

OPEN

Association between polymorphisms in the interleukin-10 gene and susceptibility to human immunodeficiency virus-1 infection

A systematic review and meta-analysis

Dan-Hui Fu, PhD^a, Wen-Juan Deng, MD^a, Zhi Yang, MD^b, Sen Hong, MD^a, Qian-Lin Ding, MD^a, Yang Zhao, PhD^a, Jia Chen, PhD^a, Dan-Ke Su, PhD^{a,*}

Abstract

Background: This study meta-analyzed the literature on possible association of 3 polymorphisms (-592, -1082, -819) in the interleukin-10 (IL-10) gene with susceptibility to human immunodeficiency virus (HIV)-1 infection.

Methods: PubMed, EMBASE, MEDLINE and Google Scholar were systematically searched to identify relevant studies in English. Meta-analyses were performed to examine the association of IL-10 polymorphisms -592, -1082, and -819 with susceptibility to HIV-1 infection.

Results: A significant association between the -592 polymorphism and susceptibility to HIV-1 infection was found in the total population (recessive model, odds ratios (OR) = 1.44, 95% CI = 1.06–1.96, P=.02; homozygous model, OR = 1.44, 95% CI = 1.02–2.02, P=.04). However, these results were not observed in subgroups based on ethnicity. The -1082 polymorphism was significantly associated with susceptibility to HIV-1 infection in Caucasians (OR = 1.30, 95% CI = 1.05–1.62, P=.02; recessive model, OR = 1.49, 95% CI = 1.09–2.03, P=.01; homozygous model, OR = 1.58, 95% CI = 1.01–2.46, P=.04), but not in Asians or the total population. None of the 5 genetic models suggested a significant association between the -819 polymorphism and HIV-1 infection.

Conclusion: The available evidence indicates that the AA genotype of IL-10 -592 may confer increased susceptibility to HIV-1 infection, and that the AA genotype of -1082 may confer increased susceptibility in Caucasians. In contrast, the -819 polymorphism may not be associated with HIV-1 infection risk. These conclusions should be verified in large, well-designed studies.

Abbreviations: AIDS = acquired immune deficiency syndrome, HIV = human immunodeficiency virus, IL = interleukin, OR = odds ratios.

Keywords: human immunodeficiency virus-1, interleukin -10, meta-analysis, polymorphism, susceptibility

Editor: Uddyalok Banerjee.

This study was supported by grants from the Guangxi Science and Technology Plan Project (Key Research and Development Plan) (AB16380201), the Project on HIV-related Neurocognitive Impairment based on MRI and PET/CT, the Youth Science Fund of Guangxi Medical University (GXMUYSF201728), and the Project on HIV-associated Mild Neurocognitive Disorder and Diagnostic Efficacy of MRI.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

^a Department of Radiology, ^b Department of Nuclear Medicine, Tumor Hospital Affiliated to Guangxi Medical University, Nanning, China.

^{*} Correspondence: Dan-Ke Su, Department of Radiology, Tumor Hospital Affiliated to Guangxi Medical University, He Di Rd. #71, Nanning 530021, China (e-mail: sudanke66@sina.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Fu DH, Deng WJ, Yang Z, Hong S, Ding QL, Zhao Y, Chen J, Su DK. Association between polymorphisms in the interleukin-10 gene and susceptibility to human immunodeficiency virus-1 infection: A systematic review and meta-analysis. Medicine 2020;99:48(e23069).

Received: 25 November 2019 / Received in final form: 12 August 2020 / Accepted: 29 September 2020

http://dx.doi.org/10.1097/MD.00000000023069

1. Introduction

Increasing data on the genes in infected hosts has widened our vision regarding the importance of host factors in mediating pathogenesis and limiting the progression of disease to acquired immune deficiency syndrome (AIDS).^[1] In order to effectively prevent and treat human immunodeficiency virus (HIV), understanding the etiology of HIV infection and how it may be influenced by genetic variation in the host genome is of vital importance. Recent evidence has indicated that HIV infection and progression to AIDS in humans are significantly associated with host genetic factors, such as the cytokines.^[2] Moreover, it has been suggested that cytokines play a vital role in regulating the homoeostasis of the immune system and alterations in their relative levels play critical roles in the immune response against HIV-1 infection and the progression of HIV-1 infection to clinical AIDS.^[3]

Interleukin (IL)-10 is an immunoregulatory cytokine produced mainly by monocytes, macrophages, T-helper 2 cells and B lymphocytes. It can inhibit secretion of interferon γ (IFN- γ) and IL-2 from T cells, as well as IL-1, IL-6, IL-8 and tumor necrosis factor α (TNF- α) from monocytes and macrophages. IL-10 also inhibits different immune reactions such as antigen presentation, macrophage activation, antigen-specific T cell proliferation and cell-mediated immunity.^[4,5] Increasing evidence has suggested that IL-10 can have beneficial but also detrimental effects during HIV-1 infection. The timing and cellular source of IL-10 production are essential for the balance between successful pathogen clearance by innate and adaptive responses and the prevention of immune pathology.^[6] Several previous reports have suggested that IL10 production was associated with genetic variations.^[7–10]

Numerous case-control studies^[6–16] have investigated whether -592, -1082, -819 polymorphisms in the IL-10 gene influence susceptibility to HIV-1 infection. The results have been inconclusive and contradictory, prompting us to perform this comprehensive meta-analysis of all available evidence on these potential associations. To the best of our knowledge, this is the largest meta-analysis concerning the 3 polymorphisms and susceptibility to HIV-1 infection.

2. Materials and Methods

2.1. Ethics statement

This study was approved by the Institutional Review Board of Tumor Hospital Affiliated to Guangxi Medical University.

2.2. Search strategy

All clinical and experimental case–control studies of polymorphisms in the IL-10 gene and HIV-1 infection published in English through May 20, 2020 were identified through systematic searches in PubMed, EMBASE, MEDLINE and Google Scholar. The search terms used were: interleukin-10; IL-10; these 2 terms in combination with polymorphism, polymorphisms, SNP, variant, variants, variation, genotype, genetic or mutation; and all of the above terms in combination with acquired immune deficiency syndrome, human immunodeficiency virus 1 or HIV-1. Reference lists in identified articles and reviews were also searched manually to identify additional eligible studies.

2.3. Inclusion criteria

To be included in our review and meta-analysis, studies had to

- have a case-control design for assessing the association of HIV-1 infection risk with IL-10 -592, -1082 and -819 polymorphisms;
- (2) be accessible as a full-text article and report sufficient data for estimating odds ratios (ORs) with 95% confidence intervals (CIs);
- (3) report genotype frequencies; and
- (4) involve humans rather than animal models.

2.4. Data extraction

Two authors (DHF and WJD) independently extracted the following data from included studies: first author's family name, year of publication, ethnicity, testing methods, control source, age, sex, P value for Hardy-Weinberg equilibrium (HWE) in controls, numbers and genotypes of cases and controls, and frequencies of genotypes in cases and controls. Discrepancies were resolved by consensus. Only those studies that met the predetermined inclusion criteria were included.

2.5. Assessment of methodological quality

To assess the quality of the studies included in this analysis, the Newcastle–Ottawa Scale was applied independently by 2 assessors (DHF and WJD)^[18] (Table 1). On the 10-point Newcastle–Ottawa Scale, scores of 5 to 9 points (stars) are considered to indicate generally high methodological quality, while scores of 0 to 4 stars are considered to indicate poor quality.^[19] Any disagreements about Newcastle–Ottawa scores were resolved by other authors following a comprehensive reassessment. Only high-quality studies were included in the meta-analysis.

2.6. Statistical analysis

Unadjusted ORs with 95% confidence intervals (CIs) were used to assess the strength of the association of HIV-1 infection risk with IL-10 -592, -1082 and -819 polymorphisms based on genotype frequencies in cases and controls. The significance of pooled ORs was determined using the *Z* test, with P < .05 defined

Table 1

Methodological quality of studies included in the meta-analysis, based on the Newcastle–Ottawa Scale for assessing the quality of casecontrol studies.

		Selection (sco	ore)		Comparability (score)	Exposure (score)				
Study	Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate [*]	Total Score [†]	
Erikstrup ^[7]	1	1	1	1	1	0	1	1	7	
Chatterjee ^[8]	1	1	0	1	1	0	1	1	6	
Naicker ^[9]	1	1	0	1	1	0	1	1	6	
Sobti ^[10]	1	1	0	1	1	0	1	1	6	
Sunder ^[11]	1	1	0	1	1	0	1	1	6	
Corchado ^[12]	1	1	0	1	2	0	1	1	7	
Piddubna ^[13]	1	1	1	1	0	0	1	1	6	
Freitas ^[14]	1	1	0	1	1	0	1	1	6	
Ramezani ^[15]	1	1	0	1	2	0	1	1	7	
Kallas ^[16]	1	1	1	1	0	0	1	1	6	
Singh ^[17]	1	1	1	1	2	0	1	1	8	

*When there was no significant difference in the response rate between both groups based on a chi-squared test (P>.05), 1 point was awarded.

[†] Total score was calculated by adding up the points awarded for each item.



as the significance threshold. Meta-analysis was conducted using a fixed-effect model when P > .10 for the Q test, indicating lack of heterogeneity among studies; otherwise, a random-effect model was used. All these statistical tests were performed using Review Manager 5.2 (Cochrane Collaboration).

Publication bias was assessed using Begg funnel plots and Egger weighted regression in Stata 12.0 (Stata Corp., College Station, TX), with P < .05 considered statistically significant.

3. Results

3.1. Description of studies

Fig. 1 is a flowchart illustrating the process of searching for and selecting studies. A total of 184 potentially relevant publications were identified. Of these, we excluded 156 studies during initial screening based on review of the titles and abstracts. During analysis of the full text of the remaining articles, 4 studies were excluded for not being case-control studies, 3 studies were excluded because they were review articles, and 2 studies were excluded because they did not report precise genotypes.

In the end, 11 studies^[7–17] were included in this meta-analysis based on our search strategy and inclusion criteria. Their characteristics are summarized in Table 2. Of these, 9 studies^[7– 10,12,13,15–17] (Table 4) involving 1,405 cases and 1,842 controls evaluated the association between -592 polymorphism and HIV-1 infection risk. Eight studies^[6–9,11,14–17] (Table 4) involving 1,278 cases and 1,858 controls evaluated the association between -1082 polymorphism and HIV-1 infection risk. Two studies^[8,17] (Table 4) involving 440 cases and 565 controls evaluated -819 polymorphism and HIV-1 infection risk. The distribution of genotypes in controls was consistent with HWE (P > .05) in all studies. The overall quality of the included studies was adequate, and the mean Newcastle-Ottawa score for the included studies was 6.45 (Table 1).

3.2. Quantitative data synthesis

3.2.1. *HIV-1* infection risk and *IL-10 -592* polymorphism. The overall results for IL-10 -592 are summarized in Table 4 and Figure 2. On the basis of 1,405 cases and 1,842 controls from 9 studies,^[7–10,12,13,15–17] the overall results indicated that the AA genotype of -592 may be associated with increased HIV-1 infection risk according to the recessive model (OR = 1.20, 95% CI=1.02–1.42, P=.03, Fig. 2B) and homozygous model (OR = 1.44, 95% CI=1.02–2.02, P=.04, Fig. 2D).

Next we meta-analyzed data for subgroups based on ethnicity. Meta-analysis of 4 studies^[8,10,15,17] involving 809 Asian cases and 896 Asian controls showed no evidence of a significant association between -592 polymorphism and HIV-1 infection risk in any of the 5 genetic models (Table 4): allelic model, OR = 1.16, 95% CI 1.00–1.33, P=.05; recessive model, OR=1.25, 95% CI=0.99-1.59, P=0.06; dominant model, OR=0.86, 95% CI=0.69-1.07, P=.19; homozygous model, OR=1.33, 95% CI=0.98-1.79, P=.07; and heterozygous model, OR=1.08, 95% CI=0.85-1.36, P=.54. Similarly, no evidence of an association was identified in meta-analysis of 4 studies^[9,12,13,16] involving 402 Caucasian cases and 772 Caucasian controls (Table 3): allelic model, OR = 1.43, 95% CI = 0.82–2.50, P = .21; recessive model, OR = 1.74, 95% CI = 0.72 - 4.19, P = .22; dominant model, OR=0.74, 95% CI=0.41-1.32, P=.31; homozygous model, OR=1.79, 95% CI=0.69-4.68, P=.23; and heterozygous model, OR=1.14, 95% CI=0.70-1.83, P = .60.

Table 2

Characteristics	i of	studies	included	in	the	meta-ar	nalysis.
-----------------	------	---------	----------	----	-----	---------	----------

						Sampl	e size (n)	
First author	Year	Ethnicity	Country	Testing method	Control source	Cases	Controls	SNP
Erikstrup ^[7]	2007	African	Zimbabwe	PCR	Population-based healthy volunteers	198	180	IL-10 -1082
Chatterjee ^[8]	2009	Asian	India	PCR-RFLP	Hospital-based healthy volunteers	180	305	IL-10 -592; IL-10 -1082; IL-10 -819
Naicker ^[9]	2009	Caucasian	South Africa	ARMS-PCR	Hospital-based healthy volunteers	64	195	IL-10 -592; IL-10 -1082
Sobti ^[10]	2010	Asian	India	PCR-RFLP	Hospital-based healthy volunteers	300	300	IL-10 -592; IL-10 -1082
Sunder ^[11]	2012	Asian	India	PCR-RFLP	Hospital-based healthy volunteers	121	102	IL-10 -1082
Corchado ^[12]	2013	Caucasian	Spain	PCR	Hospital-based healthy volunteers	91	55	IL-10 -592
Piddubna ^[13]	2013	Caucasian	Ukraine	PCR-RFLP	Population-based healthy volunteers	78	100	IL-10 -592
Freitas ^[14]	2015	Mixed	Brazil	PCR-RFLP	Hospital-based healthy volunteers	216	294	IL-10 -1082
Ramezani ^[15]	2015	Asian	Iran	PCR	Hospital-based healthy volunteers	70	31	IL-10 -592
Kallas ^[16]	2015	Caucasian	Estonia	TaqMan	Population-based healthy volunteers	172	496	IL-10 -592; IL-10 -1082
Singh ^[17]	2016	Asian	India	PCR-RFLP	Population-based healthy volunteers	260	260	IL-10 -592; IL-10 -1082; IL-10 -819

ARMS = amplification refractory mutation system, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SNP = single-nucleotide polymorphism.

Table 3

Distributions of IL-10 -592, -1082, and -819 genotypes

First author	Year		<i>P</i> for HWE	Sample size (Cases/Controls)		No. of cases		Allele fre in cases	equencies s, n, (%)		No. of controls	S	Allele fre	equencies Is, n, (%)
IL-10 -592					CC	CA	AA	С	А	CC	CA	AA	С	А
Erikstrup ^[7]	2007	African	0.912	194/174	80	71	43	231 (59.5)	157 (40.5)	68	81	25	217 (62.4)	131 (37.6)
Chatterjee ^[8]	2009	Asian	0.055	180/305	67	74	39	208 (57.8)	152 (42.2)	140	122	43	402 (65.9)	208 (34.1)
Naicker ^[9]	2009	Caucasian	0.798	64/195	24	23	17	71 (55.5)	57 (44.5)	97	80	18	274 (70.3)	116 (29.7)
Sobti ^[10]	2010	Asian	0.295	299/300	36	136	127	208 (34.8)	390 (65.2)	34	146	120	214 (35.7)	386 (64.3)
Corchado ^[12]	2013	Caucasian	0.672	88/51	43	38	7	124 (70.5)	52 (29.5)	24	21	6	69 (67.6)	33 (32.4)
Piddubna ^[13]	2013	Caucasian	0.619	78/30	42	28	8	112 (71.8)	44 (28.2)	25	5	0	55 (91.7)	5 (8.3)
Ramezani ^[15]	2015	Asian	0.358	70/31	31	35	4	97 (69.3)	43 (30.7)	16	11	4	43 (69.4)	19 (30.6)
Kallas ^[16]	2015	Caucasian	0.972	172/496	113	49	10	275 (79.9)	69 (20.1)	306	167	23	779 (78.5)	213 (21.5)
Singh ^[17]	2016	Asian	0.555	260/260	106	115	39	327 (62.9)	193 (37.1)	109	122	29	340 (65.4)	180 (34.6)
IL-10 -1082					GG	GA	AA	G	А	GG	GA	AA	G	Α
Erikstrup ^[7]	2007	African	0.448	195/175	22	73	100	117 (30.0)	273 (70.0)	17	82	76	116 (33.1)	234 (66.9)
Chatterjee ^[8]	2009	Asian	0.653	180/305	20	60	100	100 (27.8)	260 (72.2)	27	122	156	176 (28.9)	434 (71.1)
Naicker ^[9]	2009	Caucasian	0.206	64/195	5	22	37	32 (25.0)	96 (75.0)	27	80	88	134 (34.3)	256 (65.6)
Sunder ^[11]	2012	Asian	0.057	121/303	2	83	36	87 (36.0)	155 (64.0)	2	43	57	47 (23.0)	157 (77.0)
Freitas ^[14]	2015	Mixed	0.459	216/294	14	79	123	107 (24.8)	325 (75.2)	24	111	159	159 (27.0)	429 (73.0)
Ramezani ^[15]	2015	Asian	0.655	70/31	10	32	28	52 (37.1)	88 (62.9)	3	15	13	21 (33.9)	41 (66.1)
Kallas ^[16]	2015	Caucasian	0.692	172/496	32	78	62	142 (41.3)	202 (58.7)	104	251	141	459 (46.3)	533 (53.7)
Singh ^[17]	2016	Asian	0.098	260/260	21	119	120	161 (31.0)	359 (69.0)	21	125	114	167 (32.1)	353 (67.9)
IL-10 -819					Π	TC	CC	Т	С	Π	TC	CC	Т	C
Chatterjee ^[8]	2009	Asian	0.327	180/305	39	74	67	152 (42.2)	208 (57.8)	43	122	140	495 (34.1)	251 (65.9)
Singh ^[17]	2016	Asian	0.398	260/260	29	122	109	180 (34.6)	340 (65.4)	39	115	106	193 (37.1)	327 (62.9)

HWE = Hardy-Weinberg equilibrium.

Table 4

Overall meta-analysis of the association between HIV-1 infection and IL-10 -592, -1082, and -819 polymorphisms.

			Hete	erogeneity of study de	sign	
Genetic model	OR [95% CI]	Z (P value)	χ 2	df (P value)	<i>ľ</i> ² (%)	Analysis mode
IL-10 -592 in total population from 9 case contr	rol studies (1405 cases an	d 1,842 controls)				
Allelic model (A-allele vs. C-allele)	1.10 [0.99, 1.44]	1.90 (.06)	19.02	8 (.01)	58	Random
Recessive model (AA vs. CA + CC)	1.44 [1.06, 1.96]	2.31 (.02)	15.00	8 (.06)	47	Random
Dominant model (CC vs. CA + AA)	0.88 [0.70, 1.10]	1.14 (.25)	13.89	8 (.08)	42	Random
Homozygous model (AA vs. CC)	1.44 [1.02, 2.02]	2.09 (.04)	14.09	8 (.08)	43	Random
Heterozygous model (CA vs. CC)	1.00 [0.84, 1.18]	0.01 (.99)	10.72	8 (.22)	25	Fixed
IL-10 -592 in Asian population from 4 case-con	trol studies (809 cases an	d 896 controls)				
Allelic model (A-allele vs. C-allele)	1.16 [1.00, 1.33]	2.00 (.05)	3.18	3 (.36)	6	Fixed
Recessive model (AA vs. CA + CC)	1.25 [0.99, 1.59]	1.89 (.06)	4.48	3 (.21)	33	Fixed
Dominant model (CC vs. CA + AA)	0.86 [0.69, 1.07]	1.32 (.19)	2.35	3 (.50)	0	Fixed
Homozygous model (AA vs. CC)	1.33[0.98, 1.79]	1.84 (.07)	4.40	3 (.22)	32	Fixed
Heterozygous model (CA vs. CC)	1.08 [0.85, 1.36]	0.61 (.54)	2.32	3 (.51)	0	Fixed
IL-10 -592 in Caucasian population from 4 case	e-control studies (402 case	s and 772 controls)				
Allelic model (A-allele vs C-allele)	1.43 [0.82, 2.50]	1.27 (0.21)	15.73	3 (.001)	81	Random
Recessive model (AA vs. CA + CC)	1.74 [0.72, 4.19]	1.23 (.22)	8.03	3 (.05)	63	Random
Dominant model (CC vs. CA + AA)	0.74 [0.41, 1.32]	1.02 (.31)	10.58	3 (.01)	72	Random
Homozygous model (AA vs CC)	1.79 [0.69, 4.68]	1.20 (.23)	8.72	3 (.03)	66	Random
Heterozygous model (CA vs CC)	1.14 [0.70, 1.83]	0.52 (.60)	6.43	3 (.09)	53	Random
IL-10 -1082 in total population from 8 case-cor	trol studies (1278 cases a	nd 1858 controls)				
Allelic model (A-allele vs. G-allele)	1.06 [0.89, 1.26]	0.63 (.53)	15.35	7 (.03)	54	Random
Recessive model (AA vs. GA + GG)	1.08 [0.81, 1.43]	0.54 (.59)	23.14	7 (.002)	70	Random
Dominant model (GG vs. GA +AA)	0.95 [0.75, 1.21]	0.40 (.69)	3.74	7 (.81)	0	Fixed
Homozygous model (AA vs. GG)	1.18 [0.91, 1.52]	1.24 (.22)	4.49	7 (.72)	0	Fixed
IL-10 -1082 in Asian population from 4 case-co	ontrol studies (631 cases a	nd 698 controls)				
Allelic model (A-allele vs. G-allele)	0.87 [0.64, 1.19]	0.86 (.39)	8.44	3 (.04)	64	Random
Recessive model (AA vs. GA + GG)	0.81 [0.47, 1.41]	0.73 (.46)	15.83	3 (.001)	81	Random
Dominant model (GG vs. GA +AA)	1.16 [0.77, 1.74]	0.70 (.48)	0.60	3 (.90)	0	Fixed
Homozygous model (AA vs. GG)	0.90 [0.59, 1.38]	0.48 (.63)	0.55	3 (.91)	0	Fixed
Heterozygous model (GA vs. GG)	0.81 [0.53, 1.25]	0.95 (.34)	1.42	3 (.70)	0	Fixed

(continued)

Та	bl	е	4
loor	tii	211	bd

(continued).						
			Hete	erogeneity of study de	esign	
Genetic model	OR [95% CI]	Z (P value)	χ 2	df (P value)	<i>ľ</i> (%)	Analysis model
IL-10 -1082 in Caucasian population from	n 2 case-control studies (236 cas	es and 691 controls)				
Allelic model (A-allele vs G-allele)	1.30 [1.05, 1.62]	2.37 (.02)	0.89	1 (.34)	0	Fixed
Recessive model (AA vs GA + GG)	1.49 [1.09, 2.03]	2.53 (.01)	0.22	1 (.64)	0	Fixed
Dominant model (GG vs GA +AA)	0.79 [0.53, 1.18]	1.16 (.24)	0.78	1 (.38)	0	Fixed
Homozygous model (AA vs GG)	1,58 [1.01, 2.46]	2.01 (.04)	0.63	1 (.43)	0	Fixed
Heterozygous model (GA vs GG)	1.08 [0.70, 1.66]	0.35 (.73)	0.42	1 (.52)	0	Fixed
IL-10 -819 in total population from 2 cas	e-control studies (440 cases and	565 controls)				
Allelic model (C-allele vs T-allele)	1.73 [0.73, 4.12]	1.25 (.21)	22.90	1 < .001)	96	Random
Recessive model (CC vs TC + TT)	0.86 [0.58, 1.28]	0.73 (.46)	2.40	1 (.12)	58	Random
Dominant model (TT vs TC + CC)	1.10 [0.47, 2.56]	0.22 (.82)	5.78	1 (.02)	83	Random
Homozygous model (CC vs TT)	0.85 [0.33, 2.19]	0.34 (.74)	6.20	1 (.01)	84	Random

0.07 (.94)

95%CI=95% confidence interval, OR=odds ratios

Heterozygous model (TC vs TT)

3.2.2. HIV-1 infection risk and IL-10 -1082 polymorphism. The overall results are summarized in Table 4 and Fig. 3. On the basis of 1,278 cases and 1,858 controls from 8 studies, [7-9,11,14-^{17]} IL-10 -1082 polymorphism did not show significant association with HIV-1 infection risk in any of the 5 genetic models: allelic model, OR = 1.06, 95% CI = 0.89-1.26, P = .53 (Fig. 3A); recessive model, OR = 1.08, 95% CI = 0.81 - 1.43, P = .59 (Fig. 3B); dominant model, OR = 0.95, 95% CI = 0.75-1.21, P = .69 (Fig. 3C); homozygous model, OR = 1.18, 95% CI = 0.91 - 1.52, P = .22 (Fig. 3D); or heterozygous model, OR =0.93, 95% CI=0.72-1.21, P=.59 (Fig. 3E).

0.97 [0.46, 2.04]

Similarly, no significant association was observed for the subgroup of 631 Asian cases and 698 Asian controls in 4 studies^[8,11,15,17] (Table 4): allelic model, OR=0.87, 95% CI 0.64-1.19, P=.39; recessive model, OR=0.81, 95% CI=0.47-1.41, P = .46; dominant model, OR = 1.16, 95% CI = 0.77-1.74, P = .48; homozygous model, OR = 0.90, 95% CI = 0.59-1.38, P=.63; and heterozygous model, OR=0.81, 95% CI=0.53-1.25, P = .34. However, meta-analysis of 2 studies^[9,16] involving 236 Caucasian cases and 691 Caucasian controls indicated that the AA genotype of -1082 may be associated with increased HIV-1 infection risk according to the allelic model (OR = 1.30, 95%CI=1.05-1.62, P=.02), recessive model (OR=1.49, 95% CI= 1.09-2.03, P=.01) and homozygous model (OR=1.58, 95% CI = 1.01 - 2.46, P = .04)

3.2.3. HIV-1 infection risk and IL-10 -819 polymorphism. The overall results are summarized in Table 4 and Figure 4. On the basis of 440 cases and 565 controls from 2 studies,^[8,17] IL-10 -819 polymorphism did not show significant association with HIV-1 infection risk in any of the 5 genetic models: allelic model, OR=1.73, 95% CI=0.73-4.12, P=.21 (Fig. 4A); recessive model, OR = 0.86, 95% CI = 0.58 - 1.28, P = .46 (Fig. 4B); dominant model, OR=1.10, 95% CI=0.47-2.56, P=.82 (Fig. 4C); homozygous model, OR=0.85, 95% CI=0.33-2.19, P = .74 (Fig. 4D); or heterozygous model, OR = 0.97, 95% CI=0.46-2.04, P=.94 (Fig. 4E).

3.3. Publication bias

Potential publication bias in this meta-analysis was assessed using Begg funnel plot and Egger test. No obvious asymmetry was observed in Begg funnel plots of the recessive models of the -592 polymorphism (Fig. 5A) or -1082 polymorphism (Fig. 5C). P values for Egger tests were greater than 0.05 for -592 polymorphism (Fig. 5B) and -1082 polymorphism (Fig. 5D). These results suggest no potential publication bias. Begg funnel plot and Egger test for the -819 polymorphism were not performed because they involved only 2 studies.

1 (.05)

74

4. Discussion

0.89

IL-10 is an important anti-inflammatory, immunosuppressive and immunomodulatory cytokine that is associated with many diseases^[20] and is involved in the regulation of inflammatory response, autoimmunity, infection progression, tumorigenesis and transplantation tolerance.^[21-23] Interleukin 10 is a major regulator of innate immunity and prevents the development of immunopathological lesions that result from exacerbated protective immune response to acute and chronic infections.^[24] It has been reported that HIV-1-infected individuals with a particular IL-10 promoter haplotype may progress to AIDS more rapidly, but with a late effect manifested primarily about 5 years post-HIV-1 seroconversion.^[25] IL-10 may promote viral persistence by inactivation of effect or immune mechanisms.^[26] And it has been indicated that IL-10 acts as a general inhibitor of proliferative and cytokine responses of both T-helper-Th1 and Th2 cells in vitro and in vivo.^[10] IL-10 could limit viral replication in vivo by inducing secretion of inflammatory cytokines and limiting replication of T cells. In addition, Previous studies have demonstrated that IL-10 can affect several aspects of immune reaction and suppress HIV replication in vivo.^[8] Increasing evidence has suggested that polymorphisms in IL-10 may influence susceptibility to HIV infection and rate of progression to AIDS.^[7-17,27,28] Nevertheless, some of those literatures have shown IL-10 polymorphisms were protective factors against HIV infection.^[7,9,10] While the others have got different conclusions.^[8,11-17] Limited sample size and ethnic differences among the various populations examined have contributed to a lack of consensus in this literature. Therefore, we conducted the present meta-analysis on all eligible studies to provide a more precise estimate of the association of HIV-1 infection risk with IL-10 -592, -1082, and -819 polymorphisms.

A recent meta-analysis by Tsiara et al^[24] found no significant association of -592 or -1082 polymorphism with HIV susceptibility. Our meta-analysis, in contrast, suggests that the AA

Random

there are a series of the seri	1152 52 52 52 57 44 43 193 390 1157 0.04; Chi Z = 1.90 (HIV- Events 39 7 43 10 10 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (360 360 176 388 344 128 156 140 520 598 2810 P = 0.0 Total 180 88 8194 172 64 764 764 70 260 299	2088 2088 33 131 213 116 5 19 1800 386 1291 1291 12, df = 8 6) HIV- Events 43 6 25 23 18 0 4 29 18 0 4 29 18 0 4 29 18 10 20 20 20 20 20 20 20 20 20 2	6100 6102 348 992 390 60 62 520 600 3684 (P = 0. 700 174 496 51 174	14.7% 7.8% 13.7% 13.5% 10.4% 3.0% 5.9% 15.2% 15.8% 100.0% 01); P = 51 Weinht 16.6% 5.7% 5.7%	1.41 (1.08, 1.85) 0.88 (0.52, 1.48) 1.13 (0.84, 1.51) 0.92 (0.68, 1.24) 1.90 (1.26, 2.86) 4.32 (1.62, 1.92) 1.10 (0.52, 1.92) 1.11 (0.87, 1.44) 1.04 (0.82, 1.32) 1.20 (0.99, 1.44] 3% Odds Ratio M.H. Random, 95% CI 1.69 (1.04, 2.72) 0.65 (0.21, 2.05)	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
Anange 2009 Anange 2009 Anange 2009 Anange 2003 Anange 2013 Anange 2013 Anang	1157 69 57 44 43 193 390 1157 0.04; Chi Z = 1.90 (HIV- Events 39 7 43 10 39 7 43 10 10 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (300 176 388 344 128 140 520 598 2810 ₽=19.0 P=0.0 Total 180 88 194 172 64 70 260 299 1405	208 33 131 213 116 5 19 180 386 1291 12, df = 8 6) HIV. Events 23 18 0 4 29	102 348 992 390 60 62 520 600 3684 (P = 0.	13.7% 13.7% 13.5% 10.4% 3.0% 5.9% 15.2% 100.0% 001); F = 51 Weight 16.8% 5.7% 14.9%	0.88 (0.52, 1.48) 1.13 (0.84, 1.51) 0.92 (0.68, 1.24) 1.90 (1.26, 2.86) 4.32 (1.62, 1.51) 1.00 (0.52, 1.92) 1.11 (0.87, 1.44) 1.04 (0.82, 1.32) 1.20 (0.99, 1.44] 3% Odds Ratio M.H. Random, 95% CI 1.69 (1.04, 2.72) 0.65 (0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% CI
chado 2013 skrup 2007 las 2015 cker 2009 dubna 2015 mezani 2015 gh 2016 til 2010 al (95% CI) al events erogeneity. Tau ² = tfor overall effect: accessive model dy or Subaroup theraic 2009 chado 2013 cker 2009 dubna 2013 mezani 2015 cker 2009 dubna 2013 mezani 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 du 2013 al (95% CI) al events tro overall effect: ominant model	52 157 69 57 44 43 193 390 1157 0.04; Chi Z = 1.90 (HIV- Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (178 388 344 128 156 520 598 2810 ² = 19.0 598 ² = 19.0 ² = 1	33 131 213 116 5 19 180 386 1291 12, df = 8 6) HIV. Events 43 6 25 23 18 0 4 29	102 348 992 390 60 62 520 600 3684 (P = 0. Total 305 51 174 496	7.8% 13.7% 13.5% 10.4% 3.0% 5.9% 15.2% 15.2% 15.8% 100.0% 01); I ² = 51 001; I ² = 51 16.6% 5.7% 14.9%	0.38 (0.2, 1, 49) 1.3 (0.48, 1.51) 0.92 (0.68, 1.24) 1.90 (1.26, 2.86) 4.32 (1.62, 11.51) 1.00 (0.52, 1.92) 1.11 (0.87, 1.44) 1.04 (0.82, 1.32) 1.20 (0.99, 1.44] 3% Odds Ratio M-H.Random, 95% C1 1.69 (1.04, 2.72) 0.65 (0.21, 2.05)	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% CI
strup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 hi 2010 al (95% Cl) al events errogeneity: Tau [#] = t for overall effect: eccessive model dv or Sutharoup strup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 hi 2010 al (95% Cl) al events errogeneity: Tau [#] = t for overall effect: ominant model	1157 699 57 44 43 193 390 1157 0.04; Chi Z = 1.90 (HIV- Events 399 7 43 100 17 8 4 39 127 294 0.09; Chi Z = 2.31 (388 344 128 128 156 598 2810 ₹= 19.0 598 ₹= 19.0 7 7 0 88 194 172 64 70 260 299 1405	131 213 116 5 19 180 386 1291 12, df = 8 6) HIV. Events 43 6 255 23 18 0 4 29	348 992 390 62 520 600 3684 (P = 0. Total 305 51 174 496	13.7% 13.5% 10.4% 3.0% 5.9% 15.2% 15.2% 100.0% 01); I ^p = 51 18.6% 5.7% 14.9%	1.13 (0.84, 1.51) 0.92 (0.88, 1.24) 1.90 (1.26, 2.86) 4.32 (1.62, 1.151) 1.00 (0.52, 1.92) 1.11 (0.87, 1.44) 1.04 (0.82, 1.32) 1.20 (0.99, 1.44] 3% Odds Ratio <u>M.H. Random, 95% (C1</u> 1.69 (1.04, 2.72) 0.65 (0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 ti 2010 al (95% CI) al events erogeneity. Tau [#] = tf or overall effect: eccssive model dw of Sutharoup atterjee 2009 chado 2013 sterup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 dubna 2013 mezani 2015 gh 2017 dubna 2017 cker 2009 dubna 2013 dubna 2013 dubna 2013 dubna 2014 dubna 2013 dubna 2015 cker 2009 dubna 2013 dubna 2014 dubna 2014 dubna 2015 gh 2016 dubna 2017 cker 2009 dubna 2013 dubna 2013 dubna 2013 dubna 2013 dubna 2013 dubna 2013 dubna 2013 dubna 2014 dubna 2013 dubna 2013 dubna 2015 dubna 2	69 57 44 43 193 390 1157 0.04; Chi Z = 1.90 (HIV- Events 39 7 7 43 10 177 8 43 10 177 8 43 10 127 294 0.09; Chi Z = 2.31 (344 128 156 520 598 2810 *= 19.0 9 88 194 172 64 172 64 78 70 260 299 1405	213 116 5 19 180 386 1291 12, df = 8 6) HIV. Events 43 6 5 25 23 18 0 4 29	992 390 60 62 520 600 3684 (P = 0. Total 305 51 174 496	13.5% 10.4% 3.0% 5.9% 15.2% 15.8% 100.0% 01); I [≠] = 51 16.6% 5.7% 14.9%	0.92 (0.68, 1.24) 1.90 (1.26, 2.86) 4.32 (1.62, 2.16.1) 1.00 (0.52, 1.92) 1.11 (0.87, 1.44) 1.04 (0.82, 1.32) 1.20 (0.99, 1.44] 3% Odds Ratio M.H. Random, 95% C1 1.69 (1.04, 2.72) 0.65 (0.21, 2.05)	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% CI
cker 2009 dubna 2013 mezani 2015 gh 2016 shi 2010 al (95% Cl) al events erogeneity: Tau [#] = t for overall effect eccessive model dv or Suthgroup chado 2013 sstrup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 shi 2010 al (95% Cl) al events erogeneity: Tau [#] = t for overall effect ominant model	57 44 43 193 390 1157 0.04; Chi Z = 1.90 (HIV- Events 39 7 43 10 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (128 156 520 598 2810 P = 0.0 Total 180 88 194 172 64 78 70 260 299	116 5 19 1800 386 1291 12, df = 8 6) HIV. Events 6 25 23 18 0 4 29	390 60 62 520 600 3684 (P = 0. <u>Total</u> 305 51 174 496	10.4% 3.0% 5.9% 15.2% 15.8% 100.0% 01); I [≠] = 50 <u>Weight</u> 16.6% 5.7% 14.9%	1.90 [1.26, 2.86] 4.32 [1.62, 11.51] 1.00 [0.52, 1.92] 1.11 [0.87, 1.44] 1.04 [0.82, 1.32] 1.20 [0.99, 1.44] 3% Odds Ratio M.H. Random, 95% CI 1.69 [1.04, 2.72] 0.85 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
dubna 2013 mezani 2015 gh 2016 di 2010 al (95% CI) al events erogeneiky: Tau ² = it for overall effect: eccessive model dv or subnroup atterjee 2009 chado 2013 estrup 2009 dubna 2013 estrup 2007 las 2015 cker 2009 dubna 2013 gh 2016 dt 2019 dubna 2013 gh 2016 dt 2019 dt 2019 dt 2010 dt 2010 d	44 43 193 390 1157 Z = 1.90 (HIV+ Events 39 7 43 10 17 8 8 4 39 127 294 0.09; Chi Z = 2.31 (156 140 520 598 2810 ₽ = 19.0 P = 0.0	5 19 180 386 1291 12, df = 8 6) HIV- Events 25 23 18 6 25 23 18 0 4 29	60 62 520 600 3684 (P = 0. <u>Total</u> 305 51 174 496	3.0% 5.9% 15.2% 15.8% 100.0% 01); I ² = 51 <u>Weight</u> 16.6% 5.7% 14.9%	4.32 [1.62, 11.51] 1.00 [0.52, 1.92] 1.11 [0.87, 1.44] 1.04 [0.82, 1.32] 1.20 [0.99, 1.44] 9% Odds Ratio M.H. Random, 95% CI 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
mezani 2015 gh 2016 til 2010 al (95% CI) al events erogeneity: Tau [#] = t for overall effect ecossive model dv or Suthgroup throid 2013 tetriese 2009 chado 2013 tetriese 2009 dubna 2013 mezani 2015 gh 2016 otil 2010 al (95% CI) al events terogeneity: Tau [#] = t for overall effect cominant model	43 193 390 1157 0.04; Chi Z = 1.90 (HIV+ Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (140 520 598 2810 F = 19.0 F = 0.0	19 180 386 1291 12, df = 8 6) HIV Events 43 6 25 23 18 0 4 29	62 520 600 3684 (P = 0. <u>Total</u> 305 51 174 496	5.9% 15.2% 15.8% 100.0% 01); I ² = 51 <u>Weight</u> 16.6% 5.7% 14.9%	1.00 [0.52, 1.92] 1.11 [0.87, 1.44] 1.04 [0.82, 1.32] 1.20 [0.99, 1.44] 3% Odds Ratio <u>M-H. Random, 95% C1</u> 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
All parts and a second	193 390 1157 0.04; Chi Z = 1.90 (HIV+ Events 39 7 4 33 10 17 8 8 4 39 127 294 0.09; Chi Z = 2.31 (520 598 2810 ≈=19.0 P = 0.0 Total 180 88 194 172 64 78 70 260 299 1405	1291 1291 12, df = 8 6) HIV. Events 43 6 25 23 18 0 4 25 23 18 0 4 29	520 600 3684 (P = 0. <u>Total</u> 305 51 174 496	5.5% 15.2% 15.8% 100.0% 01); I [≠] = 5i <u>Weight</u> 16.6% 5.7% 14.9%	1.11 [0.87, 1.44] 1.04 [0.82, 1.32] 1.20 [0.99, 1.44] 3% Odds Ratio <u>M.H. Random, 95% C1</u> 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% CI
gn 2016 sti 2010 al (95% CI) al events erogeneity. Tau ² = t for overall effect: accessive model dy or Subharoup atterjee 2009 chado 2013 estrup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 sti 2010 al (95% CI) al events erogeneity. Tau ² = t for overall effect: ominant model	193 390 1157 0.04; Chi Z = 1.90 (HIV+ Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (520 598 2810 ₽ = 19.0 P = 0.0	1291 12, df = 8 6) HIV- Events 43 6 25 23 18 0 4 29	520 600 3684 (P = 0. <u>Total</u> 305 51 174 496	15.2% 15.8% 100.0% 01); I [≠] = 58 <u>Weight</u> 16.6% 5.7% 14.9%	1.11 [0.37, 1.44] 1.04 [0.82, 1.32] 1.20 [0.99, 1.44] 3% Odds Ratio <u>M.H. Random, 95% C1</u> 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
al (95% CI) al events errogeneity: Tau [#] = it for overall effect: eccessive model dv or Sutharoup atteries 2009 chado 2013 estrup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 ht 2010 al (95% CI) al events errogeneity: Tau [#] = it for overall effect: ominant model	1157 0.04; Chi Z = 1.90 (HIV- Events 39 7 43 10 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (2810 = 19.0 P = 0.0 Total 180 88 194 172 64 78 70 260 299 1405	1291 12, df = 8 6) HIV- Events 43 6 25 23 18 0 4 29	3684 (P = 0. <u>Total</u> 305 51 174 496	100.0% 100.0% 01); I ² = 51 <u>Weight</u> 16.6% 5.7% 14.9%	1.04 [0.82, 1.32] 1.20 [0.99, 1.44] 3% Odds Ratio <u>M.H. Random, 95% CI</u> 1.89 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
al (95% CI) al events errogeneity: Tau*= it for overall effect: eccessive model dv or. Subarroup atterjee 2009 atterjee 2009 atterjee 2009 dubna 2013 cker 2009 dubna 2013 dubna 2014 dubna	1157 0.04; Chi Z = 1.90 (HIV+ Events 39 7 43 10 17 17 8 4 39 39 127 294 0.09; Chi Z = 2.31 (2810 = 19.0 P = 0.0 Total 180 88 194 172 64 78 70 260 299 1405	1291 12, df = 8 6) HIV. <u>Events</u> 43 6 25 23 18 0 4 29	3684 (P = 0. Total 305 51 174 496	100.0% 01); I ² = 51 Weight 16.6% 5.7% 14.9%	1.20 [0.99, 1.44] 3% Odds Ratio <u>M.H. Random, 95% CI</u> 1.89 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 11/+ HIV- Odds Ratio M-H, Random, 95% Cl
al events erogeneily. Tau [#] = t for overall effect: eccessive model dv or Suthproup atterjee 2009 chado 2013 strup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 thi 2010 al (95% CI) al events erogeneily. Tau [#] = t for overall effect cominant model	1157 0.04; Chi Z = 1.90 (HIV+ Events 39 7 43 10 17 7 8 4 39 127 294 0.09; Chi Z = 2.31 (*= 19.0 P = 0.0 180 88 194 172 64 78 70 260 299 1405	1291 12, df = 8 6) HIV- <u>Events</u> 43 6 25 23 18 0 4 29	(P = 0. Total 305 51 174 496	01); I ² = 58 <u>Weight</u> 16.6% 5.7% 14.9%	Odds Ratio M.H. Random, 95% CI 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 1 HIV+ HIV- Odds Ratio M.H. Random, 95% Cl
erogeneity, Tau [#] = t for overall effect: accessive model dy or Subgroup atterjee 2009 chado 2013 cstrup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 oti 2010 al (95% CI) al events erogeneity, Tau [#] = t for overall effect ominant model	0.04; Chi Z = 1.90 (HIV+ Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (*= 19.0 P = 0.0 Total 180 88 194 172 64 78 70 260 299 1405	12, df = 8 6) HIV- Events 43 6 25 23 18 0 4 29	(P = 0. Total 305 51 174 496	01); I ² = 58 Weight 16.6% 5.7% 14.9%	Odds Ratio M-H. Random, 95% CI 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.5 1 2 5 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
It for overall effect: eccessive model dv or Subgroup atterjee 2009 chado 2013 estrup 2007 las 2015 cker 2009 dubna 2013 gh 2016 hi 2010 al (95% CI) al events tro overall effect: ominant model	Z = 1.90 (HIV+ Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (P = 0.0 Total 180 88 194 172 64 78 70 260 299 1405	6) HIV: Events 43 6 25 23 18 0 4 29	Total 305 51 174 496	Weight 16.6% 5.7% 14.9%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	0.1 0.2 0.3 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl
ecessive model dv or Suhgrroup atterjee 2009 chado 2013 sstrup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 thi 2010 al (95% CI) al events errogeneity: Tau ^e = thor overall effect: cominant model	HIV- Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (Total 180 88 194 172 64 78 70 260 299 1405	HIV- Events 43 6 25 23 18 0 4 29	Total 305 51 174 496	Weight 16.6% 5.7% 14.9%	Odds Ratio M-H, Random, 95% CI 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	Odds Ratio M-H, Random, 95% Cl
dv or Subgroup atterjee 2009 chado 2013 sistup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 ti 2010 al (95% CI) al events erogeneity: Tau ^s = t for overall effect cominant model	Events 39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (Total 180 88 194 172 64 78 70 260 299 1405	Events 43 6 25 23 18 0 4 29	Total 305 51 174 496	Weight 16.6% 5.7% 14.9%	M-H, Random, 95% Cl 1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	M-H, Random, 95% Cl
atterjee 2009 crhado 2013 strup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 thi 2010 al (95% CI) al events erogeneity. Tau ^s = t for overall effect <i>cominant model</i>	39 7 43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (180 88 194 172 64 78 70 260 299 1405	43 6 25 23 18 0 4 29	305 51 174 496	16.6% 5.7% 14.9%	1.69 [1.04, 2.72] 0.65 [0.21, 2.05]	
chado 2013 (strup 2007) (as 2015) cker 2009 dubna 2013 mezani 2015 gh 2016 oti 2010 al (95% CI) al events errogeneity: Tau ^e = t for overall effect: ominant model	7 43 10 17 8 4 39 127 294 0.09; Chi Z=2.31 (88 194 172 64 78 70 260 299 1405	6 25 23 18 0 4 29	51 174 496	5.7% 14.9%	0.65 [0.21, 2.05]	
estrup 2007 las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 thi 2010 al (95% CI) al events erogeneity: Tau [*] = t for overall effect cominant model	43 10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (194 172 64 78 70 260 299	25 23 18 0 4 29	174 496	14.9%		
las 2015 cker 2009 dubna 2013 mezani 2015 gh 2016 obi 2010 al (95% CI) al events erogeneity: Tau ² = t for overall effect: ominant model	10 17 8 4 39 127 294 0.09; Chi Z = 2.31 (172 64 78 70 260 299	23 18 0 4 29	496		1 70 (0 99 2 92)	
cker 2009 dubna 2013 mezani 2015 gh 2016 til 2010 al (95% CI) al events erogeneity: Tau ² = t for overall effect: ominant model	17 8 4 39 127 294 0.09; Chi Z = 2.31 (64 78 70 260 299	18 0 4 29	450	10 2%	1 27 (0 59 2 72)	
dubna 2013 mezani 2015 gh 2016 thi 2010 al (95% CI) al events erogeneity: Tau ² = thor overall effect: cominant model	17 8 4 39 127 294 0.09; Chi Z = 2.31 (64 78 70 260 299	18 0 4 29		10.3%	0.59 (0.58, 2.72)	
dubna 2013 mezani 2015 gh 2016 tti 2010 al (95% CI) al events terogeneity: Tau ² = tt for overall effect: ominant model	8 4 39 127 294 0.09; Chi Z = 2.31 (78 70 260 299	0 4 29	195	10.7%	3.56 [1.70, 7.43]	
nezani 2015 gh 2016 oti 2010 al (95% CI) al events erogeneity: Tau ² = it for overall effect: ominant model	4 39 127 294 0.09; Chi Z = 2.31 (70 260 299	4 29	30	1.1%	7.35 [0.41, 131.49]	
gh 2016 bti 2010 al (95% CI) al events erogeneity: Tau ² = t for overall effect ominant model	39 127 294 0.09; Chi Z = 2.31 (260 299	29	31	3.9%	0.41 [0.10, 1.76]	
oti 2010 al (95% CI) al events erogeneity: Tau ² = t for overall effect ominant model	127 294 0.09; Chi Z = 2.31 (299		260	15.6%	1.41 (0.84, 2.35)	+
al (95% CI) al events erogeneity: Tau ² = t for overall effect ominant model	294 0.09; Chi Z = 2.31 (1405	120	300	21.2%	1.11 [0.80, 1.53]	+
al (95% CI) al events erogeneity: Tau ² = ti for overall effect: ominant model	294 0.09; Chi Z = 2.31 (1405				terest real	116
ai events erogeneity: Tau ² = it for overall effect: ominant model	294 0.09; Chi Z = 2.31 (1842	100.0%	1.44 [1.06, 1.96]	•
erogeneity: Tau ² = it for overall effect: ominant model	Z = 2.31 (268	0.0	000.0	204	
ominant model		P = 0.0	iu, af = 8 2)	(12 = 0.	00), (*= 4)	/ 70	0.05 0.2 1 5 20 HIV+ HIV-
annant model	HD/4		HM			Odds Ratio	Odds Ratio
dy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
atteriee 2000	67	180	140	305	15 5%	0 70 /0 48 1 02	
abodo 2005	10	00	140	503	7.50	1.07 [0.40, 1.02]	2 2 2 2
chado 2013	43	88	24	51	1.5%	1.07 [0.54, 2.14]	
strup 2007	80	194	68	174	14.0%	1.09 [0.72, 1.66]	
las 2015	113	172	306	496	16.0%	1.19 [0.83, 1.71]	
cker 2009	24	64	97	195	9.6%	0.61 (0.34, 1.08)	
dubna 2012	42	70	25	20	3 000	0 23 10 09 0 671	
aabila 2013	42	70	20	30	5.0%	0.25 [0.00, 0.07]	
nezani 2015	31	70	16	31	5.5%	0.75 [0.32, 1.74]	8
gh 2016	106	260	109	260	16.5%	0.95 [0.67, 1.35]	
oti 2010	36	299	34	300	11.6%	1.07 [0.65, 1.76]	-
al (95% Cl)		1405		1842	100.0%	0.88 [0.70, 1.10]	•
al events	542		819		0.00.17	-	205 Y 1 2 12 1
erogeneity: Tau ² = t for overall effect:	U.U5; Chi Z=1.14 (P = 0.2	19, af = 8 5)	(P = 0.	08); 1* = 4;	2%	0.1 0.2 0.5 1 2 5 1
			110.4			Odde Datia	Odda Datia
omozygous mode	Events	Total	HIV.	Total	Weight	M-H. Random, 95% Cl	M-H. Random, 95% Cl
atterjee 2009	39	106	43	183	17.0%	1.90 [1.12. 3.19]	
chado 2013	7	50	6	30	6.3%	0.65 [0.20.2.16]	
estrup 2007	42	122	25	02	15 296	1 46 10 91 2 641	
lan 2007	43	123	20	93	14.500	1.40 [0.81, 2.64]	and the second second
las 2015	10	123	23	329	11.5%	1.18 [0.54, 2.55]	- Description
cker 2009	17	41	18	115	11.1%	3.82 [1.72, 8.49]	
dubna 2013	8	50	0	25	1.3%	10.20 [0.56, 184.29]	-
mezani 2015	4	35	4	20	4.3%	0.52 [0.11, 2.34]	
gh 2016	39	145	29	138	16.3%	1.38 [0.80, 2.40]	
oti 2010	127	163	120	154	16.8%	1.00 [0.59, 1.70]	+
al (95% CI)		836		1087	100.0%	1.44 [1.02, 2.02]	•
al events	294		268				
eroneneite Tau?-	011.04		0 df - 0	(P = 0	08) 12 - 4	296	
t for overall effect:	Z= 2.09 (P = 0.0	4)	v = 0.	007,1"= 4.		0.05 0.2 1 5 20 HIV+ HIV
	1.1.1.10		100	,		Odda Patia	Odde Datia
eterozygous mod	Events	Total	Events	Tota	Weight	M-H. Fixed, 95% Cl	M-H, Fixed, 95% Cl
atterjee 2009	74	141	122	262	14.8%	1.27 [0.84, 1.91]	
chado 2013	39	81	21	44	5 294	1 01 10 49 2 101	
cetrup 2007	74	164	21	4.40	15.00	0 75 10 47 4 471	
anup 2007	11	101	81	145	15.8%	0.75 [0.47, 1.17]	
las 2015	49	162	167	4/3	\$ 21.7%	0.79 [0.54, 1.17]	
cker 2009	23	47	80	177	6.3%	1.16 [0.61, 2.21]	
	28	70	5	30	1.5%	3.33 [1.14, 9.74]	
dubna 2013		66	11	27	27%	1.64 [0.66 4.07]	
dubna 2013 mezani 2015	35	224	122	224	20.00	0.07 [0.67 1.40]	
dubna 2013 mezani 2015 ob 2016	35	221	146	180	10.9%	0.88 [0.52, 1.49]	
dubna 2013 mezani 2015 gh 2016 oti 2010	35 115 136	172				the second second	
dubna 2013 mezani 2015 gh 2016 oti 2010	35 115 136	172	140	4574	100.00	10010.01 1 100	
dubna 2013 mezani 2015 gh 2016 oti 2010 al (95% CI) al events	35 115 136	172	756	1574	100.0%	1.00 [0.84, 1.18]	•
	ker 2009 lubna 2013 hezani 2015 h 2016 li 2010 li (95% CI) l events arogeneity: Tau ² = tor overall effect: bmozygous modu by or Subgroup theriee 2009 chado 2013 stup 2007 as 2015 ker 2009 lubna 2013 hezani 2015 h 2016 li 2010 d (95% CI) l events arogeneity: Tau ² = tor overall effect: terjee 2009 chado 2013 stup 2007 as 2015	ker 2009 24 hezani 2013 42 hezani 2013 42 hezani 2015 31 hi 2016 106 ti 2010 36 id (95% CI) ievents ievents 542 progeneity: Tau*= 0.05; Chi for overall effect Z = 1.14 (pmozygous model HIV-/h hy or Subgroup Events tterijee 2009 39 scholz 2013 7 strup 2007 43 as 2015 10 ixer 2009 17 hubna 2013 8 hezani 2015 4 h 2016 39 ti 2010 127 di (95% CI) Ievents tterjee 2009 74 vor Subgroup Events tterjee 2009 74 chor Subgroup Events tterjee 2009 74 strup 2007 71 sc 2015 49	ker 2009 24 64 ker 2009 24 64 hezani 2013 42 78 hezani 2015 31 70 h/ 2016 106 260 it 2010 36 299 it (95% CI) 1405 1405 it events 542 arogeneity: Tau*= 0.05; Chi*= 13.8 tor oreall effect Z = 1.14 (P = 0.2 bmozygous model HIV+ by or Subgroup Events Total theripe 2009 3 106 chado 2013 7 50 strup 2007 43 123 sker 2009 17 41 ubna 2013 8 50 hezani 2015 4 35 jh 2016 39 145 tit 2010 127 163 id (95% CI) 836 145 rogeneity: Tau*= 0.11; Chi*= 14.0 160 ror overall effect Z = 2.09 (P = 0.0 events 24 erogeneity: Tau*= 0.11; Chi*= 14.0 160 14 <td>ker 2009 24 64 97 hezani 2013 42 78 25 hezani 2015 31 70 16 h 2016 106 260 109 ti 2010 36 299 34 dt (95% CI) 1405 1405 progeneity. Tau² = 0.05; Ch² = 13.89, df = 8 16 tor overall effect. Z = 1.14 (P = 0.25) pmozygous model HIV+ HIV by or Subgroup Events Total Events 123 25 pmozygous model HIV+ HIV HIV HIV HIV HIV by or Subgroup Events Total 23 25 23 shup 2007 43 123 25 25 24 24 24 24 24 24 24 24 24 24 24 24 24 26 26 26 26 26 26 26 26 26 26 26 26 26 26</td> <td>Idex 2009 24 64 97 195 hezani 2013 42 78 25 30 hezani 2015 31 70 16 31 h2016 106 260 109 260 h2016 106 260 109 260 h2010 36 299 34 300 h(95% CI) 1405 1842 819 progeneity: Tau*= 0.05; Ch*= 13.89, df= 8 (P = 0. 160 43 183 prozgous model HIV+ HIV- Mor Subgroup Events Total Events Total Events Total 832 329 329 329 329 329 329 329 329 3329 329 323 329 329 323 329 329 323 329 329 323 329 329 345 4 20 34 300 323 329 323 329 345 32015 10 123<td>Idea 2009 24 64 97 195 9.6% hezani 2013 42 78 25 30 3.8% hezani 2013 42 78 25 30 3.8% hezani 2015 31 70 16 31 5.5% h 2016 106 260 10.9 260 16.5% ti 2010 36 299 34 300 11.6% it overall effect Z = 1.14 (P = 0.25) 20 30 16 43 183 17.0% bro Subgroup Events Total Events Total Events 15.3% strup 2007 43 123 25 93 15.3% strup 2015 4 35 4 20 4.3%</td><td>$\label{eq:constraint} \begin{array}{ c c c c c c c c c c c c c c c c c c c$</td></td>	ker 2009 24 64 97 hezani 2013 42 78 25 hezani 2015 31 70 16 h 2016 106 260 109 ti 2010 36 299 34 dt (95% CI) 1405 1405 progeneity. Tau ² = 0.05; Ch ² = 13.89, df = 8 16 tor overall effect. Z = 1.14 (P = 0.25) pmozygous model HIV+ HIV by or Subgroup Events Total Events 123 25 pmozygous model HIV+ HIV HIV HIV HIV HIV by or Subgroup Events Total 23 25 23 shup 2007 43 123 25 25 24 24 24 24 24 24 24 24 24 24 24 24 24 26 26 26 26 26 26 26 26 26 26 26 26 26 26	Idex 2009 24 64 97 195 hezani 2013 42 78 25 30 hezani 2015 31 70 16 31 h2016 106 260 109 260 h2016 106 260 109 260 h2010 36 299 34 300 h(95% CI) 1405 1842 819 progeneity: Tau*= 0.05; Ch*= 13.89, df= 8 (P = 0. 160 43 183 prozgous model HIV+ HIV- Mor Subgroup Events Total Events Total Events Total 832 329 329 329 329 329 329 329 329 3329 329 323 329 329 323 329 329 323 329 329 323 329 329 345 4 20 34 300 323 329 323 329 345 32015 10 123 <td>Idea 2009 24 64 97 195 9.6% hezani 2013 42 78 25 30 3.8% hezani 2013 42 78 25 30 3.8% hezani 2015 31 70 16 31 5.5% h 2016 106 260 10.9 260 16.5% ti 2010 36 299 34 300 11.6% it overall effect Z = 1.14 (P = 0.25) 20 30 16 43 183 17.0% bro Subgroup Events Total Events Total Events 15.3% strup 2007 43 123 25 93 15.3% strup 2015 4 35 4 20 4.3%</td> <td>$\label{eq:constraint} \begin{array}{ c c c c c c c c c c c c c c c c c c c$</td>	Idea 2009 24 64 97 195 9.6% hezani 2013 42 78 25 30 3.8% hezani 2013 42 78 25 30 3.8% hezani 2015 31 70 16 31 5.5% h 2016 106 260 10.9 260 16.5% ti 2010 36 299 34 300 11.6% it overall effect Z = 1.14 (P = 0.25) 20 30 16 43 183 17.0% bro Subgroup Events Total Events Total Events 15.3% strup 2007 43 123 25 93 15.3% strup 2015 4 35 4 20 4.3%	$\label{eq:constraint} \begin{array}{ c c c c c c c c c c c c c c c c c c c$

Figure 2. Forest plot describing the association between the IL-10 -592 polymorphism and HIV-1 infection risk according to different genetic models: (A) allelic, (B) recessive, (C) dominant, (D) homozygous and (E) heterozygous.

genotype of IL-10 -592 may increase susceptibility to HIV-1 infection in the total population, though not specifically in Asian or Caucasian subpopulations. This suggests that the association may not depend on ethnicity. In contrast, our meta-analysis found a significant association between the -1082 polymorphism

and susceptibility to HIV-1 infection in Caucasians, but not in Asians or the total population. Our results may be more reliable than those of Tsiara et al^[24] because of our larger sample, which can increase the statistical power for detecting significant correlations. Our meta-analysis did not identify a significant

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Chatterjee 2009	260	360	434	610	14.5%	1.05 (0.79, 1.41)	
Erikstrup 2007	273	390	234	350	137%	1 16 10 85 1 581	
Eroitae 2015	225	422	420	600	14 7%	1 12 0 05 1 501	
Vellas 2015	323	932	423	000	19.770	1.13 [0.05, 1.50]	
Kallas 2015	202	344	533	992	10.2%	1.23 [0.96, 1.57]	
Naicker 2009	96	128	256	390	9.2%	1.57 [1.00, 2.47]	
Ramezani 2015	88	140	41	62	5.8%	0.87 [0.46, 1.62]	
Singh 2016	359	520	353	520	15.7%	1.05 [0.81, 1.37]	
Sunder 2012	155	242	157	204	10.1%	0.53 (0.35, 0.81)	
Total (95% CI)		2556		3716	100.0%	1.06 [0.89, 1.26]	+
Total events	1758		2437				
Heterogeneity: Tau* = Test for overall effect:	Z = 0.63 (P = 0.5	35, df = 7 (3)	(P = 0.0	03); 1* = 5	4%	0.2 0.5 1 2
	110.7		1007			Odda Datia	HIV+ HIV-
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Random, 95% Cl
Chatteriee 2009	100	180	156	305	14 3%	1 19 10 82 1 73	
Critetrue 2003	100	105	76	175	13.50	1.13 [0.02, 1.73]	
Enkstrup 2007	100	195	10	1/5	13.3%	1.37 [0.91, 2.07]	
Freitas 2015	123	216	159	294	14.6%	1.12 [0.79, 1.60]	
Kallas 2015	62	172	141	496	14.3%	1.42 [0.98, 2.05]	
Naicker 2009	37	64	88	195	10.7%	1.67 [0.94, 2.95]	
Ramezani 2015	28	70	13	31	6.9%	0.92 [0.39, 2.18]	
Singh 2016	120	260	114	260	14.7%	1.10/0 78 1 551	-
Sunder 2012	36	121	57	102	11.0%	0.33 10 19 0 591	
	50		UT.	102	11.070	0.00 [0.10, 0.00]	
Total (95% CI)		1278	001	1858	100.0%	1.08 [0.81, 1.43]	+
total events	606		804			2001	A 1 4 1 1 1 1
Heterogeneity: Tau ² = Test for overall effect:	Z = 0.54 (P = 0.5	14, df = 7 (9)	(P = 0,0	002); I²=	10%	0.1 0.2 0.5 1 2 5
Openant Annual State			-				HIV+ HIV-
Dominant model	HIV	+ Total	HIN Events	- Total	Weight	Odds Ratio	Odds Ratio
Chatteries 2000	20	100	27	206	12 200	1 20 10 70 2 271	
Challengee 2009	20	100	21	305	13.3%	1.29 [0.70, 2.37]	
Erikstrup 2007	22	195	17	1/5	11.9%	1.18 [0.61, 2.31]	
Freitas 2015	14	216	24	294	14.2%	0.78 [0.39, 1.55]	
Kallas 2015	32	172	104	496	32.6%	0.86 [0.55, 1.34]	
Naicker 2009	5	64	27	195	9.2%	0.53 [0.19, 1.43]	
Ramezani 2015	10	70	3	31	2.7%	1.56 (0.40, 6.10)	
Singh 2016	21	260	21	260	14 496	1 00 00 52 1 991	_
Sunder 2012	2	121	2	102	1.6%	0.84 [0.12, 6.07]	
Total (95% CI)		1278		1858	100.0%	0.95 [0.75, 1.21]	•
Total events	126		225				
Heterogeneity: Chi ² =	3.74, df=	= 7 (P =	: 0.81); P	= 0%			0.1 0.2 0.5 1 2 5
rest for overall ellect	. 2 = 0.40	(== 0,	09)				HIV+ HIV-
Homozygous mod	el HIV	+ Total	HN	/. Total	Moight	Odds Ratio	Odds Ratio
Study of Subgroup	Evenus	Total	Events	Total	vveigni	M-H, FIXeu, 95% CI	M-H, Fixed, 95% CI
Chatterjee 2009	100	120	156	183	19.3%	0.87 [0.46, 1.63]	
Erikstrup 2007	100	122	76	93	14.6%	1.02 [0.51, 2.05]	
Freitas 2015	123	137	159	183	13.0%	1.33 [0.66, 2.67]	
Kallas 2015	62	94	141	245	24.9%	1.43 [0.87, 2.35]	+
Naicker 2009	37	42	88	115	5.2%	2.27 [0.81, 6.35]	+
Ramezani 2015	28	39	13	16	4 5%	0.65 (0.15, 2.75)	
Singh 2016	120	1.44	114	125	16 200	1.05 (0.55, 2.03)	_
Sunder 2012	36	38	57	59	2.2%	0.63 [0.09, 4.68]	
Total (95% Ch		733		1020	100.0%	1.1810.01.1.521	
Total events	606	132	804	1029	100.07	1.10[0.01, 1.02]	100
Hotorogonoity Ohiz-	4 40 46	7 /0 -	0 731-12	- 0%			
Test for overall effect	Z= 1.24	(P = 0.	22)	- 0.0			0.1 0.2 0.5 1 2 5 1 HIV+ HIV-
Heterozyaous mod	lel HN		HD	1.		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Tota	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Chatterjee 2009	60	80	122	149	17.9%	0.66 [0.34, 1.28]	
Erikstrup 2007	72	06	92	00	15 796	0.69 (0.34 1.40)	
Eroites 2015	70	03	111	125	11 50	1 22 10 50 2 541	_
Vellas 2015	19	93	111	135	11.5%	1.22 [0.59, 2.51]	
Kallas 2015	78	110	251	355	29.1%	1.01 [0.63, 1.62]	T
Mainlan 2000	22	27	80	107	5.0%	1.49 [0.51, 4.31]	
Naicker 2009	32	42	15	18	4.2%	0.64 [0.15, 2.67]	
Ramezani 2015			125	146	15.5%	0.95 [0.49, 1.83]	
Ramezani 2009 Singh 2016	119	140	120	1.40			
Ramezani 2015 Singh 2016 Sunder 2012	119 83	140	43	45	1.1%	1.93 [0.26, 14.18]	
Ramezani 2009 Ramezani 2015 Singh 2016 Sunder 2012 Total (95% CI)	119 83	140 85	43	45	1.1%	0.93 [0.72, 1.21]	•
Naicker 2009 Ramezani 2015 Singh 2016 Sunder 2012 Total (95% CI) Total events	119 83 546	140 85 672	43	45 1054	1.1%	1.93 [0.26, 14.18] 0.93 [0.72, 1.21]	•

Figure 3. Forest plot describing the association between the IL-10 -1082 polymorphism and HIV-1 infection risk according to different genetic models: (A) allelic, (B) recessive, (C) dominant, (D) homozygous and (E) heterozygous.

relationship between IL-10 -819 polymorphism and HIV-1 infection risk.

To the best of our knowledge, this is the largest meta-analysis so far investigating the possible association between polymorphisms in interleukin-10 gene and susceptibility to HIV-1 infection. Nevertheless, the meta-analysis is limited by the designs of the included studies. First, the results may be affected by both genetic and environmental factors, but most studies did not report environmental exposure, making it impossible to include them in the meta-analysis. Second, the studies may be

	Allelic model	HIV	+	HIV			Odds Ratio	Odds Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	
	Chatteriee 2009	208	360	251	746	50.0%	2.70 [2.08, 3.49]		
	Singh 2016	340	520	327	520	50.0%	1.11 [0.87, 1.44]	•	
	Total (95% CI)		880		1266	100.0%	1.73 [0.73, 4.12]	•	
	Total events	548		578			22.1 22 12		
	Heterogeneity: Tau ² =	0.37; Ch	2= 22.	90, df = 1	(P < 0.	00001); P	² = 96%	tana ali da	
51 61	Test for overall effect:	Z=1.25	(P = 0.2	!1)				0.002 0.1 1 10 HIV+ HIV-	500
	Recessive model	HIV	•	HIV	1		Odds Ratio	Odds Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
	Chatteriee 2009	67	180	140	305	48.4%	0.70 [0.48, 1.02]		
	Singh 2016	109	260	106	260	51.6%	1.05 [0.74, 1.49]	+	
	Total (95% CI)		440		565	100.0%	0.86 [0.58, 1.28]	•	
	Total events	176		246					
	Heterogeneity Tau ² =	0.05 Ch	2= 24	0 df=1 (P = 0.1	2): IF = 58	196		-
	Test for overall effect:	Z = 0.73	P = 0.4	(6)	- 0.1	2/,1 = 30		0.1 0.2 0.5 1 2 5	10
				-/				HIV+ HIV-	
	Dominant model	HIV	F.	HIV			Odds Ratio	Odds Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
	Chatterjee 2009	39	180	43	305	50.6%	1.69 [1.04, 2.72]	-	
	Singh 2016	29	260	39	260	49.4%	0.71 [0.43, 1.19]	•	
	Total (95% CI)		440		565	100.0%	1.10 [0.47, 2.56]	+	
	Total events	68		82					
	Heterogeneity: Tau ² =	0.31; Ch	r= 5.7	8, df = 1 (P = 0.0	2); 2 = 83	1%		500
	Test for overall effect: 2	Z = 0.22	(P = 0.8	(2)				HIV+ HIV-	500
	Homozygous mode	HIV		HIV			Odde Ratio	Odds Ratio	
	Study or Subgroup						Ouus nauo		
-	orday of ourshould	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
	Chatteriee 2009	Events 67	Total 106	Events 140	Total 183	Weight 50.4%	M-H, Random, 95% CI 0.53 [0.31, 0.89]	M-H, Random, 95% Cl	
-	Chatterjee 2009 Singh 2016	Events 67 109	Total 106 138	Events 140 106	Total 183 145	Weight 50.4% 49.6%	<u>M-H, Random, 95% Cl</u> 0.53 [0.31, 0.89] 1.38 [0.80, 2.40]	M-H, Random, 95% Cl	
-	Chatterjee 2009 Singh 2016 Total (95% CI)	Events 67 109	Total 106 138 244	Events 140 106	<u>Total</u> 183 145 328	Weight 50.4% 49.6%	<u>M-H, Random, 95% CI</u> 0.53 (0.31, 0.89) 1.38 (0.80, 2.40) 0.85 (0.33, 2.19)	M-H, Random, 95% Cl	
	Chatterjee 2009 Singh 2016 Total (95% CI) Total events	Events 67 109 176	Total 106 138 244	Events 140 106 246	Total 183 145 328	Weight 50.4% 49.6% 100.0%	<u>M-H, Random, 95% CI</u> 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19]	M-H, Random, 95% Cl	
	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² =	Events 67 109 176 0.39: Ch	Total 106 138 244 F = 6.2	Events 140 106 246 0 df = 1 (<u>Total</u> 183 145 328 P = 0.0	Weight 50.4% 49.6% 100.0%	<u>M-H, Random, 95% CI</u> 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19]	M-H, Random, 95% Cl	
	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect :	Events 67 109 176 0.39; Ch Z = 0.34	Total 106 138 244 P = 6.20 (P = 0.7	Events 140 106 246 D, df = 1 ('4)	<u>Total</u> 183 145 328 P = 0.0	Weight 50.4% 49.6% 100.0% 1); I ² = 84	<u>M-H, Random, 95% CI</u> 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19]	M-H, Random, 95% Cl	500
-	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2	Events 67 109 176 0.39; Ch Z = 0.34	<u>Total</u> 106 138 244 i ² = 6.2 (P = 0.7	Events 140 106 246 0, df = 1 ('4)	<u>Total</u> 183 145 328 P = 0.0	Weight 50.4% 49.6% 100.0% 1); I ² = 84	<u>M-H, Random, 95% CI</u> 0.53 (0.31, 0.89) 1.38 (0.80, 2.40) 0.85 [0.33, 2.19]	M-H, Random, 95% Cl	500
,	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : Heterozygous mode	Events 67 109 176 0.39; Ch Z = 0.34	Total 106 138 244 P= 6.2 (P = 0.7	Events 140 106 246 0, df = 1 ('4) HIV-	<u>Total</u> 183 145 328 P = 0.0	Weight 50.4% 49.6% 100.0% 1); I ² = 84	<u>M-H, Random, 95% CI</u> 0.53 (0.31, 0.89) 1.38 (0.80, 2.40) 0.85 [0.33, 2.19]	M-H, Random, 95% Cl	500
,	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : Heterozygous mode Study or Subgroup	Events 67 109 176 0.39; Ch Z = 0.34 e/ HIV4 Events	<u>Total</u> 106 138 244 i ² = 6.2 (P = 0.7 , <u>Total</u>	Events 140 106 246 0, df = 1 ('4) HIV- Events	<u>Total</u> 183 145 328 P = 0.0 <u>Total</u>	Weight 50.4% 49.6% 100.0% 1); I ² = 84 Weight	M-H, Random, 95% CI 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19] % Odds Ratio M-H, Random, 95% CI	M-H, Random, 95% Cl 	500
	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: J Heterozygous mode Study or Subgroup Chatterjee 2009	Events 67 109 176 0.39; Ch Z = 0.34 e/ HIV4 Events 74	Total 106 138 244 P = 6.2 (P = 0.7 <u>F</u> Total 113	Events 140 106 246 0, df = 1 ('4) HIV: Events 122	<u>Total</u> 183 145 328 P = 0.0 <u>Total</u> 165	<u>Weight</u> 50.4% 49.6% 100.0% 1); I ² = 84 <u>Weight</u> 50.6%	M-H, Random, 95% CI 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19]	M-H, Random, 95% Cl 	500
	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: J Heterozygous mode Study or Subgroup Chatterjee 2009 Singh 2016	Events 67 109 176 0.39; Ch Z = 0.34 Events 74 122	Total 106 138 244 i ² = 6.2 (P = 0.7 F Total 113 151	Events 140 106 246 0, df = 1 ('4) HIV. Events 122 115	<u>Total</u> 183 145 328 P = 0.0	Weight 50.4% 49.6% 100.0% 1); I ² = 84 <u>Weight</u> 50.6% 49.4%	M-H, Random, 95% CI 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.67 [0.40, 1.13] 1.43 [0.83, 2.46]	M-H, Random, 95% Cl 	500
,	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: J Heterozygous mode Study or Subgroup Chatterjee 2009 Singh 2016 Total (95% CI)	Events 67 109 176 0.39; Ch Z = 0.34 e/ HIV4 Events 74 122	Total 106 138 244 ² = 6.2 (P = 0.7 <u>Total</u> 113 151 264	Events 140 106 246 0, df = 1 ('4) HIV- Events 122 115	<u>Total</u> 183 145 328 P = 0.0 <u>Total</u> 165 154 319	Weight 50.4% 49.6% 100.0% 1); I ² = 84 Weight 50.6% 49.4% 100.0%	M-H, Random, 95% CI 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.85 [0.33, 2.19] 0.97 [0.46, 2.04]	M-H, Random, 95% Cl 	500
-	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : Heterozygous mode Study or Subgroup Chatterjee 2009 Singh 2016 Total (95% CI) Total events	Events 67 109 176 0.39; Ch Z = 0.34 e/ HIV4 Events 74 122	Total 106 138 244 ² = 6.2((P = 0.7) <u>Total</u> 113 151 264	Events 140 106 246 0, df = 1 ('4) HIV- Events 122 115 237	<u>Total</u> 183 145 328 P = 0.0	<u>Weight</u> 50.4% 49.6% 100.0% 1); I ² = 84 <u>Weight</u> 50.6% 49.4% 100.0%	<u>M-H, Random, 95% CI</u> 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19] % Odds Ratio <u>M-H, Random, 95% CI</u> 0.67 [0.40, 1.13] 1.43 [0.83, 2.46] 0.97 [0.46, 2.04]	M-H, Random, 95% Cl 	500
,	Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect : Heterozygous mode Study or Subgroup Chatterjee 2009 Singh 2016 Total (95% CI) Total events Heterogeneity: Tau ² =	Events 67 109 176 0.39; Ch Z = 0.34 e/ HIV4 Events 74 122 196 0.21: Ch	Total 106 138 244 ² = 6.2((P = 0.7) <u>Total</u> 113 151 264 ² = 3.8	Events 140 106 246 0, df = 1 ('4) HIV- Events 122 115 237 9, df = 1 (<u>Total</u> 183 145 328 P = 0.0 <u>Total</u> 165 154 319 P = 0.0	Weight 50.4% 49.6% 100.0% 1); I ² = 84 Weight 50.6% 49.4% 100.0% 5); I ² = 74	M-H, Random, 95% CI 0.53 [0.31, 0.89] 1.38 [0.80, 2.40] 0.85 [0.33, 2.19] % Odds Ratio M-H, Random, 95% CI 0.67 [0.40, 1.13] 1.43 [0.83, 2.46] 0.97 [0.46, 2.04]	M-H, Random, 95% Cl M-H, Random, 95% Cl 0.002 0.1 1 10 HIV+ HIV- Odds Ratio M-H, Random, 95% Cl	500

Figure 4. Forest plot describing the association between the IL-10 -819 polymorphism and HIV-1 infection risk according to different genetic models: (A) allelic, (B) recessive, (C) dominant, (D) homozygous and (E) heterozygous.

subject to performance, attrition and reporting biases, although Newcastle-Ottawa scores were at least 6 for all 11 studies, indicating high quality. Third, our exclusion of unpublished data and of papers published in languages other than English may have biased our results. Fourth, there were only 2 case-control studies^[8,17] concerning IL-10 -819 polymorphism, and all subjects in those studies were Asian. The relatively small Asian sample in our meta-analysis may bias our results and limit the relevance of our results. Finally, for lack of data, we were unable to examine whether any of the genetic associations varied with



Figure 5. Begg funnel plot and Egger test to assess publication bias in the meta-analysis of potential associations between HIV-1 infection risk and (A, B) IL-10 -592 polymorphism or (C, D) IL-10 -1082 polymorphism. All analyses were performed using a recessive genetic model.

age, sex, HIV-1 subtype, or family history of HIV infection. Future studies should examine these additional factors.

Despite these limitations, this meta-analysis provides evidence that the AA genotype of IL-10 -592 may confer increased susceptibility to HIV-1 infection, and that the AA genotype of -1082 may be associated with increased HIV-1 infection risk in Caucasians. However, the -819 polymorphism may not be associated with HIV-1 infection risk. These conclusions should be verified in large, well-designed studies.

Author contributions

Designed the study: Dan-Ke Su and Dan-Hui Fu. Searched databases and collected full-text papers: Wen-Juan Deng, Zhi Yang, Sen Hong. Extracted and analyzed the data: Qian-Lin Ding, Yang Zhao. Statistical analyses: Jia Chen. Wrote the manuscript: Dan-Hui Fu. All authors reviewed the manuscript.

References

- Martin MP, Carrington M. Immunogenetics of HIV disease. Immunol Rev 2013;254:245–64.
- [2] Weiler A, May GE, Qi Y, et al. Polymorphisms in eight host genes associated with control of HIV replication do not mediate elite control of viral replication in SIV-infected Indian rhesus macaques. Immunogenetics 2006;58:1003–9.
- [3] Shimizu YY, et al. Induction of immune response in macaque monkeys infected with simian-human immunodeficiency virus having the TNF-α gene at an early stage of infection. Virology 2005;343:151–61.

- [4] Mocellin S, Marincola FM, Young HA. Interleukin-10 and the immune response against cancer: a counterpoint. J Leukoc Biol 2005;78:1043– 51.
- [5] Shrestha S, Wiener HW, Aissani B, et al. Interleukin-10 (IL-10) pathway: genetic variants and outcomes of HIV-1 infection in African American adolescents. PloS one 2010;5:e13384.
- [6] Kwon DS, Kaufmann DE. Protective and detrimental roles of IL-10 in HIV pathogenesis. Eur Cytokine Netw 2010;21:208–14.
- [7] Erikstrup C, Kallestrup P, Zinyama-Gutsire RB, et al. Reduced mortality and CD4 cell loss among carriers of the interleukin-10-1082G allele in a Zimbabwean cohort of HIV-1-infected adults. Aids 2007;21:2283–91.
- [8] Chatterjee A, Rathore A, Sivarama P, et al. Genetic association of IL-10 gene promoter polymorphism and HIV-1 infection in North Indians. J Clin Immunol 2009;29:71–7.
- [9] Naicker DD, Werner L, Kormuth E, et al. Interleukin-10 promoter polymorphisms influence HIV-1 susceptibility and primary HIV-1 pathogenesis. J Infect Dis 2009;200:448–52.
- [10] Sobti RC, Berhane N, Mahedi SA, et al. Polymorphisms of IL-6 174 G/C, IL-10-592 C/A and risk of HIV/AIDS among North Indian population. Mol Cell Biochem 2010;337:145–52.
- [11] Sunder SR, Hanumanth SR, Nagaraju RT, et al. IL-10 high producing genotype predisposes HIV infected individuals to TB infection. Hum Immunol 2012;73:605–11.
- [12] Corchado S, Marquez M, de Oca MM, et al. Influence of genetic polymorphisms of tumor necrosis factor alpha and interleukin 10 genes on the risk of liver cirrhosis in HIV-HCV coinfected patients. PLoS One 2013;8:e66619.
- [13] Piddubna AI. IL-4, IL-10 and TNF-α Promotor Gene Polymorphism in North-Eastern Ukrainian HIV-1 Infected Individuals. 2013;Global HIV Vaccine Enterprise,
- [14] Bonfim Freitas F, Souza Lima S, et al. Polymorphisms in the IFN γ , IL-10, and TGF β genes may be associated with HIV-1 infection. Dis Markers 2015;2015.

- [15] Ramezani A, Kalantar E, Aghakhani A, et al. Lack of association between interleukin-10 gene promoter polymorphisms with HIV susceptibility and progression to AIDS. Iran J Pathol 2015;10:141.
- [16] Kallas E, Huik K, Pauskar M, et al. Influence of interleukin 10 polymorphisms-592 and-1082 to the HIV, HBV and HCV serostatus among intravenous drug users. Infect Genet Evol 2015;30:175–80.
- [17] Singh S, Sharma A, Arora SK. Combination of low producer AAgenotypes in IFN-γ and IL-10 genes makes a high risk genetic variant for HIV disease progression. Cytokine 2016;77:135–44.
- [18] Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/ox ford.htm.
- [19] Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis. Arch Gen Psychiatry 2006;63:530–8.
- [20] Lu YL, Wu X, Huang HL, et al. Allele polymorphisms of interleukin-10 and hepatitis B, C virus infection. Chin Med J (Engl) 2010;123:1338–44.
- [21] Murray PJ, Wang L, Onufryk C, et al. T cell-derived IL-10 antagonizes macrophage function in mycobacterial infection. J Immunol 1997; 158:315–21.

- [22] Llorente L, Richaud-Patin Y, Fior R, et al. In vivo production of interleukin-10 by non-T cells in rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus. A potential mechanism of B lymphocyte hyperactivity and autoimmunity. Arthr Rheum 1994;37:1647–55.
- [23] Mason D, Powrie F. Control of immune pathology by regulatory T cells. Curr Opin Immunol 1998;10:649–55.
- [24] Mege JL, et al. The two faces of interleukin 10 in human infectious diseases. Lancet Infect Dis 2006;6:557–69.
- [25] Anastassopoulou CG, Kostrikis LG. The impact of human allelic variation on HIV-1 disease. Curr HIV Res 2003;1:185–203.
- [26] Mahajan SD, et al. Role of chemokine and cytokine polymorphisms in the progression of HIV-1 disease. Biochemical and Biophysical Research Communications 2010;396:348–52.
- [27] Weiler A, et al. Polymorphisms in eight host genes associated with control of HIV replication do not mediate elite control of viral replication in SIV-infected Indian rhesus macaques. Immunogenetics 2006; 58:1003–9.
- [28] Tsiara CG, Nikolopoulos GK, Dimou NL, et al. Interleukin gene polymorphisms and susceptibility to HIV-1 infection: a meta-analysis. J Genet 2018;97:235–51.