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RESEARCH ARTICLE

Interleukin gene polymorphisms and susceptibility to HIV-1 infection: a meta-analysis

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Abstract. Some subjects are repeatedly exposed to human immunodeficiency virus (HIV), yet they remain uninfected. This suggests the existence of host-resistance mechanisms. The current study synthesizes the evidence regarding the association between interleukin (IL) gene polymorphisms and HIV susceptibility. Medline, Scopus and the Web of Science databases were systematically searched, and a meta-analysis of case–control studies was conducted. Univariate and bivariate methods were used. The literature search identified 42 eligible studies involving 15,727 subjects. Evidence was obtained on eight single-nucleotide polymorphisms (SNPs): *IL1A* −889 C>T (rs1800587), *IL1B* +3953/4 C>T (rs1143634), *IL4* −589/90 C>T (rs2243250), *IL6* −174 G>C (rs1800795), *IL10* −592 C>A (rs1800872), *IL10*−1082 A>G (rs1800896), *IL12B* −1188 A>C (rs3212227) and *IL28B* C>T (rs12979860). The *IL1B* +3953/4 C>T variant appears to increase the risk of HIV acquisition, under the assumption of a recessive genetic model (odds ratio (OR): 4.47, 95% CI: 2.35–8.52). The AA homozygotes of the *IL10* -592 C>A SNP had an increased, marginally nonsignificant, risk (OR: 1.39, 95% CI: 0.97–2.01). It reached, however, significance in subanalyses (OR: 1.49, 95% CI: 1.04–2.12). Finally, the well-studied hepatitis C virus (HCV) infection *IL28B* (rs12979860) CT/TT genotypes were associated with a 27% decrease in HIV infection risk, especially in populations infected with HCV (OR: 0.73, 95% CI: 0.57–0.95). Interleukin signalling is perhaps important in HIV infection and some interleukin genetic variants may affect the risk of HIV acquisition. Approaches targeting specific genes and genomewide association studies should be conducted to decipher the effect of these polymorphisms.

Keywords. human immunodeficiency virus; susceptibility; interleukin; gene polymorphism; single-nucleotide polymorphisms; meta-analysis.

Introduction

Despite decreases in morbidity and mortality of people infected by human immunodeficiency virus (HIV) (Puhan *et al.* 2010), the disease remains a major public health problem. Without cure or vaccines, and with almost 36.7 million HIV-infected individuals worldwide (UNAIDS 2016, http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016), prevention is at the top of the

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HIV agenda. Elucidation of aetiological mechanisms that result in HIV transmission is essential for developing novel preventive or therapeutic measures.

It is interesting that some subjects remain uninfected in spite of multiple exposures to HIV, while others become infected upon first exposure (Jennes *et al.* 2004; Levy 2009). This phenomenon implies the existence of host resistance to HIV that includes innate and adaptive immune mechanisms (Kaur and Mehra 2009; Miyazawa *et al.* 2009). Present evidence supports a genetic component in HIV susceptibility and progression to acquired immune deficiency syndrome (AIDS). The 32 bp deletion in CCR5 (CCR5Δ32, rs333), the major coreceptor for HIV-1, results in a truncated protein product that is not expressed on the cell surface, and yields almost complete protection against HIV-1 infection in homozygous individuals (Dean *et al.* 1996; Samson *et al.* 1996; Ioannidis *et al.* 2001).

Cytokines comprise a significant part of the host immune response (Alfano *et al.* 2008; Levy 2009). A variety of polymorphisms in genes that encode cytokines were identified. Many researchers have examined the association of the interleukin (IL) gene polymorphisms with the risk of HIV acquisition and HIV disease progression (Nakayama *et al.* 2002; Wichukchinda and Nakayama 2006; Chatterjee *et al.* 2009a,b; Naicker *et al.* 2009; Sobti *et al.* 2010a,b; Pontillo *et al.* 2012), with various findings with respect to whether *IL* gene polymorphisms play a role or not in HIV infection. In an era of massive and inexpensive gene-sequencing techniques, determination of genetic risk for HIV infection could be an important tool for preventive or therapeutic strategies. The aim of the current work was to synthesize existing evidence, identify *IL* gene variants that affect HIV susceptibility, and explore the causes of between-studies heterogeneity.

Methods

Eligibility criteria, data sources and search strategy

This systematic review and meta-analysis was conducted according to the MOOSE guidelines (Stroup *et al.* 2000), and the PRISMA statement (Moher *et al.* 2010) (see table 1 in electronic supplementary material at http://www.ias.ac.in/jgenet/). Case–control studies were considered in the analysis if they had examined the association between risk of HIV acquisition and polymorphisms in interleukin genes, and provided sufficient data to estimate an odds ratio (OR) along with its 95% confidence interval (CI).

We systematically searched Medline, Scopus and the Web of Science databases using a combination of the following terms: HIV, interleukin, IL, polymorphism and genotype (last search: September 2015). Irrelevant records were excluded after the initial screening of titles and abstracts. Full-text versions of the remaining articles were evaluated for eligibility. References of eligible publications and abstracts from conference meetings were also appraised to identify additional studies for inclusion.

Data extraction and quality assessment

Data extraction was undertaken by two independent reviewers (Chrissa G. Tsiara and Georgios K. Nikolopoulos). Any discrepancy was resolved by consensus, referring to the original article. The following data, if available, were retrieved from each eligible study: (i) first author's name, year of publication, race/ethnicity of participants, geographic setting, study design; (ii) subjects' characteristics, including age, sex and AIDS diagnosis; (iii) genotyping procedures; (iv) polymorphisms under investigation; and (v) frequency of genotypes and alleles in cases and controls.

The quality of primary studies was evaluated based on clear description of the adopted inclusion criteria and proper use of statistical methods. Exclusions, however, if a study was perceived of poor quality or biased were avoided. Yet, the potential influential role of each study was explored by rerunning the analysis after the transient removal of that study.

Statistical analysis

The OR was the metric of choice for the allelic and genotypic comparisons between cases and controls. The normality of the natural logarithms of the ORs was assessed by the Shapiro–Wilk test. Combined effect estimates were calculated across different groups (Caucasians, Asians and mixed/others) and types of controls (HIV seronegatives, HIV-exposed seronegatives (HES)). Deviations from the Hardy–Weinberg equilibrium (HWE) were explored by a χ^2 test in control groups (Schaid and Jacobsen 1999). When violations were detected, sensitivity analysis was conducted to estimate their impact on the OR.

The between-studies heterogeneity was assessed using the Cochran's Q test (Petitti 2000), and quantified with the I^2 statistic (Higgins *et al.* 2003). The ORs from primary studies were synthesized using both fixed-effect and random-effect methods (DerSimonian and Laird 1986). Unless stated differently, only random-effect estimates are presented. The analysis was also performed using a genetic model-free approach based on a bivariate pairwise analysis (Minelli *et al.* 2005).

The methods of Begg (Begg and Mazumdar 1994) and Egger (Egger *et al.* 1997) were used to detect publication bias. Cumulative meta-analyses were also performed to detect potential time trends in the effect estimates (Lau *et al.* 1992).

All P values were two-tailed. For all tests (except for heterogeneity), a probability level <0.05 was considered statistically significant. Stata 12.0 software was used for all statistical analyses (Stata, College Station, USA).

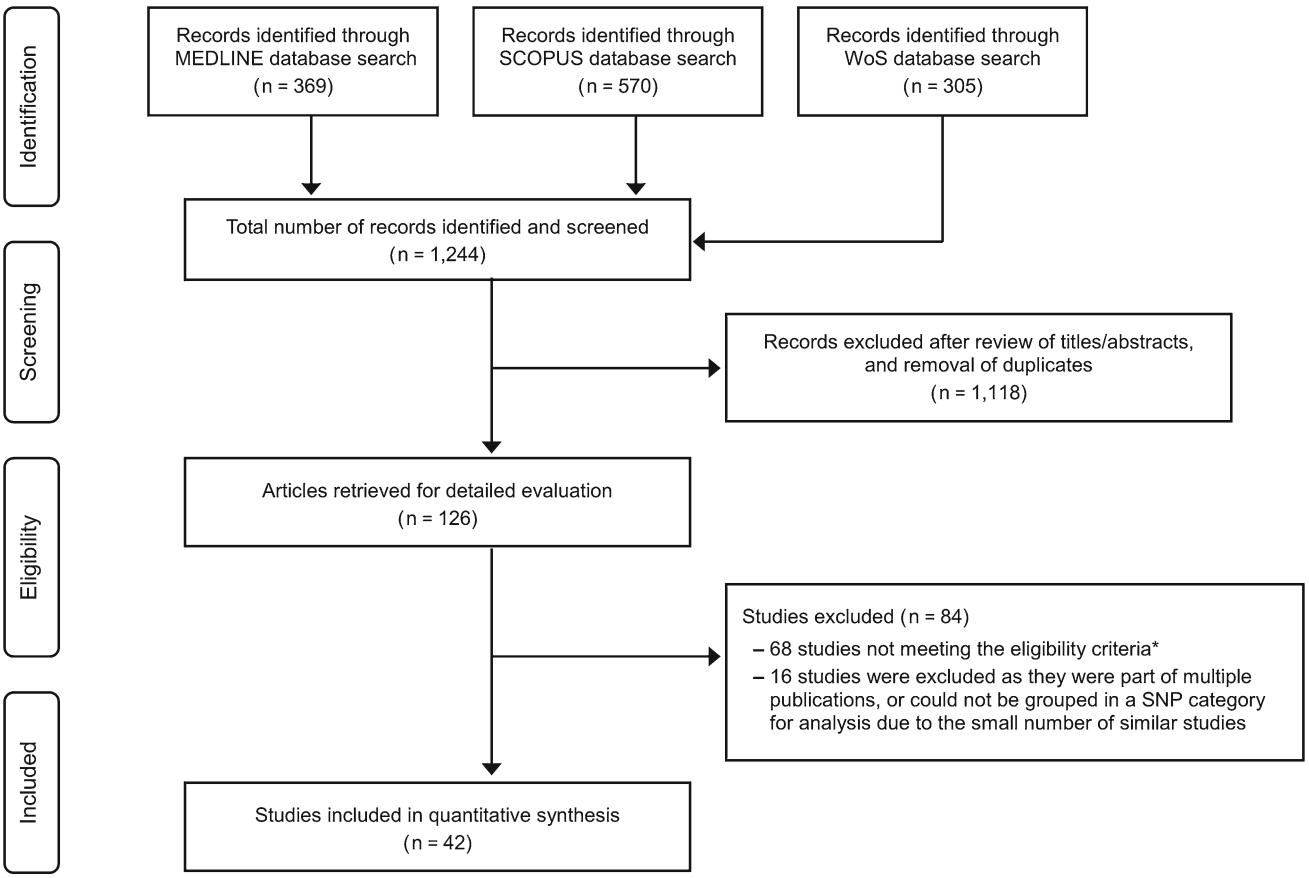

Figure 1. Summary of the evidence search and selection process (flow diagram). *Case–control studies (of HIV seropositive cases and HIV seronegative controls) were considered in the analysis, if they had examined the association between the risk of HIV acquisition and polymorphisms in interleukin genes, and provided sufficient data (interleukin gene polymorphism distributions in cases and controls) to estimate an OR along with its 95% CI. WoS, Web of Science.

Results

Description of eligible studies

A summary of the literature search and selection process is presented in figure 1 (flow diagram). A total of 42 studies, involving 8953 HIV seropositives and 6774 HIV seronegatives, were included in the meta-analysis. Data were provided for the following eight single-nucleotide polymorphisms (SNPs): *IL1A* –889 C>T (rs1800587), *IL1B* +3953/4 C>T (rs1143634), *IL4* –589/90 C>T (rs2243250), *IL6* –174 G>C (rs1800795), *IL10* –592 C>A (rs1800872), *IL10* –1082 A>G (rs1800896), *IL12B* –1188 A>C (rs3212227) and *IL28B* C>T (rs12979860) (table 1). All the studies have assessed the cytokine gene polymorphisms by using polymerase chain reaction (PCR). Twenty-one studies were considered, only individuals of Caucasian descend, nine included Asians, while the rest evaluated subjects belong to another racial group. The allelic and genotypic distributions of the *IL* genes SNPs are presented in table 2, whereas the results of the meta-analyses are shown in table 3.

Susceptibility to HIV infection

IL1A -889 C>T (rs1800587): The comparison of allelic frequencies from four primary studies (Price *et al.* 1999, 2002; Asensi *et al.* 2008; Pemberton *et al.* 2008) failed to support an association between the mutant T allele and HIV risk (OR: 1.06, 95% CI: 0.84–1.34). The genotypic analysis was not conducted because only two studies (Asensi *et al.* 2008; Pemberton *et al.* 2008) provided the necessary information.

IL1B +3953l4 C >T (rs1143634): The T versus C allele contrast included six studies (Price *et al.* 1999, 2002; Asensi *et al.* 2008; Pemberton *et al.* 2008; Gonçalves *et al.* 2009; Pontillo *et al.* 2012) and yielded an OR of 1.38 (95% CI: 0.87–2.17). The effect estimate became significant (OR: 2.50, 95% CI: 1.48–4.21) in the meta-analysis of two studies involving Brazilian subjects (Gonçalves *et al.* 2009; Pontillo *et al.* 2012) (figure 2). The synthesis of four studies (Asensi *et al.* 2008; Pemberton *et al.* 2008; Gonçalves *et al.* 2009; Pontillo *et al.* 2012) in the context of a recessive genetic model showed that HIV(+) individuals were

Table 1. Characteristics of the primary studies.

Study	Country	Race	Age[a] (year)		Number of subjects				Cytokine	SNP
							Males			
			Case	Control	HIV(+)	HIV(−)	Case	Control		
Asensi *et al.* (2008)	Spain	Caucasian	42.7	40.6	228	109	177	182	IL1B	+3953/4 C>T
		Caucasian	42.7	40.6	228	109	177	182	IL1A	−889 C>T
Chatterjee *et al.* (2009a)	India	Asian	57.0	58.1	180	355	160	305	IL4	−589/90 C>T
Gonçalves *et al.* (2009)	Brazil	Mixed	39.0	39.4	59	46	37	19	IL1B	+3953/4 C>T
Kwa *et al.* (2003)	Netherlands	Caucasian	NA	NA	342	73	432	NA	IL4	−589/90 C>T
Martin *et al.* (2010)	USA	Caucasian	NA	NA	1221	291	NA	NA	IL28B	rs 12979860 (C>T)
Naicker *et al.* (2009)	South Africa	African	NA	NA	64	195	NA	NA	IL10	−1082 A>G
		African	NA	NA	64	195	NA	NA	IL10	−592 C>A
Nakayama *et al.* (2000)	Japan	Asian	NA	NA	339	52	307	NA	IL4	−589/90 C>T
Nakayama *et al.* (2002)	France	Caucasian	NA	NA	427	86	332	NA	IL4	−589/90 C>T
Nattermann *et al.* (2007)	Germany	Caucasian	43.7	45.2	309	310	280	185	IL6	−174 G>C
Rallon *et al.* (2011)	Spain	Caucasian	NA	NA	29	29	NA	NA	IL28B	rs 12979860 (C>T)
Ramaseri Sunder *et al.* (2012)	India	Asian	NA	NA	227	206	NA	NA	IL10	−1082 A>G
Saumoy *et al.* (2008)	Spain	Caucasian	42.0	41.0	273	385	194	249	IL6	−174 G>C
Erikstrup *et al.* (2007)	Zimbabwe	African	33.0	33.0	194	174	34	42	IL10	−592 C>A
		African	33.0	33.0	195	175	34	42	IL10	−1082 A>G
Jabłonowska *et al.* (2010)	Poland	Caucasian	34.7	38.0	39	71	NA	NA	IL6	−174 G>C
Naggie *et al.* (2012)	USA, Germany	Mixed	48.0	43.0	44	44	39	23	IL28B	rs 12979860 (C>T)
Pemberton *et al.* (2008)	Australia	Caucasian	NA	NA	228	60	NA	NA	IL1A	−889 C>T
		Caucasian	NA	NA	242	60	NA	NA	IL1B	+3953/4 C>T
		Caucasian	NA	NA	262	96	NA	NA	IL12B	3′ UTR -1188 A>C
Pontillo *et al.* (2012)	Brazil	African, Caucasian	34.0	29.0	150	158	80	72	IL1B	+3953/4 C>T
Price *et al.* (1999)	Australia	Caucasian	NA	NA	33	60	33	NA	IL1A	−889 C>T
		Caucasian	NA	NA	33	60	33	NA	IL1B	+3953/4 C>T
Smolnikova *et al.* (2001)	Russia	Caucasian	NA	NA	71	58	NA	NA	IL4	−589/90 C>T
Sobti *et al.* (2010b)	India	Asian	35.2	36.2	300	300	193	195	IL12B	3′ UTR -1188 A>C
Sobti *et al.* (2010a)	India	Asian	35.2	36.2	300	300	193	195	IL6	−174 G>C
		Asian	35.2	36.2	300	300	193	195	IL10	−592 C>A

Table 1 (*contd*)

Study	Country	Race	Age[a] (year)		Number of subjects		Males		Cytokine	SNP
			Case	Control	HIV(+)	HIV(−)	Case	Control		
Wichukchinda and Nakayama (2006)	Thailand	Asian	31.0	NA	246	119	NA	NA	IL4	−589/90 C>T
Chatterjee *et al.* (2009b)	India	Asian	59.0	58.0	180	355	160	305	IL10	−1082 A>G
		Asian	59.0	58.0	180	355	160	305	IL10	−592 C>A
Konenkov and Smolnikova (2002)	Russia	Cascasian	NA	NA	120	52	85	27	IL4	−589/90
Modi *et al.* (2003)	USA	African-American, Caucasian	NA	NA	865	230	NA	NA	IL4	−589/90
Sajadi *et al.* (2011)	USA	African-American	47.9	50.0	172	173	91	61	IL28B	rs 12979860 (C>T)
Jabłonowska *et al.* (2012)	Poland	Caucasian	32.0	33.5	33	90	16	56	IL28B	rs 12979860 (C>T)
Price *et al.* (2002)	Australia	Caucasian	NA	NA	70	60	NA	NA	IL1A	−889 C>T
		Caucasian	NA	NA	70	60	NA	NA	IL1B	+3953/4 C>T
		Caucasian	NA	NA	82	100	NA	NA	IL12B	−1188 A>C
Shin *et al.* (2000)	USA	Mixed	NA	NA	377	72	377	72	IL10	−592 C>A
Wang *et al.* (2004)	USA	African-American, Hispanic	NA	NA	319	258	NA	NA	IL4	−589/90 C>T
		African-American, Hispanic	NA	NA	321	258	NA	NA	IL6	−174 G>C
		African-American, Hispanic	NA	NA	415	334	NA	NA	IL10	−1082 A>G
		African-American, Hispanic	NA	NA	321	258	NA	NA	IL10	−592 C>A
Avihingsanon *et al.* (2014)	Thailand	Asian	NA	NA	94	136	NA	NA	IL28B	rs 12979860 (C>T)
Burlone *et al.* (2013)	Italy	Caucasian	48.0	58.0	75	112	64	50	IL28B	rs 12979860 (C>T)
Di Lello *et al.* (2013)	Spain	Caucasian	41.5	42.3	314	109	251	91	IL28B	rs 12979860 (C>T)
Grebely *et al.* (2012)	Canada, Australia	Caucasian	41.6	31.0	31	56	32	35	IL28B	rs 12979860 (C>T)
Neukam *et al.* (2013)	Spain	Caucasian	41.0	43.0	160	62	134	49	IL28B	rs 12979860 (C>T)
Yuan *et al.* (2012)	USA	Mixed	NA	NA	25	8	NA	NA	IL28B	rs 12979860 (C>T)
Stenkvist *et al.* (2013)	Sweden	Caucasian	51.0	48.0	13	100	11	48	IL28B	rs 12979860 (C>T)
Ramezani *et al.* (2015)	Iran	Asian	36.0	NA	70	31	41	NA	IL10	−1082 A>G
		Asian	36.0	NA	70	31	41	NA	IL10	−592 C>A
Kallas *et al.* (2015)	Estonia	Caucasian	30.0	NA	172	669	133	15	IL10	−1082 A>G
		Caucasian	30.0	NA	172	669	133	15	IL10	−592 C>A
Corchado *et al.* (2013)	Spain	Caucasian	49.5	NA	88	51	75	NA	IL10	−592 C>A
Freitas *et al.* (2015)	Brazil	Mixed	39.0	29.0	216	294	130	191	IL10	−1082 A>G
			39.0	29.0	216	294	130	191	IL6	−174 G>C
Zeremski *et al.* (2013)	USA	African-American, Hispanic, Caucasian	46.7	50.5	113	222	81	151	IL28B	rs 12979860 (C>T)

[a]Mean or median; HIV, human immunodeficiency virus; SNP, single-nucleotide polymorphism; IL, interleukin.

Table 2. Allelic and genotypic frequencies of interleukin SNPs.

Cytokine	SNP	Study	Genotype frequency HIV(+)			Genotype frequency HIV(−)			Allele frequency HIV(+)		Allele frequency HIV(−)		HWE test (P value)
IL1A	−889 C>T		CC	CT	TT	CC	CT	TT	C	T	C	T	
		Asensi *et al.* (2008)	117	87	24	57	43	9	321	135	157	61	0.81
		Pemberton *et al.* (2008)	129	80	19	33	24	3	338	118	90	30	0.74
		Price *et al.* (1999)	24	4	5				52	14	90	30	
		Price *et al.* (2002)							71	69	66	54	
IL1B	+3953/4 C>T		CC	CT	TT	CC	CT	TT	C	T	C	T	
		Asensi *et al.* (2008)	134	75	19	72	35	2	343	113	179	39	0.51
		Gonçalves *et al.* (2009)	43	8	8	35	10	1	94	24	80	12	0.56
		Pemberton *et al.* (2008)	151	86	5	36	23	1	388	96	95	25	0.43
		Price *et al.* (1999)	22	8	3				52	14	95	25	
		Price *et al.* (2002)							81	59	64	56	
		Pontillo *et al.* (2012)	57	62	31	106	44	8	176	124	256	60	0.30
IL4	−589/90 C>T		CC	CT	TT	CC	CT	TT	C	T	C	T	
		Wichukchinda and Nakayama (2006)	12	87	147				111	381	48	190	
		Chatterjee *et al.* (2009a)	122	53	5	229	111	15	297	63	569	141	0.74
		Kwa *et al.* (2003)	243	89	10	55	16	2	575	109	126	20	0.61
		Nakayama *et al.* (2000)	44	157	138	5	22	25	245	433	32	72	1.00
		Nakayama *et al.* (2002)	315	98	14	63	21	2	728	126	147	25	1.00
		Smolnikova *et al.* (2001)	39	26	6	35	17	6	104	38	87	29	0.15
		Konenkov and Smolnikova (2002)	65	47	8	31	20	1	177	63	82	22	0.42
		Wang *et al.* (2004)							293	345	251	265	
			CC	CT+TT		CC	CT+TT		C	T	C	T	
		Modi *et al.* (2003)	416	449		108	122						
IL6	−174 G>C		GG	GC	CC	GG	GC	CC	G	C	G	C	
		Nattermann *et al.* (2007)	114	135	60	99	150	61	363	255	348	272	0.82
		Saumoy *et al.* (2008)	108	114	51	182	154	49	330	216	518	252	0.08
		Jabłonowska *et al.* (2010)	23	15	1	41	29	1	17	61	111	31	0.16
		Sobti *et al.* (2010a)	161	94	45	152	106	42	416	184	410	190	0.00
		Freitas *et al.* (2015)	142	70	4	184	96	14	354	78	464	124	0.73
		Wang *et al.* (2004)							555	87	438	78	
IL10	−592 C>A		CC	CA	AA	CC	CA	AA	C	A	C	A	
		Naicker *et al.* (2009)	24	23	17	97	80	18	71	57	274	116	0.86
		Erikstrup *et al.* (2007)	80	71	43	68	81	25	231	157	217	131	1.00
		Sobti *et al.* (2010a)	36	137	127	34	146	120	209	391	214	386	0.32
		Chatterjee *et al.* (2009b)	67	74	39	163	141	51	208	152	467	243	0.03
		Ramezani *et al.* (2015)	31	35	4	16	11	4	97	43	43	19	0.40
		Kallas *et al.* (2015)	113	49	10	405	232	32	275	69	1,042	296	1.00
		Corchado *et al.* (2013)	43	38	7	24	21	6	124	52	69	33	0.75
		Wang *et al.* (2004)							420	222	321	195	
			CC	CA+AA		CC	CA+AA		C	A	C	A	
		Shin *et al.* (2000)	207	170		50	22						

Table 2 (*contd*)

Cytokine	SNP	Study	Genotype frequency						Allele frequency				HWE test
			HIV(+)			HIV(−)			HIV(+)		HIV(−)		(*P* value)
IL10	−1082 A>G		AA	AG	GG	AA	AG	GG	A	G	A	G	
		Naicker *et al.* (2009)	37	22	5	88	80	27	96	32	256	134	0.21
		Ramaseri Sunder *et al.* (2012)	96	120	11	133	68	5	312	142	334	78	0.37
		Erikstrup *et al.* (2007)	100	73	22	76	82	17	273	117	234	116	0.50
		Chatterjee *et al.* (2009b)	100	60	20	183	141	31	260	100	507	203	0.60
		Freitas *et al.* (2015)	123	79	14	159	111	24	325	107	429	159	0.46
		Ramezani *et al.* (2015)	28	32	10	13	15	3	88	52	41	21	1.00
		Kallas *et al.* (2015)	62	78	32	196	332	141	202	142	724	614	1.00
		Wang *et al.* (2004) (Hispanic)	27	61	6	39	33	4	115	73	111	41	0.56
		Wang *et al.* (2004) (mixed)							413	229	370	146	
IL12B	−1188 A>C		AA	AC	CC	AA	AC	CC	A	C	A	C	
		Sobti *et al.* (2010b)	135	159	6	141	150	9	429	171	432	168	0.00
		Pemberton *et al.* (2008)	155	91	16	68	24	4	401	123	160	32	0.29
		Price *et al.* (2002)							107	57	138	62	
IL28B	rs12979860(C>T)		CC	CT	TT	CC	CT	TT	C	T	C	T	
		Martin *et al.* (2010)	446	586	189	105	136	50	1478	964	346	236	0.63
		Rallon *et al.* (2011)	13	11	5	18	10	1	37	21	46	12	1.00
		Naggie *et al.* (2012)	15	13	16	11	28	5	43	45	50	38	0.07
		Sajadi *et al.* (2011)	27	87	58	20	95	58	141	203	135	211	0.05
		Jabłonowska *et al.* (2012)	17	12	4	19	55	16	46	20	93	87	0.06
		Avihingsanon *et al.* (2014)	83	10	1	116	14	6	176	12	246	26	0.00
		Burlone *et al.* (2013)	34	29	12	39	60	13	97	53	138	86	0.23
		Di Lello *et al.* (2013)	180	121	13	62	41	6	481	147	165	53	1.00
		Grebely *et al.* (2012)	18	9	4	24	27	5	45	17	75	37	0.76
		Neukam *et al.* (2013)	59	76	25	23	29	10	194	126	75	49	1.00
		Stenkvist *et al.* (2013)	6	6	1	44	52	4	18	8	140	60	0.03
		Zeremski *et al.* (2013)	34	55	24	66	119	37	123	103	251	193	0.22
			CC	CT+TT		CC	CT+TT		C	T	C	T	
		Yuan *et al.* (2012)	13	12		0	8						

Table 3. The results of meta-analyses regarding the association of interleukin gene SNPs with HIV-1 susceptibility.

SNP	Contrast	Race	Studies	HIV(+) / HIV(−)	OR	(95% CI)	*P* value	I-squared (%)	Egger's test (*P* value)
IL1A −889 C>T	T versus C allele	All	4	559/289	1.06	(0.84, 1.34)	0.60	0.0	0.33
		Caucasian	4	559/289	1.06	(0.84, 1.34)	0.60	0.0	
IL1B +3953/4 C>T	T versus C allele	All	6	782/493	1.38	(0.87, 2.17)	0.17	79.3	0.31
		Caucasian	4	573/289	1.08	(0.81, 1.45)	0.59	25.3	
		Other/mixed	2	209/204	2.50	(1.48, 4.21)	0.00	43.6	
	TT versus CT+CC (recessive model)	All	4	679/373	4.47	(2.35, 8.52)	0.00	0.0	0.59
		Caucasian	2	470/169	3.13	(0.90, 10.92)	0.07	3.7	
		Other/mixed	2	209/204	5.12	(2.40, 10.94)	0.00	0.0	
	TT+CT versus CC (dominant model)	All	4	679/373	1.53	(0.82, 2.83)	0.18	78.5	0.54
		Caucasian	2	470/169	1.15	(0.77, 1.71)	0.49	14.0	
		Other/mixed	2	209/204	2.13	(0.78, 5.81)	0.14	75.4	
IL4 −589/90 C>T	T versus C allele	All	8	2044/1053	1.01	(0.88, 1.15)	0.93	0.0	0.98
		Caucasian	4	960/269	1.14	(0.88, 1.48)	0.32	0.0	
		Asian	3	765/526	0.84	(0.68, 1.05)	0.12	0.0	
		Other/mixed	1	319/258	1.11	(0.88, 1.41)	0.36	–	
	TT versus CT+CC (recessive model)	All	6	1479/676	0.84	(0.55, 1.28)	0.43	0.0	0.07
		Caucasian	4	960/269	1.19	(0.57, 2.52)	0.64	0.0	
		Asian	2	519/407	0.72	(0.43, 1.19)	0.20	0.0	
	TT+CT versus CC (dominant model)	All	7	2344/906	0.99	(0.82, 1.18)	0.89	0.0	0.45
		Caucasian	5	1571/421	1.02	(0.80, 1.29)	0.53	0.0	
		Asian	2	519/407	0.84	(0.59, 1.20)	0.34	0.0	
		Other/mixed	1	254/78	0.72	(0.34, 1.54)	0.40	–	
IL6 −174 G>C	C versus G allele	All	6	1458/1618	1.35	(0.88, 2.06)	0.17	92.2	0.12
		Caucasian	3	621/766	2.30	(0.92, 5.76)	0.07	96.4	
		Asian	1	300/300	0.95	(0.75, 1.22)	0.71	–	
		Other/mixed	2	537/552	0.85	(0.68, 1.07)	0.16	0.0	
	CC versus GC+GG (recessive model)	All	5	1137/1360	1.09	(0.77, 1.54)	0.63	39.3	0.60
		Caucasian	3	621/766	1.24	(0.86, 1.78)	0.24	22.6	
		Asian	1	300/300	1.08	(0.69, 1.71)	0.73	–	
		Other/mixed	1	216/294	0.38	(0.12, 1.16)	0.09	–	
	CC+GC versus GG (dominant model)	All	5	1137/1360	0.97	(0.78, 1.20)	0.75	38.5	0.84
		Caucasian	3	621/766	1.03	(0.69, 1.54)	0.87	62.4	
		Asian	1	300/300	0.89	(0.64, 1.22)	0.46	–	
		Other/mixed	1	216/294	0.87	(0.60, 1.26)	0.46	–	
IL10 −592 C>A	A versus C allele	All	8	1389/2033	1.10	(0.92, 1.31)	0.31	58.5	0.72
		Caucasian	2	260/720	0.88	(0.68, 1.14)	0.34	0.0	
		Asian	3	550/686	1.17	(0.93, 1.48)	0.17	35.4	

Table 3 (*contd*)

SNP	Contrast	Race	Studies	HIV(+) / HIV(−)	OR	(95% CI)	*P* value	I-squared (%)	Egger's test (*P* value)
		Other/mixed	3	579/627	1.19	(0.79, 1.79)	0.39	80.7	
	AA versus AC+CC (recessive model)	All	7	1068/1775	1.39	(0.97, 2.01)	0.08	56.4	0.85
		Caucasian	2	260/720	1.02	(0.55, 1.89)	0.94	0.0	
		Asian	3	550/686	1.19	(0.75, 1.88)	0.46	52.1	
		Other/mixed	2	258/369	2.35	(1.14, 4.83)	0.02	60.2	
	AA+AC versus CC (dominant model)	All	8	1445/1847	1.15	(0.91, 1.45)	0.25	42.7	0.43
		Caucasian	2	260/720	0.83	(0.60, 1.13)	0.23	0.0	
		Asian	3	550/686	1.24	(0.94, 1.65)	0.12	0.0	
		Other/mixed	3	635/441	1.37	(0.86, 2.19)	0.19	60.8	
IL10 −1082 A>G	G versus A allele	All	8	1445/2183	1.03	(0.81, 1.31)	0.80	77.8	0.86
		Caucasian	1	172/669	0.83	(0.65, 1.05)	0.13	–	
		Asian	3	477/592	1.30	(0.78, 2.17)	0.31	81.6	
		Other/mixed	4	796/922	0.94	(0.68, 1.29)	0.69	75.9	
	GG versus AG+AA (recessive model)	All	8	1218/2001	1.00	(0.78, 1.29)	0.97	0.0	0.43
		Caucasian	1	172/669	0.86	(0.56, 1.31)	0.47	–	
		Asian	3	477/592	1.46	(0.90, 2.38)	0.12	0.0	
		Other/mixed	4	569/740	0.89	(0.59, 1.34)	0.59	0.0	
	GG+AG versus AA (dominant model)	All	8	1218/2001	1.05	(0.72, 1.53)	0.78	82.2	0.65
		Caucasian	1	172/669	0.73	(0.52, 1.05)	0.09	–	
		Asian	3	477/592	1.34	(0.61, 2.95)	0.47	87.5	
		Other/mixed	4	569/740	0.97	(0.58, 1.62)	0.92	78.3	
IL12B −1188 A>C	C versus A allele	All	3	644/496	1.17	(0.93, 1.47)	0.19	21.4	0.37
		Caucasian	2	344/196	1.35	(0.99, 1.84)	0.05	0.0	
		Asian	1	300/300	1.02	(0.80, 1.32)	0.85	–	
IL28B (rs12979860)	T versus C allele	All	12	2299/1424	0.95	(0.83, 1.08)	0.44	16.9	0.91
		Caucasian	7	1863/749	0.91	(0.74, 1.12)	0.39	38.3	
		Asian	1	94/136	0.64	(0.32, 1.31)	0.23	–	
		Other/mixed	4	342/539	1.04	(0.85, 1.27)	0.35	0.0	
	TT versus CT+CC (recessive model)	All	12	2299/1424	1.11	(0.84, 1.47)	0.44	25.4	0.31
		Caucasian	7	1863/749	0.95	(0.73, 1.25)	0.73	0.0	
		Asian	1	94/136	0.23	(0.03, 1.97)	0.18	–	
		Other/mixed	4	342/539	1.51	(0.85, 2.68)	0.15	50.6	
	TT+CT versus CC (dominant model)	All	13	2324/1432	0.80	(0.64, 1.01)	0.06	35.3	0.07
		Caucasian	8	1910/878	0.74	(0.52, 1.06)	0.10	61.8	
		Asian	1	94/136	0.77	(0.35, 1.69)	0.51	–	
		Other/mixed	5	328/500	0.81	(0.54, 1.21)	0.30	8.0	

SNP, single nucleotide polymorphism; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; IL, interleukin.

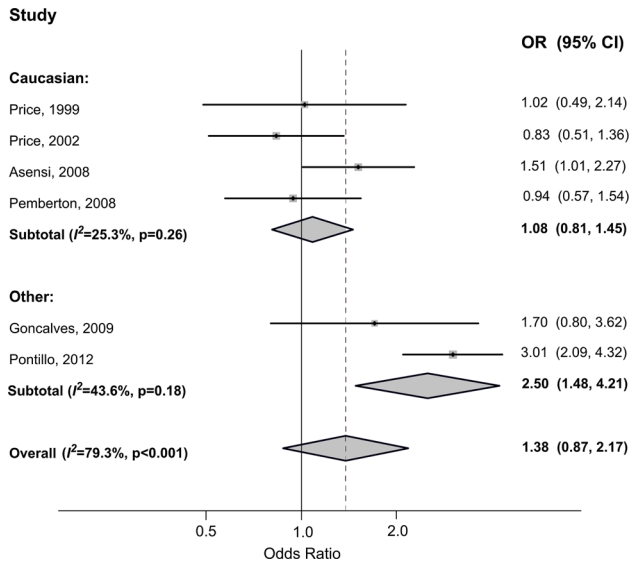

Figure 2. Effect of the *IL1B* +3953/4 (rs1143634) T variant on HIV-1 susceptibility: results from individual studies and random-effects meta-analysis (forest plot). OR, odds ratio; CI, confidence interval.

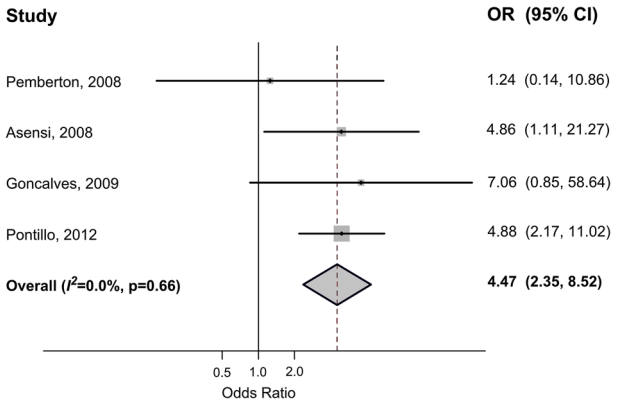

Figure 3. Effect of the *IL1B* +3953/4 C>T (rs1143634) polymorphism on HIV-1 susceptibility, in the context of a recessive genetic model: results from individual studies and random-effects meta-analysis (forest plot).

4.5 times as likely to carry the TT genotype as HIV seronegatives (OR: 4.47, 95% CI: 2.35–8.52) (figure 3). For this comparison, there was no evidence of heterogeneity or publication bias (table 3). The studies of Price *et al.* (1999, 2002) presented data only on allele frequencies and were thus excluded from this analysis.

IL4 –589l90 C >T (rs2243250): The allelic contrast that involved eight publications (Nakayama *et al.* 2000, 2002; Smolnikova *et al.* 2001; Konenkov and Smolnikova 2002; Kwa *et al.* 2003; Wang *et al.* 2004; Wichukchinda and Nakayama 2006; Chatterjee *et al.* 2009a) suggested no association between T allele and risk for getting HIV (OR: 1.01, 95% CI: 0.88–1.15). The analysis of genotypes yielded similar results under the assumption of either a recessive (Nakayama *et al.* 2000; Smolnikova *et al.* 2001; Konenkov and Smolnikova 2002; Nakayama *et al.* 2002; Kwa *et al.* 2003; Chatterjee *et al.* 2009a) or a dominant model of inheritance (Nakayama *et al.* 2000, 2002; Smolnikova *et al.* 2001; Konenkov and Smolnikova 2002; Kwa *et al.* 2003; Modi *et al.* 2003; Chatterjee *et al.* 2009a) (OR: 0.84, 95% CI: 0.55–1.28; and OR: 0.99, 95% CI: 0.82–1.18, respectively). The Begg test indicated the existence of publication bias in the TT versus CT and CC comparison (P = 0.024).

IL6 –174 G >C (rs1800795): In total, six studies (Wang *et al.* 2004; Nattermann *et al.* 2007; Saumoy *et al.* 2008; Jabłonowska *et al.* 2010; Sobti *et al.* 2010a; Freitas *et al.* 2015) provided data on allelic distributions. The pooled OR of C versus G allele was 1.35 (95% CI: 0.88–2.06) and there was evidence of substantial between-studies heterogeneity (I^2= 92.2%). The genotypic contrasts resulted in nonsignificant results. The pooled OR remained nonsignificant for all contrasts after excluding the one study (Sobti *et al.* 2010a) with HWE violation (P < 0.01).

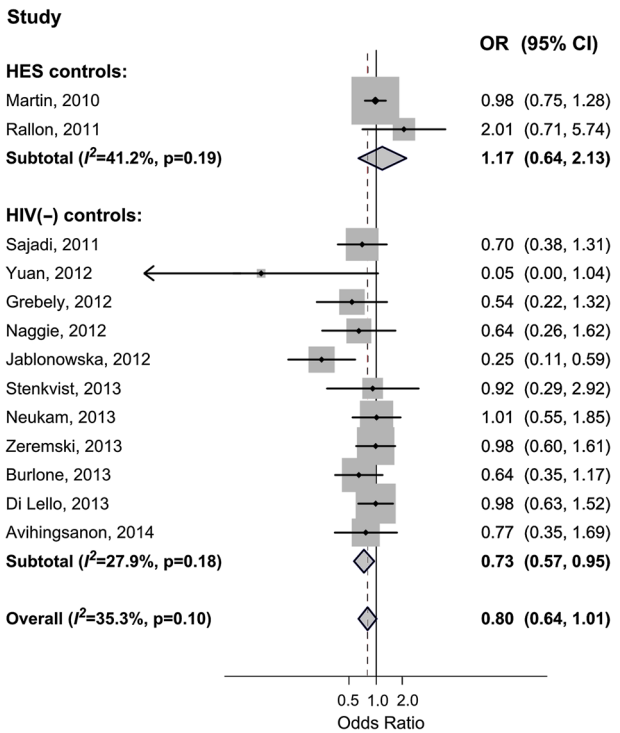

Figure 4. Effect of the *IL28B* (rs12979860) (C>T) polymorphism on HIV-1 susceptibility, in the context of a dominant genetic model: results from individual studies and random-effects meta-analysis (forest plot). No data were provided on HIV exposure levels for the HIV(−) subjects (controls) included in the subgroup analysis of 11 studies. However, all participants of these studies were positive for HCV (except the study of Sajadi *et al* (2011), in which only the control group was infected by HCV). Given the common routes of HIV and HCV transmission, the control groups of these studies include individuals at high risk of HIV infection. HES, HIV-exposed seronegatives.

IL10 –592 C >A (rs1800872): Nine studies addressed the potential involvement of this polymorphism in HIV susceptibility (Shin *et al.* 2000; Wang *et al.* 2004; Erikstrup *et al.* 2007; Chatterjee *et al.* 2009b; Naicker *et al.* 2009; Sobti *et al.* 2010a; Corchado *et al.* 2013; Kallas *et al.* 2015; Ramezani *et al.* 2015). There was a deviation from HWE in one report (Chatterjee *et al.* 2009b) (P= 0.03). The perallelic OR (A versus C) was 1.10 (95% CI: 0.92–1.31). The AA versus AC and CC comparison (Erikstrup *et al.* 2007; Naicker *et al.* 2009; Chatterjee *et al.* 2009b; Sobti *et al.* 2010a; Corchado *et al.* 2013; Kallas *et al.* 2015; Ramezani *et al.* 2015) resulted in a marginally nonsignificant estimate (OR: 1.39, 95% CI: 0.97–2.01) (table 3). After excluding the studies of either Ramezani *et al.* (2015) or Corchado *et al.* (2013) in the context of sensitivity analysis to test the effect of removing studies one at a time on the overall estimate, the summary of ORs became significant (OR: 1.49, 95% CI: 1.04–2.12; and OR: 1.48, 95% CI: 1.02–2.16, respectively). Subgroup analysis of HES controls (Chatterjee *et al.* 2009b; Naicker *et al.* 2009; Kallas *et al.* 2015) also supported an increased HIV risk for AA homozygotes (OR: 2.38, 95% CI: 1.24–4.55). The synthesis of studies including individuals of Asian descent (Chatterjee *et al.* 2009b; Sobti *et al.* 2010a; Ramezani *et al.* 2015) failed to confirm an association (OR: 1.19, 95% CI: 0.75–1.88). Under the assumption of a dominant genetic model, the genotypic comparison (AA and AC versus CC genotypes) (Shin *et al.* 2000; Erikstrup *et al.* 2007; Chatterjee *et al.* 2009b; Naicker *et al.* 2009; Sobti *et al.* 2010a; Corchado *et al.* 2013; Kallas *et al.* 2015; Ramezani *et al.* 2015) and the subgroup analysis of studies with HES controls (Shin *et al.* 2000; Chatterjee *et al.* 2009b; Naicker *et al.* 2009; Kallas *et al.* 2015) yielded nonsignificant estimates (OR: 1.15, 95% CI: 0.91–1.45; and OR: 1.23, 95% CI: 0.68–2.21, respectively). The exclusion of the study with deviation from HWE (Chatterjee *et al.* 2009b) yielded non-significant results.

IL10 –1082 A >G (rs1800896): Eight studies (Wang *et al.* 2004; Erikstrup *et al.* 2007; Chatterjee *et al.* 2009b; Naicker *et al.* 2009; Ramaseri Sunder *et al.* 2012; Freitas *et al.* 2015; Kallas *et al.* 2015; Ramezani *et al.* 2015) evaluated the role of this polymorphism in relation to HIV risk. All contrasts (G versus A allele, GG versus AG and AA genotype, GG and AG versus AA genotype) yielded nonsignificant results (OR: 1.03, 95% CI: 0.81–1.31; OR: 1.00, 95% CI: 0.78–1.29; OR: 1.05, 95% CI: 0.72–1.53, respectively). Heterogeneity was absent only in the analysis of GG versus AG and AA.

IL12B –1188 A >C (rs3212227): The statistical synthesis of three studies (Price *et al.* 2002; Pemberton *et al.* 2008; Sobti *et al.* 2010b) yielded a nonsignificant perallelic effect estimate (OR: 1.17, 95% CI: 0.93–1.47). The pooled OR remained nonsignificant after excluding the study with violation of HWE (Sobti *et al.* 2010b). Data on genotype frequencies were unavailable.

IL28B C >T (rs12979860): The influence of the IL-28B (rs12979860) T variant was assessed in 13 studies (Martin *et al.* 2010; Rallon *et al.* 2011; Sajadi *et al.* 2011; Yuan *et al.* 2012; Grebely *et al.* 2012; Jabłonowska *et al.* 2012; Naggie *et al.* 2012; Burlone *et al.* 2013; Stenkvist *et al.* 2013; Zeremski *et al.* 2013; Di Lello *et al.* 2013; Neukam *et al.* 2013; Avihingsanon *et al.* 2014). Deviation from the HWE was present in two of them (Stenkvist *et al.* 2013; Avihingsanon *et al.* 2014) (P = 0.03; P < 0.01, respectively). The pooled OR of T versus C allele was 0.95 (95% CI: 0.83–1.08). Similarly, the contrasts of genotypes failed to reach significance. The exclusion of either the study of Stenkvist *et al.* (2013) or Avihingsanon *et al.* (2014) or both of them resulted in nonsignificant results in all the contrasts. However, in a subgroup analysis of 11 studies that involved subjects (cases and controls) infected by HCV (Sajadi *et al.* 2011; Grebely *et al.* 2012; Jabłonowska *et al.* 2012; Naggie *et al.* 2012; Yuan *et al.* 2012; Burlone *et al.* 2013; Di Lello *et al.* 2013; Neukam *et al.* 2013; Stenkvist *et al.* 2013; Zeremski *et al.* 2013; Avihingsanon *et al.* 2014) and assuming a dominant genetic model, the combined OR suggested a protective role of the T variant against HIV (OR: 0.73, 95% CI: 0.57–0.95) (figure 4). The protective effect of *IL28B* (rs12979860) T was also observed when we were excluding, each time, one of the two studies of Martin *et al.* (2010) or Rallon *et al.* (2011) with HES controls that were not considered in the aforementioned subgroup analysis (OR: 0.76, 95% CI: 0.58–1.00; and OR: 0.78, 95% CI: 0.63–0.98, respectively). There was moderate heterogeneity in some analyses.

Bivariate meta-analysis: Pooling the studies that addressed the *IL1B* +3953/4 C>T (rs1143634) polymorphism using the genetic model-free bivariate approach produced, as in univariate analysis, a significant OR for the TT versus the CC contrast (OR: 4.48, 95% CI: 1.85–10.86). The bivariate technique supported a recessive model of inheritance in agreement with the univariate results.

The bivariate method also confirmed the protective effect of the *IL28B* (rs12979860) T variant based on data from 11 studies that had recruited people with HCV. In particular, the summary OR for CT versus CC was 0.69 (95% CI: 0.51–0.93). Importantly, the bivariate approach supported the protective role of this polymorphism in overall analysis (13 studies), regardless the subjects' risk factors, and suggested a dominant genetic model (CT versus CC, OR: 0.76, 95% CI: 0.59–0.99).

Discussion/conclusions

Evidence from 42 studies, involving 8953 HIV seropositives and 6774 HIV uninfected individuals, was made in an attempt to investigate the association between HIV status and eight interleukin gene polymorphisms: *IL1A* −889 C>T (rs1800587), *IL1B* +3953/4 C>T (rs1143634), *IL4* −589/90 C>T (rs2243250), *IL6* −174 G>C (rs1800795),

IL10 −592 C>A (rs1800872), *IL10* −1082 A>G (rs1800896), *IL12B* −1188 A>C (rs3212227) and *IL28B* C>T (rs12979860). Under the assumption of a recessive model of inheritance, the *IL1B* +3953/4 C>T (rs1143634) and the *IL10* −592 C>A (rs1800872) variants were related to an increased risk of being HIV positive. On the other hand, both univariate and bivariate approaches showed the well-studied HCV infection *IL28B* (rs12979860) T variant, according to a dominant genetic model, probably decreases the likelihood of HIV acquisition, especially in populations infected with HCV.

Elucidation of HIV transmission is important to create protective tools and define new targets for drug development. HIV susceptibility, however, is the result of a complex interplay among the virus, the host and the environment. Gene polymorphisms can influence some host components of the infection process including parts of the immune response. Cytokines, which are important regulators of the inflammatory homeostasis, are prime candidates involved in HIV pathogenesis (Fellay 2009; Levy 2009).

Our meta-analysis evaluated IL gene polymorphisms and led to a couple of biologically reasonable findings. The T allele of the *IL1B* +3953/4 C>T SNP that increases HIV risk was associated with elevated IL1B production (Pociot *et al.* 1992). This proinflammatory cytokine was reported to enhance HIV replication and found at heightened levels in HIV-infected individuals (Poli *et al.* 1994). IL10 is a pleiotropic cytokine that can repress proinflammatory responses (Mosser 2008; Ouyang *et al.* 2011). Through its immuno-inhibitory and anti-inflammatory activities and, in particular, by suppressing the production of molecules like TNF-α or by preventing cell maturation, IL10 was shown to inhibit HIV replication in macrophages/monocytes (Weissman *et al.* 1994; Chang *et al.* 1996). The A allele at the 592 position in the promoter region of the *IL10* gene was associated with reduced IL10 production (Crawley *et al.* 1999).

The *IL28B* gene on chromosome 19 encodes interferon lambda 3 (IFNλ3), which belongs to type III interferons (Sheppard *et al.* 2003; Ank *et al.* 2006; Li *et al.* 2009; Bellanti *et al.* 2012). Based on their molecular structure, type III interferons are grouped in the IL-10 superfamily, but functionally they are related to type I interferons (Lange and Zeuzem 2011). Peripheral blood mononuclear cells (PBMCs) and dendritic cells are main producers of IFNλ3. The biological properties of IFNλ3 include antiviral, antiproliferative and immunoregularory functions in a variety of cells. It was also found to inhibit *in vitro* HCV (Li *et al.* 2009; Bellanti *et al.* 2012). IFNλ3 induces interferon-stimulated genes (ISG) expression, but also enhances adaptive immunity (Morrow *et al.* 2009). A recent study reported that IFNλ3 has anti-HIV function by activating the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)-mediated innate immunity in macrophages (Liu *et al.* 2012). Another study has shown that IFNλ2, which is almost identical to IFNλ3, inhibits HIV infection and suppresses replication in macrophages (Hou *et al.* 2009). However, one study (Serra *et al.* 2008) has given opposite results: there was increased HIV uptake and replication in human PBMCs and C8166 T cells treated with IFNλ2.

The rs12979860 C>T polymorphism located 3 kb upstream of the IL-28B gene was studied in HCV infection. The link, however, between this variation and IFNλ3 signalling is poorly understood. One study has shown that in the setting of chronic HCV infection, nonCC genotypes exhibited higher intrahepatic level of ISG expression than the CC genotype (Urban *et al.* 2010). Another research found higher serum IFNλ3 levels in rs12979860 C carriers than in TT homozygotes (Langhans *et al.* 2011). Despite the limited knowledge about the functional role of the *IL28B* (rs12979860) C>T polymorphism, previous research has consistently showed that individuals carrying the TT or the CT genotypes are less likely than CC persons to spontaneously clear HCV and respond to peginterferon/ribavirin treatment (Thomas *et al.* 2009; Chen *et al.* 2012; Duggal *et al.* 2013; Hajarizadeh *et al.* 2013; Mangia *et al.* 2013; Yang *et al.* 2013; Zheng *et al.* 2013; De Re *et al.* 2014; Grebely *et al.* 2014; Gupta *et al.* 2014). Yet, these associations were not observed in HCV-infected or reinfected men who have sex with men (MSM) (Ingiliz *et al.* 2014; Seaberg *et al.* 2015). In addition, although the CC genotype is associated with initial viral control (Hajarizadeh *et al.* 2015), chronically HCV-infected CC homozygotes had higher HCV RNA levels than those with CT/TT genotypes (Uccellini *et al.* 2012; Grady *et al.* 2015). The CT/TT genotypes were related to milder hepatic damage in HIV/HCV coinfected patients and in genotype 3 HCV infections (de la Fuente *et al.* 2013; Ydreborg *et al.* 2013). In a study of 264 HIV/HCV coinfected individuals, participants with CC homozygosity experienced a 54% increase in mortality compared to those with the TT genotype (Clausen *et al.* 2012). It seems that immune responses potentially triggered by the C allele increase the chances of spontaneous and treatment-induced resolution of HCV, but also result, over the long-term, in negative histological features of chronic HCV.

In this regard, the current meta-analysis detected a potential protective role of the otherwise known as unfavourable for HCV CT/TT genotypes. Taken into account that are mentioned above, we can hypothesize that the *IL28B* (rs12979860) C>T polymorphism may have a differential impact across population groups and conditions, including susceptibility to HIV infection. For example, the less pronounced adaptive immune response induced by CT/TT genotypes that makes HCV clearance less likely, creates at the same time an unfavourable environment for HIV to establish itself in human hosts. Or the intracellular upregulation of ISG by CT/TT genotypes that

could exhaust the interferon pathway and result in poor response to exogenously administered interferon (Urban *et al.* 2010), may, on the other hand, lead to an intracellular anti-HIV state that does not favour HIV infection. As a matter of fact, a strong and rapid type I ISG upregulation was observed in acute infections of nonhuman primates by simian immunodeficiency virus (SIV) (Jacquelin *et al.* 2009). Given the limited understanding of the underlying mechanisms, the potential linkage disequilibrium between the studied and other IL-28B gene variations (Kobayashi *et al.* 2012; Bibert *et al.* 2013), and the likely biases of case–control studies, it would help to further study the role of T carriers in HIV acquisition risk.

The genetic basis of host susceptibility to infectious diseases has received enormous attention (Fellay *et al.* 2009; Jallow *et al.* 2009; Davila *et al.* 2010; Thye *et al.* 2010). The interest is growing, while ushering in the era of genomewide association studies (GWAS). Some GWAS have focussed on viral load control or HIV disease progression identifying polymorphisms that explain a small portion of the observed variation among HIV-infected individuals (Fellay *et al.* 2007; Dalmasso *et al.* 2008; Le Clerc *et al.* 2009; Pereyra *et al.* 2011; van Manen *et al.* 2012). Other GWAS were conducted on HIV-1 coreceptor usage or on HIV susceptibility without significant results after correction for multiple testing (Salanti *et al.* 2007; Joubert *et al.* 2010; Lingappa *et al.* 2011; Petrovski *et al.* 2011; Lane *et al.* 2013; McLaren *et al.* 2013; Henrich et al. 2014). However, promising results were also published. A GWAS and a two-stage meta-analysis provided evidence of a strong genetic correlation with HIV acquisition for the rs6996198 T>C polymorphism on chromosome 8 (the T allele reduces HIV risk) (Limou *et al.* 2012). Another GWAS on sex workers found that the minor allele of a guanine–cytosine polymorphism (rs1552896) in an intron of the Fras1-related extracellular matrix protein 1 (FREM1) gene was related to resistance to HIV infection (Luo *et al.* 2012). In another GWAS, an intronic polymorphism (rs4878712) in the FREM and PDZ domain containing 1 (FRMPD1) gene, met criteria for multiple testing—though it did not reach the GWAS significance in meta-analyses—and was associated with HIV acquisition (Johnson *et al.* 2015). Gene expression analyses provided biological evidence for the protective effect of the rs4878712 G allele (Johnson *et al.* 2015). Quite recently, new associations between HIV acquisition and variants in zinc-ribbon domain containing 1 (ZNRD1) and bone marrow stromal cell antigen 2 (BST2) genes were also reported (An *et al.* 2014; Hancock *et al.* 2016).

Generally, although important work was done over the recent years, to date, only variants in CCR5 gene were proven to significantly influence HIV acquisition and paved the way to entry inhibitors (Dean *et al.* 1996; Samson *et al.* 1996; Ioannidis *et al.* 2001). Whole genome sequencing (WGS) is expected to illuminate the genetic part of the HIV infection process. Till then, it seems that approaches of targeting gene variants with higher *a priori* relevance to HIV acquisition (Bigham *et al.* 2014) and new GWAS are necessary in assuring the representativeness of IL gene polymorphisms and other candidate regions on the genotyping kit, and the power to detect low frequency variants and genetic factors with small relative risks. Secondarily, in-depth analyses or meta-analyses of GWAS data would also be useful. All these approaches may help to identify additional variants that fail to meet the stringent criteria of multiple testing correction.

This evidence synthesis has limitations. In many analyses, the number of eligible studies was small decreasing statistical power and compromising our confidence to the results. Also, we cannot rule out the possibility that the significant estimates of our analyses are the result of multiple comparisons. Further, no meta-analytic method can correct inherent biases of primary research. Considering the *IL1B* +3953/4 C>T polymorphism, for instance, among the four studies in the recessive model analysis, only one specifically investigated the role of this genetic trait in HIV susceptibility. The other three studies focussed on different outcomes including periodontal disease, HIV-associated dementia and lipodystrophic syndrome (Asensi *et al.* 2008; Pemberton *et al.* 2008; Gonçalves *et al.* 2009). Similarly, for the *IL28B* (rs12979860) polymorphism, the data were retrieved from HIV/HCV coinfected populations in 11 of 13 studies. Therefore, selection or other biases and confounding may have impacted on the results. Of course, on the other hand, the analyses on HIV/HCV populations perhaps allowed the use of comparable control groups in terms of HIV exposure levels. Given the common routes of transmission for HIV and HCV (e.g., injecting drug use), the control groups consisted of individuals at high HIV risk, which limits misclassification of low exposure individuals as HIV resistant and, consequently, increases statistical power. In an attempt to minimize potential sources of errors, we expanded our search to identify studies not appeared in common databases (Ioannidis and Trikalinos 2005), we performed publication bias tests, and we searched, through cumulative syntheses, for early extreme findings that could overestimate or underestimate the true genetic effects (Ioannidis and Trikalinos 2005).

In conclusion, this meta-analysis supports the potential importance of interleukins in HIV infection risk suggesting that the *IL1B* +3953/4 (rs1143634) T variant is associated with increased risk of HIV acquisition, while the *IL28B* (rs12979860) T variant seems to reduce the risk of HIV infection. However, further investigation is warranted. The current meta-analytic evidence should direct the conduct of new research (including GWAS) involving a large well-defined population with a clear phenotype and a special focus on these SNPs. People who inject drugs could

be a good candidate group for the *IL28B* (rs12979860) C>T polymorphism. Meta-analyses of GWAS data can follow.

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