6–6.8)	5.8	(4.8–6.8)	.592
Median LDL-cholesterol at baseline, mmol/L (IQR)		3.0	(2.6–4.4)	3.3	(2.6–4.4)	.127
Median HDL-cholesterol at baseline, mmol/L (IQR)		1.0	(0.7–1.2)	1.1	(0.9–1.3)	.247
Median triglycerides at baseline, mmol/L (IQR)		2.9	(1.8–6.0)	2.7	(1.8–3.8)	.347
Statin	Pravastatin (%)	24[a]	(80.0)	44[b]	(75.9)	0.873
	Rosuvastatin (%)	0	-	2	(3.5)	
	Atovarstatin (%)	3	(10)	8	(13.8)	
	Fluvastatin (%)	1	(3.3)	2	(3.5)	
	Simvastatin (%)	2	(6.7)	2	(3.5)	
Ezetimibe (%)		1	(3.3)	3	(5.2)	.593
Fenofibrate (%)		0	-	3	(5.2)	.291

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; cART, combined antiretroviral treatment; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.
[a]Median daily pravastatin dose: 40 mg.
[b]Median daily pravastatin dose: 20 mg.

≥.2). The occurrence of myalgia after the initiation of the statin was low (1 PWH in each genotype group) and not significantly different among the 2 groups.

3.3 | Factors associated with the mean change in total cholesterol after statin initiation

The effect of various factors on the mean change in total cholesterol after initiation of the statin compared to values under LPV/r treatment was evaluated using univariate and multivariate linear regressions. Both analyses showed that the mean change in total cholesterol was only significantly correlated to the total cholesterol level under LPV/r treatment (multivariate analysis: coefficient −6.60, 95% confidence interval: −9.63 to −3.56, $P < .001$; Table 3). As depicted in Figure 1, higher lipid levels under LPV/r treatment correlated with a higher reduction in total cholesterol upon initiation of the statin regardless of the *SLCO1B1* genotype.

4 | DISCUSSION

Although there is ample evidence that the *SLCO1B1* rs4149056 polymorphism impacts the pharmacokinetics of statins, only few studies have evaluated its impact on the pharmacodynamics of statins. Our study showed that PLWH on treatment with LPV/r and carrying the TC/CC genotypes tended to have an attenuated lipid-lowering response, which, however, did not reach statistical significance

TABLE 2 Effect of *SLCO1B1* c.521T>C polymorphism on the lipid-lowering efficacy of statins in people living with HIV on lopinavir/ritonavir-containing regimen.

Variable		Genotype TC/CC $n = 30$		Genotype TT $n = 58$		*P*
Total cholesterol (mmol/L)	Median difference from baseline to LPV/r initiation (IQR)	.7	(0 to 1.6)	.8	(0 to 2.4)	.746
	% change (IQR)	9.9	(0 to 38.0)	12.7	(0 to 51.9)	.719
	Median difference from LPV/r to statin initiation (IQR)	−0.3	(−1.4 to 0.3)	−0.6	(−1.9 to 0.1)	.256
	% change (IQR)	−4.8	(−19.5 to 4.4)	−11.7	(−24.2 to 1.2)	.200
LDL-cholesterol (mmol/L)	Median difference from baseline to LPV/r initiation (IQR)	0.2	(0 to 0.8)	0.1	(−0.5 to 0.8)	.260
	% change (IQR)	7.1	(0 to 25.5)	3.3	(−16.2 to 27.2)	.420
	Median difference from LPV/r to statin initiation (IQR)	−0.3	(−1.0 to 0.2)	−0.6	(−1.3 to 0.4)	.566
	% change (IQR)	−7.4	(−23.8 to 7.2)	−20.6	(−35.8 to 5.5)	.177
HDL-cholesterol (mmol/L)	Median difference from baseline to LPV/r initiation (IQR)	0.1	(0 to 0.4)	0.1	(−0.4 to 0.3)	.331
	% change (IQR)	13.5	(0 to 47.3)	7.8	(−3.4 to 33.6)	.456
	Median difference from LPV/r to statin initiation (IQR)	0	(−0.1 to 0.2)	0	(−0.1 to 0.2)	.867
	% change (IQR)	0	(−6.8 to 19.9)	1.6	(−8.4 to 18.4)	.881
TG (mmol/L)	Median difference from baseline to LPV/r initiation (IQR)	0.1	(−0.2 to 1.5)	0.6	(−0.1 to 3.0)	.202
	% change (IQR)	11.2	(−6.7 to 77.2)	22.2	(−2.7 to 148)	.201
	Median difference from LPV/r to statin initiation (IQR)	−0.4	(−1.2 to 0.4)	−0.3	(−1.5 to 0.5)	.980
	% change (IQR)	−7.9	(−35.6 to 18.1)	−11.5	(−26.9 to 16.0)	.882
Myalgia after statin initiation (%)		1	(3.3)	1	(1.7)	0.568

Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LPV/r, lopinavir/ritonavir; TG, triglycerides.

possibly due to a power issue. This finding supports our previous observation that some PLWH on a boosted protease inhibitor-containing regimen did not achieve the lipid target despite elevated statin concentrations.[15] *SLCO1B1* rs4149056 has indeed been associated with an impaired transport function thereby reducing the amount of substrate drugs (e.g. statins[7] and protease inhibitors[16]) entering the liver for subsequent metabolism and elimination and, in the case of statins, for drug action. Given that protease inhibitors inhibit OATP1B1,[21] their higher drug exposure, as a result of *SLCO1B1* rs4149056, may further inhibit OATP1B1 and consequently further limit the entry of statins. This consideration is supported by the observation that individuals carrying *SLCO1B1* polymorphisms had higher pravastatin concentrations in presence of darunavir/ritonavir compared to those without polymorphisms.[22] Thus, an increase in the dose of the statin may not necessarily improve the lipid response. This consideration is also supported by our study as the change in lipid levels tended to be lower in the group carrying the variant despite receiving a higher median daily dose of pravastatin compared to the group not carrying the variant (i.e. 40 *vs*. 20 mg). It should be noted that, even though all statins are substrate of OATP1B1, the impact of *SLCO1B1* rs4149056 on the lipid-lowering effect or the risk of muscle toxicity may differ depending on the statin due to varying contributions of other transporters to their hepatic uptake. The changes in the area under the curve of various statins in individuals with the *SLCO1B1* CC genotype compared to those with the TT genotype were indeed shown to be: +221% for simvastatin acid[10]; +208% for pitavastatin[23]; +145% for atorvastatin[8]; +91% for pravastatin[24]; +62% for rosuvastatin[8]; and +19% (nonsignificant increase) for fluvastatin.[24]

Regardless of the *SLCO1B1* polymorphism, the pharmacodynamic effect of statins was found to decline progressively as total cholesterol under LPV/r treatment decreased. This observation is in line with previous real world clinical data showing that baseline LDL-cholesterol levels were associated with absolute reductions in LDL-cholesterol whereby lower pretreatment LDL-cholesterol levels were associated with smaller percentage LDL-cholesterol reductions.[25,26] The reasons for the reduced benefit of statin therapy in individuals with lower baseline LDL-cholesterol values are not fully understood.

This study has several limitations. The size of the population was small with only 2 individuals homozygous for the C allele, thereby reducing the power to detect a statistically significant effect of *SLCO1B1* rs4149056 on the lipid-lowering response but also possibly

TABLE 3 Linear regression for mean change in total cholesterol after statin initiation. Univariable and multivariable analyses.

		Univariable analysis			Multivariable analysis		
Variable		**Coefficient**	**95% CI**	***P***	**Coefficient**	**95% CI**	***P***
Age, per 10 years increase		−0.10	−5.44 to 5.24	.972	1.63	−4.37 to 7.63	.589
Female		−8.71	−19.1 to 1.70	.100	−1.74	−13.9 to 10.5	.775
Obesity (body mass index >30 kg/m^2)		−5.12	−20.6 to 10.5	.516	−1.43	−17.8 to 14.9	.861
Diabetes mellitus		−4.01	−19.7 to 11.6	.612	−5.24	−22.6 to 12.1	.548
Arterial hypertension		3.44	−12.3 to 19.2	.664	1.66	−16.8 to 20.2	.858
Prior cardiovascular disease		6.67	−4.87 to 18.2	.254	0.06	−12.8 to 12.9	.993
Smoking		1.09	−7.69 to 9.87	.805	−2.90	−12.9 to 7.05	.562
HCV co-infection		0.09	−11.6 to 11.7	.988	−8.33	−22.8 to 6.12	.253
CD4 at starting statin, per 100 cells increase		−1.43	−3.38 to 0.51	.145	−1.07	−13.9 to 10.5	.775
Viral suppression at statin initiation		1.86	−10.1 to 13.8	.758	6.97	−5.41 to 19.3	.264
Duration of cART treatment, per year		−0.08	−1.08 to 0.92	.872	−0.07	−1.42 to 1.29	.923
Statin	Pravastatin	*Ref.*	-	-	*Ref.*	-	-
	Rosuvastatin	0.85	−27.7 to 29.4	0.953	4.53	−32.4 to 41.5	0.807
	Atovarstatin	10.5	−2.48 to 23.5	0.111	2.99	−17.7 to 23.7	0.773
	Fluvastatin	1.61	−21.9 to 25.1	0.892	1.88	−21.7 to 25.5	0.944
	Simvastatin	7.86	−2.7 to 36.4	0.585	−1.01	−29.6 to 27.6	0.975
Dose of statin, per 10 mg/day increase of 10 mg equivalent dose		4.24	−1.64 to 10.1	.155	0.15	−8.81 to 9.09	.974
Ezetimibe		−10.8	−31.1 to 9.55	.295	1.29	−22.3 to 24.8	.913
Fenofibrate		8.79	−14.6 to 32.2	.457	13.3	−12.6 to 39.2	.309
SLCO1B1 c.521T>C polymorphism		7.78	−1.38 to 16.9	.095	4.45	−4.70 to 13.6	.334
Total cholesterol at baseline (before LPV/r)		−2.79	−5.61 to 0.03	.052	−0.71	−4.18 to 2.77	.683
Total cholesterol under LPV/r treatment		−6.23	−8.22 to −4.25	<.001	−6.60	−9.63 to −3.56	<.001

Abbreviations: cART, combined antiretroviral treatment; CI, confidence interval; HCV, hepatitis C virus; LPV/r, lopinavir/ritonavir.

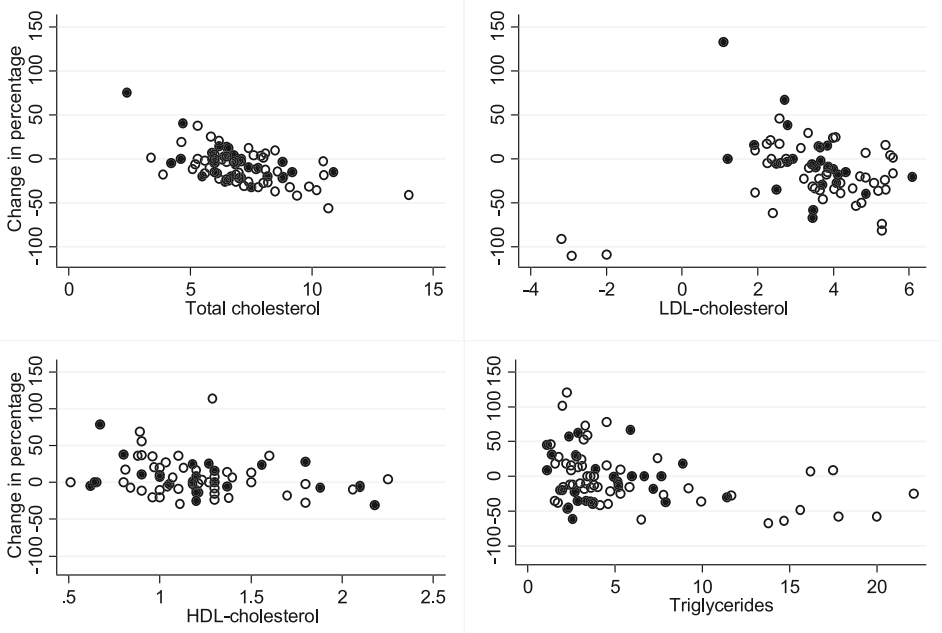

FIGURE 1 Percentage change in total cholesterol, low-density lipoprotein (LDL)–cholesterol, high-density lipoprotein (HDL)–cholesterol and triglycerides levels from treatment with lopinavir/ritonavir and after statin initiation in individuals carrying the *SLCO1B1* TT genotype (open circles) and TC/CC genotype (solid circles).

attenuating the effect on the lipid response given that the transporter function is less impacted in individuals heterozygous for the mutation. The lipid values were measured in clinical care and therefore we could not verify the fasting status. Finally, the statin concentrations were not measured.

In conclusion, the lipid-lowering effect of statins tended to be attenuated in PLWH on a boosted protease inhibitor regimen carrying the *SLCO1B1* rs4149056 polymorphism. Given that this polymorphism can also impact the concentrations of protease inhibitors and consequently the extent of the pharmacokinetic/pharmacodynamic interaction with statins, antiretroviral drugs not highly dependent on OATP1B1 transport and with no inhibitory effect on OATP1B1 (e.g. unboosted integrase inhibitors, doravirine, rilpivirine) should be favoured in PLWH with refractory dyslipidaemia. Regardless of the genetic polymorphism in *SLCO1B1*, the lipid-lowering effect of statins was shown to correlate with the total cholesterol levels with more reduction in lipid levels in individuals with higher lipid values at baseline (prestatin treatment).

AUTHOR CONTRIBUTIONS

Catia Marzolini and Luigia Elzi conceived and designed the study. Matthias Cavassini, Dominique L. Braun, Anna Hachfeld, Enos Bernasconi, Alexandra Calmy, Patrick Schmid, Manuel Battegay and Luigia Elzi provided the clinical data and had direct clinical responsibility for the participants. Catia Marzolini and Luigia Elzi analysed the data. Catia Marzolini and Luigia Elzi wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Members of the Swiss HIV Cohort Study

Abela I, Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Hachfeld A, Haerry D (deputy of *Positive Council*), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Jackson-Perry D (patient representative), Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Kusejko K (Head of Data Centre), Labhardt N, Leuzinger K, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nemeth J, Nicca D, Notter J, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Salazar-Vizcaya L, Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Wandeler G, Weisser M, Yerly S.

This study has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant #201369), by SHCS project #626. Open access funding provided by Universitat Basel.

CONFLICT OF INTEREST STATEMENT

C.M. has received speaker honoraria from MSD, ViiV and Pfizer unrelated to this work. M.C.'s institution received research grants from Gilead, MSD and ViiV. D.L.B. received honoraria for advisory boards paid to himself outside of the current work from Gilead, MSD, ViiV. A.H.'s institution has received travel grants, congress and advisory fees from MSD, ViiV and Gilead unrelated to this work. E.B.'s institution received research grants from MSD, honoraria for participation to advisory boards or travel grants from Gilead, ViiV, MSD, Pfizer, Moderna, Ely Lilly and Astra Zeneca. P.S.'s institution has received travel grants, congress and advisory fees from ViiV and Gilead unrelated to this work. All other authors report no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy restrictions.

ORCID

Catia Marzolini https://orcid.org/0000-0002-2312-7050
Matthias Cavassini https://orcid.org/0000-0003-0933-7833
Dominique L. Braun https://orcid.org/0000-0003-4036-1030
Anna Hachfeld https://orcid.org/0000-0001-9308-7130
Enos Bernasconi https://orcid.org/0000-0002-9724-8373
Alexandra Calmy https://orcid.org/0000-0002-1137-6826
Patrick Schmid https://orcid.org/0000-0002-9528-8072
Manuel Battegay https://orcid.org/0000-0002-6638-3679
Luigia Elzi https://orcid.org/0009-0002-7676-8756

REFERENCES

1. Waters DD, Hsue PY. Lipid abnormalities in persons living with HIV infection. *Can J Cardiol*. 2019;35(3):249-259. doi:10.1016/j.cjca.2018.11.005
2. Antiretroviral Therapy Cohort Collaboration. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV*. 2017;4(8):e349-e356. doi:10.1016/S2352-3018(17)30066-8
3. Pelchen-Matthews A, Ryom L, Borges AH, et al. Aging and evolution of comorbidities among HIV-positive individuals in a European cohort. *AIDS*. 2018;32(16):2404-2416. doi:10.1097/QAD.0000000000001967
4. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constitutes by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
5. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol*. 2009;158(3):693-705. doi:10.1111/j.1476-5381.2009.00430.x
6. Marzolini C, Tirona RG, Kim RB. Pharmacogenomics of the OATP and OAT families. *Pharmacogenomics*. 2004;5(3):273-282. doi:10.1517/phgs.5.3.273.29831
7. Tirona RG, Leake BF, Merino G, Kim RB. Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. *J Biol Chem*. 2001;276(38):35669-35675. doi:10.1074/jbc.M103792200
8. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharm Ther*. 2007;82(6):726-733. doi:10.1038/sj.clpt.6100220

9. Niemi M, Schaeffeler E, Lang T, et al. High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). *Pharmacogenetics*. 2004;14(7):429-440. doi:10.1097/01.fpc.0000114750.08559.32
10. Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics*. 2006;16(12):873-879. doi:10.1097/01.fpc.0000230416.82349.90
11. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy – —a genomewide study. *N Engl J Med*. 2008;359(8):789-799. doi:10.1056/NEJMoa0801936
12. Akao H, Polisecki E, Kajinami K, et al. Genetic variation at the SLCO1B1 gene locus and low density lipoprotein cholesterol lowering response to pravastatin in the elderly. *Atherosclerosis*. 2012;220(2):413-417. doi:10.1016/j.atherosclerosis.2011.09.028
13. Tachibana-Iimori R, Tabara Y, Kusuhara H, et al. Effect of genetic polymorphism of OATP-C (SLCO1B1) on lipid-lowering response to HMG-CoA reductase inhibitors. *Drug Metab Pharmacokinet*. 2004;19(5):375-380. doi:10.2133/dmpk.19.375
14. Meyer zu Schwabedissen HE, Albers M, Baumeister S, et al. Function-impairing polymorphisms of the hepatic uptake transporter *SLCO1B1* modify the therapeutic efficacy of statins in a population-based cohort. *Pharmacogenet Genomics*. 2015;25(1):8-18. doi:10.1097/FPC.0000000000000098
15. Courlet P, Livio F, Alves Saldanha S, et al. Real-life management of drug-drug interactions between antiretrovirals and statins. *J Antimicrob Chemother*. 2020;75(7):1972-1980. doi:10.1093/jac/dkaa099
16. Hartkoorn RC, Kwan WS, Shallcross V, et al. HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by SLCO1B1 polymorphisms. *Pharmacogenet Genomics*. 2010;20(2):112-120. doi:10.1097/FPC.0b013e328335b02d
17. Dragovic G, Dimitrijevic B, Kusic J, et al. Influence of *SLCO1B1* polymorphisms on lopinavir C_{trough} in Serbian HIV/AIDS patients. *Br J Clin Pharmacol*. 2020;86(7):1289-1295. doi:10.1111/bcp.14230
18. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol*. 1998;81(5):582-587. doi:10.1016/S0002-9149(97)00965-X
19. Lubomirov R, di Iulio J, Fayet A, et al. ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformuated with ritonavir. *Pharmacogenet Genomics*. 2010;20(4):217-230. doi:10.1097/FPC.0b013e328336eee4
20. Alexander SPH, Kelly E, Matthie A, et al. The concise guide to pharmacology 2019/20: transporters. *Br J Pharmacol*. 2019;176(S1):S397-S493.
21. Annaert P, Ye ZW, Stieger B, Augustijns P. Interaction of HIV protease inhibitors with OATP1B1, 1B3, and 2B1. *Xenobiotica*. 2010;40(3):163-176. doi:10.3109/00498250903509375
22. Aquilante CL, Kiser JJ, Anderson PL, et al. Influence of SLCO1B1 polymorphisms on the drug-drug interaction between darunavir/ritonavir and pravastatin. *J Clin Pharmacol*. 2012;52(11):1725-1738. doi:10.1177/0091270011427907
23. Ieiri I, Suwannakul S, Maeda K, et al. SLCO1B1 (OATP1B1, an uptake transporter) and ABCG2 (BCRP, an efflux transporter) variant alleles and pharmacokinetics of pitavastatin in healthy volunteers. *Clin Pharmacol Ther*. 2007;82(5):541-547. doi:10.1038/sj.clpt.6100190
24. Niemi M, Pasanen MK, Neuvonen PJ. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. *Clin Pharmacol Ther*. 2006;80(4):356-366. doi:10.1016/j.clpt.2006.06.010
25. De Bacquer D, De Smedt D, Reiner Z, et al. Percentage low-density lipoprotein-cholesterol response to a given statin dose is not fixed across the pre-treatment range: real world evidence from clinical practice: data from the ESC-EORP EUROASPIRE V study. *Eur J Prev Cardiol*. 2020;27(15):1630-1636. doi:10.1177/2047487319874898
26. Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22) analysis. *J Am Coll Cardiol*. 2008;52(11):914-920. doi:10.1016/j.jacc.2008.05.046

How to cite this article: Marzolini C, Cavassini M, Braun DL, et al. Effect of SLCO1B1 c.521T>C polymorphism on the lipid response to statins in people living with HIV on a boosted protease inhibitor-containing regimen. *Br J Clin Pharmacol*. 2023;89(9):2739-2746. doi:10.1111/bcp.15754