Association of toll-like receptor polymorphisms with acquisition of HIV infection and clinical findings

A protocol for systematic review and meta-analysis

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Abstract

**Background:** To find the relationship between toll-like receptor (TLR) gene variants and human immunodeficiency virus (HIV) infection and clinical findings, which could inform clinical decisions and vaccination strategies.

**Method:** Four databases were searched for articles that were published on or before Jul. 1, 2020. Review Manager 5.3 software was applied to perform meta-analysis to explore.

**Results:** A total of 10 studies involving 20 genes, 3697 cases, and 6498 controls were included in this systematic review. TLR2 –196 to –174 Ins/Del (odds ratio [OR] = 1.562; \(P = .002\)), TLR4 rs4986790 (OR = 2.06; \(P = .002\)), TLR3 rs3775291 (OR = 0.25; \(P = .03\)), TLR7 rs179008 (OR = 0.02), TLR7 rs20274109 (OR = 0.27; \(P = .019\)) were found associated with HIV infection. TLR2 –196 to –174, TLR4 rs4986790, TLR7 rs179008, TLR8 rs3764880, TLR9 rs352140 were found associated with clinical findings of HIV infection. We identified 5 case-control studies in meta-analysis, involving 695 cases and 729 controls on TLR7 rs179008 polymorphism, totaling 652 cases and 614 controls on TLR9 rs352140 polymorphism. In meta-analysis, we employed various genetic models. The T allele of TLR7 rs179008 was conferred the risk of HIV infection (T vs A: OR = 1.25, \(P_A = .02\)). An increased risk of HIV infection was found for individuals with the TLR9 rs352140 GG genotype (GG vs AA: OR = 1.50, \(P_A = .04\)).

**Conclusions:** The systematic review indicated that TLR7 rs179008 T allele provides risk effects for HIV infection. TLR9 rs352140 GG genotype may associate with HIV infection.

**Abbreviations:** 95% CIs = 95% confidence intervals, AIDS = acquired immunodeficiency syndrome, FPPR = false-positive report probability, GWAS = genome-wide association studies, HIV = human immunodeficiency virus, HWE = Hardy-Weinberg equilibrium, IRF-3 = interferon regulatory factor-3, NOS = Newcastle-Ottawa quality assessment scale, OR = odds ratio, SNPs = single-nucleotide polymorphism, TLR = toll-like receptor, TSA = trial sequential analysis.

**Keywords:** human immunodeficiency virus, infection, single nucleotide polymorphisms, systematic review, toll-like receptor

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a contagious and potentially fatal disease caused by the human immunodeficiency virus (HIV). It is now recognized that chronic, generalized immune activation is a major driving force for CD4+ T cell depletion and AIDS progression.\(^{[1]}\) With similar risk exposure levels, the course of HIV-1 infection varies widely among individuals.\(^{[2–4]}\) In addition, different AIDS patients whose rate of progression to immunodeficiency and associated complications exhibited a high differences. Without antiretroviral treatment, most HIV-positive patients develop AIDS within 10 years, but some infected persons progress to AIDS within 1 to 5 years and

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others may remain asymptomatic for over 20 years. There is extensive heterogeneity among individuals in susceptibility to infection and the time to develop AIDS-defining diseases. Therefore, the genetic background of an individual might play an important role in acquisition of HIV and disease progression after HIV infection. Using a combination of analyses is an important role in acquisition of HIV and disease progression after HIV infection. 

2. Materials and methods

2.1. Identification of eligible studies

We utilized Medline/PubMed, EMBASE, Web of Science, and the Cochrane Library until Jul.1, 2020. The following keywords were included in the search: “HIV” or “human immunodeficiency virus” or “AIDS” or “Acquired immunodeficiency syndrome” in combination with “polymorphism” or “SNP” or “variant” or “genotype” and in combination with “toll” or “TLR” or “toll-like receptor” or “toll-like receptor.” The reference lists of retrieved studies and recent reviews were also manually searched for further relevant studies.

2.2. Inclusion and exclusion criteria

Studies in this meta-analysis must meet the following inclusion criteria:

(1) evaluation of the relationship between TLR polymorphisms and HIV infection;
(2) case-control study;
(3) studies with detailed genotype data in both cases and controls.

Exclusion criteria:

(1) duplication of previous publications;
(2) case reports, basic research, review, and other non-case-control studies;
(3) studies without detailed genotype data;
(4) did not deal with humans;
(5) subject is not an adult;
(6) non-English publications.

2.3. Data extraction

The data of all eligible studies were extracted by 2 investigators independently. The following data were recorded:

(1) name of first author;
(2) year of publication;
(3) ethnicity;
(4) genotyping methods;
(5) whether the genotypes of all component studies were tested for Hardy-Weinberg equilibrium (HWE);
(6) number of cases and controls;
(7) clinical findings.

Two authors checked the extracted data and reached to consensus on all the data. If a dissent existed, the third investigators would be involved to adjudicate the disagreements.

2.4. Quality assessment

We used a risk-of-bias tool modified from the Newcastle-Ottawa quality assessment scale (NOS) to assess the quality of individual reports. The NOS is a scoring tool comprising patient selection, comparability of study groups, and ascertainment of outcome (See Table S, http://links.lww.com/MD/F402, supplemental content, which illustrates the evaluation criteria of quality scores). Quality scores ranged from 0 to 9 and the studies with more than 6 scores were considered better quality.

2.5. Trial sequential analysis (TSA) and false-positive report probability (FPRP) analysis

The reliability and authenticity of the results of meta-analysis were verified by TSA and FPRP. TSA parameter setting: type I error probability of 5%, type II error probability of 35%, and risk ratio reduction of 15% to calculate the Require Information Size (RIS). FPRP parameter setting: threshold to 0.2, prior
probability assigned 0.1 and detect an odds ratio (OR) of 0.67/1.50 (protective/risk effects) for an association with genotypes under investigation. The significant result with an FPRP value less than 0.2 was considered a noteworthy finding. All the calculations to derive FPRP were performed with the Excel spreadsheet released by Wacholder et al.\[49\]

### 2.6. Statistical analysis

HWE was calculated for the control group of studies that did not describe HWE using the Chi-square test. The crude ORs and 95% confidence intervals (95% CIs) were calculated to investigate the association strength between polymorphisms and HIV infection for each study. Pooled OR were obtained from combination of single studies by allelic comparison, dominant model, recessive model, homozygote model, and heterozygote model. Heterogeneity among different studies was assessed by the Q test and $I^2$ test.\[50\] The heterogeneity was considered significant when $P$-value was less than .1. If $P$-value more than .10, fixed-effects models are adopted, otherwise random-effects models were used. Publication bias was tested by symmetrical funnel Begg plot analysis. All statistical analyses were performed with Review Manager 5.3 software, $P<.05$ was considered statistically significant.

### 3. Results

#### 3.1. Characteristics of included studies

A total of 339 studies were acquired from above databases. After screening, 10 studies were met the inclusion criteria, which included 20 genes, totaling 3697 cases and 6498 controls (Fig. 1). These included 2, 1, 3, 4, 1, and 4 studies on TLR2, TLR3, TLR4, TLR7, TLR8, and TLR9, respectively. Meta-analysis was

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*Figure 1.* Chart of the literature search and selection process.
performed if one gene had at least three comparisons were available. These study participants were from diverse descents including Asian, European, and American. In all studies included, only the genotype distribution in the control of Joshi et al study was observed to deviate from HWE. Detailed characteristics of all the studies included are shown in Table 1. All included studies had relatively high NOS scores (ranging from 7–9) (Table 2).

3.2. Systematic review of TLR gene polymorphisms and acquisition of HIV infection

The study performed on an Indian cohort indicated that TLR2 Del to –174 Ins/Del polymorphism is a risk factor for HIV-1 infection. Compared with healthy controls, TLR2 Del mutant genotype (OR = 2.138; \( P = 0.001 \)) and allele (OR = 1.562; \( P = 0.002 \)) was higher in patients with HIV-1 infection. This correlation did not find in other TLR2 genes (rs5743708, rs5743704, rs12191786). Simultaneously, for the same research object observed that TLR4 rs4986790 was associated with HIV infection. G allele were significantly more frequent in HIV infection patients (OR = 2.05; \( P = 0.002 \)), but not observed in TLR4 rs4986791. The Caucasian cohort of the Hui study found that TLR3 rs3775291 display protective effect against HIV infection with T allele comparison (OR = 0.25; \( P = 0.01 \)). Oh et al showed that TLR7 rs179008 is associated with HIV infection, the mutant allele carriage frequency was significantly higher than that observed in healthy controls (\( P = 0.002 \)), but Shaikh et al did not find this association in Indian cohort. However, Shaikh et al reported TLR 7 rs2074109 may be associated with HIV infection, and TLR7 rs2074109 G allele was significantly higher in controls (OR = 0.27, \( P = 0.019 \)).

3.3. Systematic review of TLR gene polymorphisms and clinical findings

Among the genes of TLR2 (–196 to –174 Ins/Del, rs5743708, rs5743704, rs12191786), Vidyan found TLR2 Del homozygous genotype was lower in stage III (19.35%) as compared to stage I (50.87%); OR = 1.901 and stage II (43.05%; OR = 1.514) in patients with HIV. TLR2 Del homozygous genotype may be associated with reduced risk of HIV-1 disease progression. The results of TLR2 (rs5743708, rs5743704) were same as Soriano-Sarabia et al results. The remaining results of the Vidyan study pointed out TLR4 rs4986790 was associated with stage progression, but not observed in TLR4 rs4986791. In an Omani cohort, the relationship between TLR4 (1063A/G, 1363C/T) gene polymorphism and the CD4 and CD8 cell counts and viral load was not found. In the studies of TLR7 gene polymorphisms, Oh et al showed TLR 7 rs179008 was associated high viral loads and lower baseline CD4 T-cell counts, which was consistent with Anokhin et al., but inconsistent with Saaid et al. TLR8 rs3764880 was conferred a significantly protective effect regarding progression of the disease. The results reporting of the influence of the TLR9 rs352140 on disease progression are contradictory. A study performed in Spain and American. HIV-infected cohort showed that TLR9 rs352140 is associated with lower CD4 count and higher viral load as rapid progression. In contrast, study in Omani showed that TLR9 rs352140 is associated with high CD4 T cell count. A recent study by Shaikh et al showed that TLR9 rs352140 is associated with slow disease progression, but the relationship are not found in TLR7 (rs2074109, rs179009, chrX:12885280) and TLR9 (rs17846009, rs35342983, rs187084).

3.4. Meta-analysis results (Table 3)

3.4.1. TLR7 rs179008 polymorphism and acquisition of HIV infection. Three studies were included in the meta-analysis of this SNP, involving 695 cases and 729 controls. No heterogeneity was identified by Q-test and I-square statistic, so fixed-effects model was used. The T allele was shown the risk factor for HIV infection in the allelic model (T vs A: OR = 1.25, 95% CI: 1.04–1.50, \( P_A = 0.02 \)). The forest plots were shown in Figure 2A. In addition, the TT and TA genotypes also had risk effect against HIV infection in the dominant models, heterozygote comparison (TT + TA vs AA: OR = 1.32, 95%CI: 1.03–1.70, \( P_A = 0.03 \), TA vs AA: OR = 2.21, 95%CI: 1.20–4.07, \( P_A = 0.01 \)). The forest plots were shown in Figure 2B, E. No statistically significant results were found in recessive and homozygote models (TT vs TA + AA: OR = 1.17, 95% CI: 0.90–1.53, \( P_A = 0.23 \), TT vs AA: OR = 1.20, 95% CI: 0.92–1.57, \( P_A = 1.7 \)). The forest plots were shown in Figure 2C, D. We performed the TSA, and RIS of 1951 was calculated. Z-curve crossed conventional boundary and TSA boundary, although the sample size did not reach RIS, which confirmed the certain results (Fig. 3).

3.4.2. TLR9 rs352140 polymorphism and acquisition of HIV infection. Four studies were included in the meta-analysis of this SNP, involving 652 cases and 614 controls. We found no heterogeneity existed, so still used fixed-effects model. The homozygote comparison showed GG genotype may be a risk factor for HIV infection (GG vs AA: OR = 1.50, 95%CI: 1.01–2.21, \( P_A = 0.04 \)). The forest plots were shown in Figure 4D. We also performed comparison for the other 4 genetic models and no associations were found in any of these (G vs A: OR = 1.19, 95% CI: 0.99–1.43, \( P_A = 0.17 \)). The forest plots were shown in Figure 2A, B, C, E, respectively. TSA was executed to count the RIS of 653. The result of TSA indicated that Z-curve crossed conventional boundary, but TSA boundary and RIS was not reached (Fig. 5). It means studies of high quality and large samples are needed to verify the relationship between TLR9 rs352140 polymorphism and HIV infection.

3.5. FPRP analysis

Table 4 shows the FPRP values for our positive results using different prior probability levels. When prior probability of 0.25 was adopted, significant association for TLR7 rs179008 (T vs A, TT + TA vs AA, TA vs AA) and TLR9 rs352140 (G vs A, GG vs AA) was verified to be noteworthy.

3.6. Sensitivity analysis

To check the influence by the individual study on the overall ORs, we deleted each study once in every genetic model. The sensitivity analysis demonstrated that the TLR7 rs179008 and TLR9 rs352140 ORs were not statistically influenced, which validated the stability of our data.
| SNP | Author Year | Country | Ethnicity | HWE | HIV-1 infect | Healthy controls | Susceptibility | Clinical findings |
|-----|-------------|---------|-----------|-----|--------------|------------------|---------------|------------------|
| TLR2 2258 G/A | Soriano-Sarabia et al.[48] 2008 Spain Spanish | Y 364 4 0 | G 152 3 0 | NA | NS (VL, CD4) | NS (VL, CD4) |
| TLR2 2258 G/A | Vidyant et al.[55] 2017 India Indian | Y 349 7 0 | G 160 2 0 | NA | NS (VL, CD4) |
| TLR2 2029 C/T | Vidyant et al.[55] 2018 India Indian | C 296 1 0 | G 258 4 0 | NS | NS |
| TLR2 Ins/Del 196 to -174 | Vidyant et al.[55] 2018 India Indian | Ins/Ins 247 3 0 | Del/Del 214 5 0 | NS | NS |
| TLR3 rs3775291 | Huik et al.[57] 2013 Caucasian Caucasian | C 293 4 0 | G 287 3 0 | NA | |
| TLR4 Asp299Gly 896A/G | Soriano-Sarabia et al.[48] 2008 Spain Spanish | A 182 1 0 | G 168 2 0 | NA | NS |
| TLR4 Thr399Ile 1196C/T | Vidyant et al.[55] 2018 India Indian | T 334 1 0 | A 337 2 0 | NA | NS |
| TLR7 Gln11Leu (A/T) 1207A/G | Oh et al.[49] 2009 German Germany | A 320 1 0 | G 318 2 0 | NA | NS |
| TLR7 Ala448Val A1G 1363C/T | Shaikh et al.[58] 2019 India Indian | A 325 1 0 | G 322 2 0 | NA | NS |
| TLR7 T-120G | Shaikh et al.[58] 2019 India Indian | T 320 1 0 | G 318 2 0 | NA | NS |
| TLR7 A/G rs-Not allotted | Shaikh et al.[58] 2019 India Indian | A 320 1 0 | G 318 2 0 | NA | NS |
| TLR8 A1G rs3764880 | Oh et al.[55] 2008 German Germany | A 320 1 0 | G 318 2 0 | NA | NS |
| TLR9 1486C/T | Joshi et al.[62] 2019 America American | A 320 1 0 | G 318 2 0 | NA | NS |
| HIV = human immunodeficiency virus, HWE = Hardy-Weinberg equilibrium, NA = not available, NS = not significant, SNP = single nucleotide polymorphism. |
3.7. Publication bias

Based on symmetrical funnel plots analysis of TLR9 rs352140, no evidence of publication bias was observed (Fig. 6). Owing to the limited number of included studies, funnel plots analysis of TLR7 rs179008 was not performed.

4. Discussion

It is well known that HIV can attack the human immune system and then cause chronic activation of the immune system in association with dysfunction of cellular and humoral immune responses and failure to effectively control virus replication.\cite{154,154} Considerable variability exists among individuals in their susceptibility to HIV infection and subsequent clinical findings. Genetic variants of TLRs may influence susceptibility of HIV infection and disease outcome. To better understand the relationship between TLRs and HIV infection, we performed this systematic review.

In the present study, we totally pooled 10 articles, some of which have been proved TLR polymorphisms associated with HIV infection and clinical findings. For example, Vidyant et al has successive reported TLR2 –196 to –174 Ins/Del (Del mutant genotype, allele) and TLR4 rs4986790 (heterozygous genotype and the mutant allele G) were associated with HIV infection.\cite{154,154} A study performed on an Indian cohort study showed that TLR7 rs2074109 may have role in association with HIV infection.\cite{154} Meanwhile, in this Indian cohort study also reported TLR7 rs179008 were not associated with HIV infection, which is the opposite of the conclusion of the Germany cohort.\cite{154} The reason for this contradictory result may be due to the different ethnicity. In our study, we found TLR7 rs179008 polymorphism may be associated with increased HIV infection, which is consistent with a previous study.\cite{154} We found TLR7 rs179008 on T allele was the risk factor for HIV infection. Subsequently, significant association of TLR7 rs179008 polymorphism with HIV infection was identified in the dominant model and heterozygote model. Although the relationship between TLR9 rs352140 and HIV infection has not been studied in these articles, we found the TLR9 rs352140 GG genotype was a risk factor for HIV infection by meta-analysis. The authenticity of our meta-analysis results was verified by TSA and FPRP.

Much of the data comes from genetic analysis of populations that have an extreme phenotype in the clinical findings of HIV-1 infection, including viral load, CD4/CD8 cell counts, and disease progression. During the course of immune activation, activated T cells are produced as viral targets, further driving viral replication, and CD4 cell depletion. Immune activation and the above clinical findings are closely related in HIV-infected subjects. Genetic variants of the TLR gene are thought to regulate immune activation in HIV infection. Vidyant et al found that TLR2 Del homozygous genotypes were lower in low CD4 T-cell counts as compared to high CD4 T-cell counts and is associated with reduced risk of HIV-1 disease progression.\cite{154} The TLR7 rs179008 and TLR9 rs352140 polymorphism are the most frequently studied in clinical findings of HIV infection. TLR7 rs179008, TLR9 rs352140 were linked to the high viral loads and

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### Table 2
Newcastle-Ottawa Scale (NOS) quality assessment of included articles.

| Author            | Year | Selection score (4 Points) | Comparability score (2 Points) | Outcome score (3 Points) | Total score (9 Points) |
|-------------------|------|----------------------------|-------------------------------|--------------------------|------------------------|
| Soriano-Sarabia et al\cite{54} | 2008 | 4                          | 2                             | 1                        | 7                     |
| Oh et al\cite{49}  | 2008 | 4                          | 2                             | 2                        | 8                     |
| Oh et al\cite{50}  | 2008 | 4                          | 2                             | 2                        | 8                     |
| Huik et al\cite{57} | 2013 | 3                          | 2                             | 3                        | 8                     |
| Said et al\cite{59} | 2016 | 4                          | 2                             | 3                        | 8                     |
| Vidyant et al\cite{55} | 2017 | 4                          | 2                             | 2                        | 8                     |
| Vidyant et al\cite{56} | 2018 | 4                          | 2                             | 2                        | 8                     |
| Joshi et al\cite{58} | 2019 | 4                          | 2                             | 2                        | 8                     |
| Shaikh et al\cite{61} | 2019 | 4                          | 2                             | 2                        | 8                     |

Selection Score including; (1) Representativeness of the exposed cohort; (2) Selection of the nonexposed cohort; (3) Ascertainment of exposure; (4) Demonstration that outcome of interest was not present at start of study. Outcome Score including; (1) Assessment of outcome; (2) Was follow-up long enough for outcomes to occur; (3) Adequacy of follow up of cohorts.

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### Table 3
Meta-analysis of the association between TLR7, TLR9 polymorphisms, and HIV infection.

| SNP         | Included studies | Genetic model | OR  | 95%CI   | I² (%) | P_h | Z   | P_A |
|-------------|------------------|---------------|-----|---------|--------|-----|-----|-----|
| TLR7 Gln111Leu rs179008 (A>T) | 3                | Allelic (T vs. A) | 1.25 | 1.04–1.50 | 41     | 0.18 | 2.42 | 0.02 |
|             | 3                | Dominant (TT vs. AA) | 1.32 | 1.03–1.70 | 0      | 0.40 | 2.20 | 0.03 |
|             | 3                | Recessive (TT vs. TA+AA) | 1.17 | 0.90–1.53 | 5      | 0.35 | 1.19 | 0.23 |
|             | 3                | Homozygote (TT vs. AA) | 1.20 | 0.92–1.57 | 0      | 0.34 | 1.37 | 0.17 |
|             | 3                | Heterozygote (TA vs. AA) | 2.21 | 1.2–4.07 | 0      | 0.81 | 2.56 | 0.01 |
| TLR9 1635G/A rs352140 (G>A) | 4                | Allelic effect (G vs. A) | 1.19 | 0.99–1.43 | 0      | 0.54 | 1.80 | 0.07 |
|             | 4                | Dominant (GG vs. GA+AA) | 1.21 | 0.89–1.64 | 0      | 0.56 | 1.22 | 0.22 |
|             | 4                | Recessive (GG vs. GA+AA) | 1.30 | 0.95–1.77 | 0      | 0.43 | 1.61 | 0.11 |
|             | 4                | Homozygote (GG vs. AA) | 1.50 | 1.01–2.21 | 0      | 0.46 | 2.03 | 0.04 |
|             | 4                | Heterozygote (GG vs. AA) | 1.19 | 0.86–1.64 | 0      | 0.78 | 1.04 | 0.30 |

Cl = confidence interval, OR = odd ratio, P_h = adjusted P value (P_h < .05 means statistically significant), P_A = P value of heterogeneity, SNP = single nucleotide polymorphism.
lower CD4 T-cell counts in Germany, Spanish, American cohort respectively.\textsuperscript{[43,44,58]} However, above results were in contrast to findings of Said et al.\textsuperscript{[57]} These inconsistent findings may be due to ethnicity, sample size, or sampling error. Therefore, we need more research to expand the sample size for meta-analysis and ethnicity subgroup analysis to get more reliable conclusions.

Figure 2. Forest plot of the association between TLR7 rs179008 and HIV infection for all five models. (A) Allelic model; (B) Homozygote comparison; (C) Heterozygote comparison; (D) Dominant model; (E) Recessive model.
HIV pathogenesis is a multifactorial and complex phenomenon and the large portion of variability in the natural history of HIV remains unexplained and influence disease outcome are still largely unknown. For example, we all know that AIDS patients with low immunity often tend to have tumors. HIV-AIDS is the most common cause of acquired immune deficiency syndrome and the most important risk factor for the malignant lymphoma. The majority of HIV-related lymphomas originate from germinal center B cells or post-germinal center B cells.[61] In the last years, experimental and clinical studies have shown that chronic inflammation, immune stimulation/deregulation, and oxidative stress are involved in the lymphomagenesis/lymphoproliferative disorders. The chronic inflammation transcription factor NF-κB activation - inflammatory cytokines release - ROS generation - oxidative stress - genomic instability - clonal evolution link.[62] The results of Amelia Maria Gaman et al suggest that oxidative stress may be associated with the stage of advanced diffuse large B cell lymphoma.[63] Oxidative stress is involved in a variety of

Figure 3. Trial sequential analysis for TLR7 rs179008 polymorphism under the allele contrast model.
Figure 4. Forest plot of the association between TLR9 rs352140 and HIV infection for all five models. (A) Allelic model; (B) Homozygote comparison; (C) Heterozygote comparison; (D) Dominant model; (E) Recessive model.
human diseases and disorders, including apoptosis and carcinogenesis. The antioxidant capacity of the human body decreases with age.\textsuperscript{[64]} Therefore, the link between the HIV infection and lymphomagenesis/lymphoproliferative disorders can also be mediated by chronic inflammation and oxidative stress. It may also be related to the pathogenic properties of the virus itself, environmental factors, rare genetic variants, and other immune factors. The differences between studies may also reflect the variable nature of HIV infection among genetically different individuals. It is clear that the function and impact of genetic polymorphisms differ according to race and ethnicity. The risk of transmission and progression depends on multiple interactions between virus and host, and no single genetic variant is a crucial factor in HIV pathogenesis.
As per our knowledge, this is the first and the most comprehensive systematic review about TLR polymorphisms association with HIV infection. Moreover, most of included studies had acceptable quality and had no significant heterogeneity. However, there were also some limitations in our study that should be considered when explaining the present results. First, because only a relatively small number of studies have investigated the roles of TLR polymorphisms in HIV infection, the number of studies included in the systematic review lacked of sufficient data to detect associations within ethnic groups. Future research with diverse demographic and clinical characteristics is necessary in ethnically diverse populations. Second, analysis was only based on genotyping data. It is impossible for only single genetic polymorphism to significantly contribute to the occurrence and development of this disease. Lastly, limiting the study to English language articles may have potentially led to a language bias.

5. Conclusions
In summary, this systematic review aimed to summarize the effects of the most commonly investigated TLR SNPs in relation to HIV infection. Our results suggested that TLR7 rs179008 T allele is the risk of HIV infection. TLR9 rs352140 GG genotype may associate with increasing HIV infection. Our study may have implications for the individual risk assessment of patients infected with HIV, meanwhile, this results is benefit to identify new targets for HIV preventative and therapeutic interventions.
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References
[1] Cohen DE, Walker BD. Human immunodeficiency virus pathogenesis and prospects for immune control in patients with established infection. Clin Infect Dis 2001;32:1756–68.
[2] Goh WC, Markoe J, Akridge RE, et al. Protection against human immunodeficiency virus type 1 infection in persons with repeated exposure: evidence for T cell immunity in the absence of inherited CCR5 coreceptor defects. J Infect Dis 1999;179:548–57.
[3] Plummer FA, Ball TB, Kimani J, et al. Resistance to HIV-1 infection among highly exposed sex workers in Nairobi: what mediates protection and why does it develop? Immunol Lett 1999;66:27–34.
[4] Mazzoli S, Trabattoni D, Lo Caputo S, et al. HIV-speciﬁc mucosal and cellular immunity in HIV-seronegative partners of HIV-seropositive individuals. Nat Med 1997;3:1250–7.
[5] Buchbinder S, Vittinghoff E. HIV-infected long-term nonprogressors: epidemiology, mechanisms of delayed progression, and clinical and research implications. Microbes Infect 1999;1:1113–20.
[6] Gao Y, Qin L, Zhang L, et al. Virologic and immunologic characterization of long-term survivors of human immunodeficiency virus type 1 infection. N Engl J Med 1995;332:201–8.
[7] Pereyra F, Addo MM, Kaufmann DE, et al. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. J Infect Dis 2008;197:563–71.
[8] Buchbinder SP, Katz MH, Hessol NA, et al. Long-term HIV-1 infection without immunologic progression. AIDS 1994;8:1123–8.
[9] Mclaren PJ, Coulouge C, Bartha L, et al. Polymorphisms of large effect explain the majority of the host genetic contribution to variation of HIV-1 viral load. Proc Natl Acad Sci U S A 2015;112:14658–63.
[10] Dean M, Carrington M, Winkler C, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science 1996;273:1856–62.
[11] Winkler C, Modi W, Smith MW, et al. Genetic restriction of AIDS from HIV-1-infected patients failing antiretroviral therapy. Intervirology 2009;52:107–14.
[12] Zhou Y, Wang X, Liu M, et al. A critical functional of toll-like receptor-3 in the induction of anti-human immunodeficiency virus activities in macrophages. Immunology 2010;131:40–9.
[13] Miller Sanders C, Cruse JM, Lewis RE. Toll-like receptor and chemokine receptor expression in HIV-infected T lymphocyte subsets. Exp Mol Pathol 2010;88:26–31.
[14] Cheng JY, Luas A, Lindsay R, et al. Differential regulation of toll-like receptor pathways in acute and chronic HIV-1 infection. AIDS 2012;26:533–4.
[15] Schlaepfer E, Audige A, Joller H, et al. TLR7/8 triggering exerts opposing effects in acute versus latent HIV infection. J Immunol 2006;176:2888–95.
[16] Schlaepfer E, Speck RF. TLR8 activates HIV from latently infected cells of myeloid-monocytic origin directly via the MAPK pathway and from latently infected CD4+ T cells indirectly via TNF-alpha. J Immunol 2011;186:4314–24.
[17] Beima-Sofie KM, Bigham AW, Lingappa JR, et al. Toll-like receptor variants are associated with infant HIV-1 acquisition and peak plasma HIV-1 RNA level. AIDS 2013;27:2431–9.
[18] Bochud PY, Hersberger M, Taffe P, et al. Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection. AIDS 2007;21:441–6.
[19] Mackelprang RD, Bigham AW, Celum C, et al. Toll-like receptor polymorphism associations with HIV-1 outcomes among sub-Saharan Africans. J Infect Dis 2014;209:1623–7.
[20] Pine SO, McElrath MJ, Bochud PY. Polymorphisms in toll-like receptor 4 and toll-like receptor 9 influence viral load in a seroconvert cohort of HIV-1-infected individuals. AIDS 2009;23:2387–95.
[21] Srinivasan-Sarabia N, Vallesio A, Ramirez-Lorca R, et al. Influence of the Toll-like receptor 9 1635A/G polymorphism on the CD4 count, HIV viral load, and clinical progression. J Acquir Immune Defic Syndr (1999) 2008;49:128–35.
[22] Oh DY, Baumann K, Hamouda O, et al. A frequent functional toll-like receptor 7 polymorphism is associated with accelerated HIV-1 disease progression. AIDS 2009;23:297–307.
[23] Oh DY, Taube S, Hamouda O, et al. A functional toll-like receptor 8 variant is associated with HIV disease restriction. J Infect Dis 2008;198:701–9.
[46] Ricci E, Malacrida S, Zanchetta M, et al. Toll-like receptor 9 polymorphisms influence mother-to-child transmission of human immunodeficiency virus type 1. J Transl Med 2010;8:49.

[47] Wells GB, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses; 2018. doi: 10.1007/s11596-015-1405-6.

[48] Thakkinstian A, McEvoy M, Minelli C, et al. Systematic review and meta-analysis of the association between (beta2-adrenoceptor polymorphisms and asthma: a HuGE review. Am J Epidemiol 2005;162:201–11.

[49] Wacholder S, Chanock S, Garcia-Closas M, et al. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 2004;96:434–42.

[50] Higgins JPT, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[51] Vidyant S, Chatterjee A, Agarwal V, et al. Susceptibility to HIV-1 infection is influenced by toll-like receptor-2 (-196 to -174) polymorphism in a North Indian population. J Gene Med 2017;19: doi:10.1002/jgm.2971.

[52] Vidyant S, Chatterjee A, Dhole TN. A single-nucleotide polymorphism in TLR4 is linked with the risk of HIV-1 infection. Br J Biomed Sci 2019;76:59–63.

[53] Huik K, Avi R, Pauskar M, et al. Association between TLR3 rs3775291 and resistance to HIV among highly exposed Caucasian intravenous drug users. Infect Evol 2013;20:78–82.

[54] Shaikh N, Nirmalkar A, Thakar M. Polymorphisms in toll-like receptors (TLRs)-7 and 9 genes in Indian population with progressive and nonprogressive HIV-1 infection. AIDS Res Hum Retroviruses 2019; doi:10.1089/AID.2019.0004.

[55] Joshi A, Sedano M, Beauchamp B, et al. HIV-1 Env glycoprotein phenotype along with immune activation determines CD4+ T cell loss in HIV patients. J Immunol 2016;196;1768–79.

[56] Gaman AM, Gaman MA. A diffuse large B cell lymphoma (DLBCL) with central nervous system involvement in a HIV positive patient. La Prensa Medica Argentina 2015;101:5.

[57] Gaman AM, Moisa C, Diaconu CC, et al. Crosstalk between oxidative stress, chronic inflammation and disease progression in essential thrombocythemia. Rev Chim 2019;70:3486–9.

[58] Gaman AM, Buga AM, Gaman MA, et al. The role of oxidative stress and the effects of antioxidants on the incidence of infectious complications of chronic lymphocytic leukemia. Oxid Med Cell Longev 2014;2014:158135.