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Polymorphisms of SOCS-1 are associated with rapid HIV progression rate

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Abstract

OBJECTIVES:

Immune activation, among other driven by IFN-α and -γ activation is a main feature of progressive HIV infection. Suppressor of cytokine signaling (SOCS) 1 and 3 are negative feedback regulators of the IFN-α and -γ axis. Here, we analyzed the role of 9 single nucleotide polymorphisms (SNPs) within SOCS-1 and 3 genes for their association with HIV progression rate in a cohort of 318 rapid vs 376 slow progressors from the Swiss HIV Cohort Study.

DESIGN AND METHODS:

We analyzed 9 SNPs, which we have identified in Swiss blood donors, in a cohort of HIV-infected patients (n=1144), which have been categorized according to the decline in CD4+ T-cell counts. In all the conducted analyses, we focused on the comparison between rapid and slow progressors with regard to SNPs in SOCS1 and -3 and with regards to haplotypes using multivariate logistic regression models.

RESULTS:

Three SOCS-1 SNPs (rs193779; rs33989964; and rs4780355) are associated with a risk reduction for rapid progression. Two of these SNPs, rs33989964 and rs4780355, are in strong linkage disequilibrium forming a frequent haplotype. Homozygous carriers of this haplotype are also associated with a risk reduction for rapid progression. In contrast, the minor TT genotype of rs33977706 is associated with twice the risk for rapid progression. No associations have been observed for the four SOCS-3 SNPs or the major SOCS-3 haplotypes.

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CONCLUSION:

Our data suggest that SNPS in SOCS-1 are associated with HIV disease progression and speak in favor that immune activation is causal for the progressive immunodeficiency.

Keywords: HIV, immune activation, IFN-alpha, IFN-gamma, SOCS, single-nucleotide polymorphisms

Background:

Hallmark of HIV pathogenesis is sustained immune activation and dysfunction [1]. Chronic antigen stimulation, microbial translocation and stimulation of the innate immune response [2], all, may contribute to this phenomenon. In this context, we note sustained interferon (IFN) type I signaling in chronic HIV infection [3]. Indeed, IFN plasma levels correlated with the plasma viral load and inversely with the CD4+ T-cell count [4]. This goes together with a relative overexpression of IFN stimulated genes (ISGs). A model has been postulated on the basis of these findings that HIV promotes IFN signaling, in turn IFN promotes the activation and proliferation of CD4+ T-cells and thereby increases the number of HIV target cells while resulting in immune dysfunction and exhaustion [3]. Alternatively, these findings of increased IFN signaling might simply be interpreted as an epiphenomenon of higher viral replication and advanced disease state. In SIV infected rhesus macaques, the administration of IFN-α2 continued beyond the acute phase resulted in an IFN-desensitized state with decreased anti-viral gene expression, increased susceptibility to infection, increased cell-associated virus load and greater CD4+ T-cell depletion [5]. In chronically HIV-infected humanized mice, blocking the Interferon receptor (IFNAR) resulted in increased viral replication but rescued both total human T-cell and HIV-specific T-cell numbers [6]. Similarly, blocking IFNAR in

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HIV-infected humanized mice under suppressive combined anti-retroviral treatment restored immune function [6, 7]. These data would rather favor a causal role of chronic IFN activation in HIV pathogenesis. Notably, chronic IFN activation being at the origin of persistent infections has been convincingly demonstrated in the lymphocytic choriomeningitis model [8].

Apart of chronic IFN type I activation, low levels of IFN-γ are detected throughout the course of HIV infection [9]. It appears that IFN-γ expression has no predictive value for either HIV viral set point, mortality, or disease progression rate. Based on its poly-functional effects on immune responses, IFN-γ was even explored as treatment strategy for HIV/AIDs but had no therapeutic efficacy [9]. In contrast, IFN-γ induced protein 10 (IP10 or CXCL10) which is driven predominantly by IFN-γ shows increased plasma levels in HIV infection [10]. Most studies reported a positive correlation between IP-10 levels and disease progression rate [10]. High IP-10 levels suppress the functions of T-cells and NK cells and promote HIV latency and replication [10]. Notably, to what extent, IFN-γ adds to the HIV-associated immune activation remains largely unknown.

IFN type I and IFN-γ signal via their Jak/STAT pathway following binding to their cognate IFN receptor which results in the up-regulation of hundreds of IFN stimulated genes [11]. Effective immune responses to pathogens needs a fine tuned regulation of pro- and anti-inflammatory factors. Else, undamped immune activation results in excessive immunopathology. Thus, already in the first wave of ISGs, negative feedback regulators to the IFN axis are up-regulated, among others suppressor of cytokine signaling (SOCS) [12]. SOCS proteins inhibit signal transducer and activator of transcription proteins (STATs) phosphorylation by binding and inhibiting Janus kinases, by their increased proteosomal degradation or by competing with STATs for phosphotyrosine binding sites on cytokine

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receptors [13, 14]. The family of SOCS proteins consist of eight members, including SOCS1-7 and cytokine inducible Src homology2 (SH2)-containing protein (CIS). Mice lacking SOCS-1 show features reminiscent of HIV pathogenesis, i.e., destruction of the lymphoid organs, a loss of $CD4^+$ T-cells and sustained immune activation. SOCS are very short-lived proteins and their quantification is very delicate. A number of studies reported that HIV results in increased expression of SOCS at the mRNA level but they did not measure it at the protein level. They concluded that SOCS is increased in HIV and attenuates the anti-HIV IFN response [15-18]. In contrast we found that HIV-infected patients have lower SOCS protein levels than matched controls and interpreted the data that HIV interferes with negative SOCS feedback mechanisms [19].

Here, we hypothesized that functionally different human SOCs alleles underlie the distinct HIV progression rate, i.e., SOCS with higher activity might attenuate IFN signaling thereby lessening the immune activation state. Notably, HIV-infected patients commonly progress from transmission to late stage disease with < 200 CD4+ T cells/µl within 7.5 - 12 years. However, HIV-infected patients may show a very rapid disease progression rate (3-4 years from transmission to the AIDS phase) or be long-term non progressors [20]. LTNP are often asymptomatic for 10 to 20 years with CD4+ T-cell counts > 500 cells/µl. Because the chips used for GWAS do not cover the closer SOCS-1 and - 3 genetic region, the specific aims in this study were to define the prevalent single nucleotide polymorphisms present in SOCS-1 and - 3 in a cohort of volunteers donating blood and then to examine whether these polymorphisms may be linked to HIV progression rate.

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Material and Methods:

Swiss HIV Cohort study

The Swiss HIV Cohort study (SHCS), established in 1988, is a systematic longitudinal study enrolling HIV-infected patients in Switzerland. The patients in the SHCS have given their informed consent for genetic testing, and we have obtained the samples for this study from the biobank of the SHCs.

As we did in a previous In a previous study HIV-infected patients from the SHCS had been categorized according to the decline in CD4 counts: slow progressors, intermediate progressors and rapid progressors [21, 22]. The categories were created in two steps. First we estimated for each patient the CD4 decline over time before start of any ART. Second, we grouped the patients by tertiles of CD4 decline (top 33% of stepest decline being the rapid progessors, and the lowest 33% in decline being the slow progresssors). Thus, the rapid progressor group had an annual decline of CD4 cells larger than 101.5, and the slow progressor group of an annual decline of less than 31.7 cells/year before ART start. For patients with <2 CD4+ T-cell measurements between baseline and start of any ART we could not estimate a decline, and we exlcuded them (n = 69). Additional 24 patients without RNA measurements in the 18 months before HAART start (or stop date) have been excluded as well, resulting in a total of 1,051 patients fulfilling the criteria of < CD4+ T-cell and RNA measurements. The number of patients included in our analyses was n=1144 for which DNA could be obtained. Hence this sample is representative of the overall SHCS patient population (Table 1).

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Single nucleotide polymorphisms (SNP) and haplotypes Analysis

Screening for Polymorphisms in SOCS--1 and SOCS-3 in the General Population

We screened 96 DNA samples collected from healthy Swiss blood donors (Swiss Red Cross Zurich, https://www.blutspendezurich.ch/) by denaturing high pressure liquid chromatography (dHPLC) [23] for identifying the variations of SOCS-1 and SOCS-3 genes in our target population using the WAVE DNA fragment analysis system (Transgenomic, Berlin, Germany). These genes are located on chromosomes 16 and 17, SOCS-1: 16p13.13 and SOCS-3: 17q25.3, respectively. Screening covered the coding region and the intron-exon boundaries, and 1.5kb upstream and 1kb downstream of the genes. This screening detected the following variations in the Swiss population: SOCS-1 rs193778, rs243330, rs193779, rs33989964, rs33977706, rs4780355; and SOCS-3 rs8064821, rs7207782, rs563935021, rs199915361, rs4969169, rs4969168, rs12185261.

Genotyping and Haplotype Analysis of the Polymorphisms in SOCS-1 and SOCS-3 in the General Population

To genotype the 13 detected variations, we established genotyping assays by High Resolution Melting (HRM) technique and fluorescence resonance energy transfer (FRET) on a LightCycler 480 II instrument (Roche, Switzerland), and by allele specific amplification (ASA) on agarose gels [24]. Haplotype frequencies were estimated with the software Haploview [25].

Genotyping of additional 176 DNAs from healthy Swiss blood donors revealed that two polymorphisms are inherited together with other polymorphism in healthy Swiss volunteers and two are rare, limiting the informative polymorphisms to 5 polymorphisms for SOCS-1 and 4 polymorphisms for SOCS-3 (Supplementary Table, http://links.lww.com/QAI/B441).

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Statistical Analysis in Rapid and Slow Progressors

In all the conducted analyses we compared the rapid progressors (n=318) to the slow progressors (n=376). For univariate comparisons of these groups, we used chi-square statistics for categorical information and t-tests for continuous information.

We performed two different analyses, one comparing rapid progressors to slow progressors with regard to SNPs in SOCS-1 and SOCS-3, and a second comparing the two groups with regard to haplotypes. In both of these analyses, we fitted multivariate logistic regression models, and report odds ratios and 95% confidence intervals. The model included sex, binary risk group (intravenous drug user (IDU) vs. non-IDU), quintiles of baseline CD4 and quintiles of baseline viral load. The SNP based analyses contained three genotype groups: homozygote genotype (AA - reference), heterozygote (AB or BA) and the less frequent versions of the homozygote genotypes (BB).

In the analysis of haplotypes we first tested for linkage disequilibrium using Haploview [25]. Haplotypes were inferred using an expectation-maximization algorithm implemented in the SNPHAP program (version 1.3.1, developed by David Clayton) (*https://www-gene.cimr.cam.ac.uk/staff/clayton/software/snphap-1.3.1.zip).*

Sensitivity analyses were performed with rapid progressors versus all other (intermediate and slow progressor group combined), as well as including only Caucasian people and recessive models for the analysis of SNPs (homozygote genotypes BB versus all other (AA, AB/BA)).

All analyses were performed using STATA® version 13.1. College Station, TX: StataCorp LP, 2013] and p-values <0.05 were considered as statistically significant.

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Results:

Patient's Characteristics

Participants in the genetic study were mainly male Caucasians (74%) with a median age of 36 years, similar to those included in the entire Swiss HIV Cohort Study (Table 1). The three main risk groups for HIV infection were homosexuals (41% in the genetic cohort and 32% in the general cohort), heterosexuals (36% and 31%) and intravenous drug users (12% and 23%).

Identification of SOCS-1 and SOCS-3 Polymorphisms

To identify polymorphisms in the SOCS-1 and SOCS-3 genes, we screened the promoter, the coding region, and the 3'UTR region of SOCS-1 and SOCS-3 in in a representative population of 96 healthy Swiss blood donors. Subsequently, we selected five SNPs in SOCS-1 and four SNPs in SOCS-3 with a minor allele frequency of more than 0.05 for the analysis with the progressor status in the Swiss HIV Genetic Cohort. Analysis of these SNPs in the Swiss HIV Genetic Cohort revealed that all SNPs are in Hardy-Weinberg equilibrium (Table 2). All SNPs with negative values are located in the promoter region of the gene, while rs4780355 (c.*842A>G) and rs4969169 (c.*589A>G) are located in an intron and in the 3' UTR, respectively.

Association of SOCS-1 with the Rapid Progressor Phenotype

To investigate the association of SNPs in SOCS-1 and SOCS-3 with the HIV progressor phenotype, we divided the Swiss HIV Genetic Cohort into three groups of slow progressors, intermediate progressors, and rapid progressors according to the decline in CD4 counts [21, 22]. Comparison of the rapid and slow progressor subgroups showed clearly the distinct CD4+ T-cell decline rate and that the distribution of the ethnicities is similar (Table 3).

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Four SOCS-1 SNPs were associated with the rapid progressor phenotype (Table 4). When using genotypes, the OR was 0.39 (0.16, 0.96) for rs193779 TT versus CC, 0.34 (0.15, 0.81) for rs33989964 CA/CA versus -/-, 2.22 (1.06, 4.65] for rs33977706 TT versus GG , and 0.47 (0.25,0.90) for rs4780355 GG versus AA. Similar associations but with slightly higher significance were obtained when using a recessive allelic mode of inheritance (data not shown). In contrast, no association of these polymorphisms was detected with the viral load at the initial visit. To investigate whether a potential bias in ethnicities could interfere with the analysis, we performed a sensitivity analysis using whites only. We observed that the directions of the associations and the ORs are similar when looking at whites only to the results obtained when including all ethnicities (data not shown). In addition, we performed as sensitivity analysis the multivariate logistic regression of rapid progressors versus all others (intermediate and slow) and also obtained similar results (data not shown).

The three SOCS-1 SNPs rs193779, rs33989964, and rs4780355 show a similar risk reduction for the rapid progressor phenotype of approximately 60%, suggesting that some of these SNPs may be in linkage disequilibrium. We therefore investigated the linkage disequilibrium between all the SNPs (Suppl. Table 1, http://links.lww.com/QAI/B441) and analyzed the association of the haplotypes with the progressor phenotype (Table 5). We observed a linkage between rs33989964 and rs4780355 with an r^2 of 0.7, while none of the other SNPs were in a strong linkage disequilibrium. Accordingly, the minor alleles of these two SNPs convene on the frequent AC+GG haplotype, which is in homozygous carriers also associated with a risk reduction for the rapid progressor phenotype.

In contrast to the three SOCS-1 SNPs associated with a risk reduction for the rapid progressor phenotype, the minor TT genotype of rs33977706 is associated with twice the risk for the rapid progressor phenotype. Haplotype analysis revealed that the minor allele of this SNPs is

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mainly observed on the GC-TA haplotype, distinct from the AC+GG haplotype associated with the risk reduction. Consequently, we also observed a borderline increased risk for homozygous carriers of this GC-TA haplotype for the rapid progressor group (Table 5).

No associations have been observed for the four SOCS-3 polymorphisms or for the major SOCS-3 haplotypes (Tables 4 and 5).

Discussion:

Progressive natural HIV infection is characterized by chronic IFN-α and -γ signaling. This chronic IFN activation is thought to contribute to proliferation and activation of CD4+ T-cells thereby increasing the number of available HIV target cells while promoting T-cell exhaustion, eventually resulting in a perpetuating vicious cycle. Notably, IFN signaling is attenuated by negative feedback regulators, among others SOCS-1 and SOCS-3. Here, we wondered whether distinct polymorphism(s) in SOCS-1 and 3 are associated with HIV progression rate by comparing rapid vs slow progressors. We found i) several SNPs in the gene region of SOCS-1 and 3 -in healthy volunteers and ii) three SNPs to be directly associated and one SNP to be inversely associated with HIV progression rate. These data are consistent with impact of HIV-mediated IFN signaling being critical in HIV pathogenesis.

SNPs of SOCS--1 and -3 have not been thoroughly sought for in Caucasians and only a few SNPs in their gene region have been described but none in the promoter or coding region. Thus, we screened first 96 volunteers for SNPs in SOCS-1 and -3 and found a large number of SNPs in the promoter and coding region of SOCS-1 and -3 (Table 2). We focused on the SNPs with an allelic frequency higher than 5%, which were not inherited together to 100% in

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the general population to investigate their association with natural HIV disease progression in the genetic cohort study of the SHCS (Table 2).

We found that four polymorphisms of SOCS-1 were associated with rapid progression of HIV but none in SOCS-3. However, the polymorphisms did not show any association with the viral load at the initial visit. Thus, the effects by the SOCS-1 and -3 feedback regulators appears to be uncoupled from viral load, *i.e.*, the SNPs identified may have primarily an effect on the intricate process of CD4+ T-cell depletion but not at first hand on extent of viral replication. This comes back to the egg and hen problem whether immune activation drives CD4+ T-cell depletion and viral replication, or vice versa, viral replication drives immune activation and CD4+ T-cell depletion, or whether different mechanism(s) underlie those pathogenic events. It might even be that all three settings exist with one being more dominant than the other at different stages in HIV pathogenesis. This would explain the controversies in the literature. The lack of any association with SOCS-3 is rather astonishing in view of the data of SOCS-1. We might explain this selective association with SOCS-1 by the higher hierarchical role of SOCS-1 in attenuating rather all cytokines using Janus kinases [26]. These data corroborate the imminent role of IFN and other pathways in HIV pathogenesis.

The association of allelic variants of SOCS-1 has been explored in a variety of diseases, among others in allergic and inflammatory diseases, metabolic diseases, as well as in cancer (Suppl. Table 2, http://links.lww.com/QAI/B441). However, the results from these studies did not reveal an obvious genetic denominator SNP in SOCS-1 with an effect on disease outcome but rather indicated that the genetic locus may be associated with the investigated diseases. This is caused by the broad range of SNPs and haplotypes analyzed in these studies covering a large genetic region encompassing SOCS-1, which were often different between studies, and by the limited power of most studies to detect polygenic effects. In lack of corroborating

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associations of one SNP or haplotype with disease, studies to investigate a potential functional effect of two SOCS-1 SNPSs have been performed. The study by Harada et al. showed that the del (-) allele at rs33989963 has increased SOCS-1 protein levels in human primary nasal fibroblasts and heterozygous carriers of the deletion had a higher risk for adult asthma [27]. Similarly, the T-allelic variant of rs33977706 within the SOCS-1 promoter increases the transcriptional activity of the SOCS-1 gene in transfection experiments and was associated with lower IgE levels in plasma [29]. In our analysis, we observed associations in opposite directions for these two SNPs with a potential functional increase in SOCS-1 activity, one associated with the rapid progressor phenotype and the other associated with the slow progressor phenotype. However, there is only mechanistic data for increased SOCS-1 protein activity for rs33989963 where the del (-) allele showed increased SOCS-1 protein levels and reduced STAT-1 phosphorylation [27]. Such an increased SOCS-1 activity that results in a more efficient attenuation of the Jak/STAT pathway and is associated with the slow progressor phenotype would argue that preserved triggering via the IFN axis is beneficial to HIV infection.

However, what a less prominent ISG response finally means remains unknown – we might speculate that a less prominent ISG response promotes viral replication; on the other side, a less prominent ISG response should trigger less immune activation. In fact, the role of IFNs in HIV remains highly disputed [3]. For further defining the role of SOCS-1 in HIV infection, a quantitative analysis of SOCS-1 protein would need to be done. This task is very demanding because of their transient nature and their manifold influences they are subjected to - a single snapshot analysis would not be meaningful. Alternatively, an interventional study would be attractive modulating SOCS-1. This remains hypothetical since such compounds are lacking [27].

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We are aware of the ongoing debate about the value of candidate gene approaches as opposed to GWAS [28, 29]. It might be argued that multiple testing in studies using candidate gene approach might provide false positive results; thus the data obtained in our cohort need to be validated in other cohort of HIV-infected patients. On the other hand, GWAS are as good as is the coverage of the annotations of the genes and both SOCS genes are badly covered on the SNP chips. We consider the approaches complementary, imminent for getting a deeper insight into HIV pathogenesis and as first step for explorative studies.

In summary, SNPs in SOCS-1 are associated with HIV disease progression rate, pointing to the imminent role the Jak/STAT axis has in HIV pathogenesis. In addition, allelic variants of SOCS-1, with either decreased or increased transcriptional activity of SOCS-1 go along with slow and rapid progressor status, respectively. The latter findings imply that attenuating the Jak/STAT pathway favors HIV progression rate. Notwithstanding, we lack clinical studies which specifically interfere with the IFN axis for ultimate proof of its pathogenic significance.

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Authors' contribution:

MH and RFS were responsible overall for the concept of the study and wrote the manuscript, ES, MB and JMJ did the bench work, PYB, PV and JN gave critical input into the design of the study and MZ and KS did the statistical analyses.

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Table 1: Characteristics of Patients included in the Genetic Study and the Swiss HIV Cohort Study

		Genetic Cohort (n=1144)	General Cohort (n=12'285)
Gender	Males	0.74	0.71
	Females	0.26	0.29
Age (initial visit)	Median	36	32
Ethnicity	White	0.879	0.63
	Black	0.087	0.071
	Asian	0.017	0.018
	Hispano-American	0.014	0.011
	Other	0.003	0.001
	Unknown	0	0.27
Risk group factor	Homosexual	0.414	0.32
	Heterosexual	0.363	0.31
	Intravenous Drug User	0.122	0.23
	Drug & Sex	0.066	0.1
	Hemophilia	0.002	0.004
	Transfusion	0.007	0.008
	Other	0.009	0.005
	Unknown	0.017	0.018
CDC Stage (initial visit)	A	0.868	0.68
	B	0.078	0.19
	C	0.054	0.13

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Table 2: Genotypes in the genetic cohort study (n=1144)

SOCS1	Genotypes	Frequencies	P-HWE
rs243330	GG	0.24	
c.-1106G>A	GA	0.52	
	AA	0.24	1.0
rs193779	CC	0.64	
c.-1080C>T	CT	0.31	
	TT	0.04	0.78
rs33989964	CA/CA	0.55	
c.-928_-927delCA	CA/-	0.40	
	-/-	0.06	1.0
rs33977706	GG	0.55	
c.-270G>T	GT	0.38	
	TT	0.07	0.82
rs4780355	AA	0.42	
c.*842A>G	AG	0.48	
	GG	0.10	0.98

SOCS3	Genotypes	Frequencies	P-HWE
rs8064821	GG	0.70	
c.-1649G>T	GT	0.28	
	TT	0.02	0.69
rs7207782	CC	0.41	
c.-1636C>T	CT	0.44	
	TT	0.15	0.25
rs199915361	GG	0.88	
c.-747delG	G/-	0.11	
	-/-	0.01	0.65
rs4969169	GG	0.87	
c.*589A>G	AG	0.12	
	AA	0.01	0.56

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Table 3: Characteristics of rapid and slow progressors

		Rapid progressors (n=318)	Slow progressors (n=376)
Gender	Males	0.80	0.69
	Females	0.20	0.31
Age (initial visit)	Median	38	32
Ethnicity	White	0.87	0.86
	Black	0.10	0.093
	Asian	0.016	0.024
	Hispano-American	0.006	0.018
	Other	0.003	0.003
	Unknown	-	-
Risk group factor	Homosexual	0.50	0.34
	Heterosexual	0.37	0.37
	Intravenous Drug User	0.063	0.19
	Drug & Sex	0.044	0.074
	Hemophilia	0.003	0.003
	Transfusion	0.000	0.010
	Other	0.006	0.008
	Unknown	0.013	0.008
CDC Stage (initial visit)	A	0.86	0.93
	B	0.094	0.048
	C	0.047	0.016
Viral load*	ln	10.4 (9.3-11.4)	9.1 (7.7-10.5)
	log10	4.5 (4.0-4.9)	4.0 (3.3-4.6)
Difference in CD4 per year*	Slope	-141 (-289,-11)	-32 (-55,-14)**

* The median (p25,p75) is shown. ** $p<0.05$

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Table 4: Multivariate logistic regression model to investigate the association of polymorphisms in SOCS1 and SOCS3 with rapid versus slow progressor status (n=694)

SOCS1	Genotype	OR	p-value	[95% CI]
rs243330	GG	1		
c.-1106G>A	GA	1.13	0.61	0.72,1.76
	AA	0.84	0.51	0.49,1.42
rs193779	CC	1		
c.-1080C>T	CT	1.32	0.18	0.88,1.99
	TT	0.39	0.041	0.16,0.96
rs33989964	CA/CA	1		
c.-928_-927delCA	CA/-	1.02	0.92	0.69,1.50
	-/-	0.34	0.014	0.15,0.81
rs33977706	GG	1		
c.-270G>T	GT	0.92	0.69	0.62,1.37
	TT	2.22	0.034	1.06,4.65
rs4780355	AA	1		
c.*842A>G	AG	0.97	0.87	0.65,1.44
	GG	0.47	0.023	0.25,0.90

SOCS3	Genotype	OR	p-value	[95% CI]
rs8064821	GG	1		
c.-1649G>T	GT	0.79	0.27	0.52,1.20
	TT	1.53	0.56	0.37,6.23
rs7207782	CC	1		
c.-1636C>T	CT	0.93	0.71	0.62,1.39
	TT	0.76	0.34	0.43,1.34
rs199915361	GG	1		
c.-747delG	G/-	1.21	0.51	0.69,2.13
	-/-	1.34	0.79	0.15,11.75
rs4969169	GG	1		
c.*589A>G	AG	0.98	0.95	0.56,1.74
	AA	3.28	0.34	0.29,37.77

Multivariate logistic regression model including gender, quintiles of baseline CD4 values, quintiles of baseline viral load and IDU.

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Table 5: Multivariate logistic regression model to investigate the association of haplotypes in SOCS1 and SOCS3 with rapid versus slow progressor status (n=694)

SOCS1	Frequency*	OR (95% CI)	p-value
GC-TA	0.266	0.96 (0.65, 1.42)	0.84**
hom		2.12 (0.98, 4.56)	0.056**
AC+GG	0.262	1.01 (0.68, 1.49)	0.97**
hom		0.34 (0.14, 0.80)	0.014**
AC-GA	0.193		
GT-GA	0.184		
AC-GG	0.043		
GC-GA	0.020		
GT-GG	0.015		
GC-GG	0.014		
Others	0.033		

SOCS3	Frequency*	OR (95% CI)	p-value
GT+G	0.366	0.94 (0.63, 1.40)	0.75**
hom		0.73 (0.41, 1.29)	0.28**
GC+G	0.347	1.22 (0.82, 1.81)	0.33**
hom		1.21 (0.67, 2.21)	0.53**
TC+G	0.147		
GC+A	0.079		
GC-G	0.058		
Others	0.030		

Multivariate logistic regression model including gender, quintiles of baseline CD4 values, quintiles of baseline viral load and IDU. The haplotypes are named according to the sequence of the alleles observed along the chromosome at the analyzed SNPs. The order of the SNPs is shown in table 4 from top to bottom. For SOCS-1 five SNPs have been genotyped leading to a five position haplotype name, while for SOCS-3 four SNPs have been analyzed leading to a four position haplotype name. +, CA allele of rs33989964. -, del (-) allele of rs33989964.hom, homozygous diplotype. *Overall haplotype frequency in the cohort. ** Additive genetic model versus all other haplotypes.

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