Genetic association of co-trimoxazole-induced severe cutaneous adverse reactions is phenotype-specific: HLA class I genotypes and haplotypes

Running title: *HLA* class I associated with co-trimoxazole-induced severe cutaneous reactions

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ABSTRACT

Co-trimoxazole (CTX) causes various forms of severe cutaneous adverse reactions (SCARs). This case-control study was conducted to investigate the involvement between genetic variants of human leukocyte antigen (*HLA*) and *CYP2C9* in CTX-induced SCARs, including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) in Thai patients. Thirty cases of CTX-induced SCARs were enrolled and compared with 91 CTX-tolerant controls and 150 general Thai population. Cases comprised 18 SJS/TEN and 12 DRESS patients. This study demonstrated that genetic association of CTX-induced SCARs was phenotype-specific. *HLA-B*15:02* and *HLA-C*08:01* alleles were significantly associated with CTX-induced SJS/TEN, whereas the *HLA-B*13:01* allele was significantly associated with CTX-induced DRESS. In addition, a significant higher frequency of *HLA-A*11:01-B*15:02* and *HLA-B*13:01-C*03:04* haplotypes were detected in the group of CTX-induced SJS/TEN and DRESS cases, respectively. Genetic association of co-trimoxazole-induced severe cutaneous adverse reactions is phenotype-specific. Interestingly, these association was observed only in HIV infected patients but not in non-HIV-infected patients.

Keywords: Co-trimoxazole, Pharmacogenomics, HLA, SCARs, SJS, DRESS, Thai

Introduction

Co-trimoxazole (CTX), a combination of sulfamethoxazole and trimethoprim, sequentially blocks bacterial folate synthesis.[1] CTX is useful in the treatment of a variety of bacterial, fungal, and protozoal infections.[2, 3] The World Health Organization (WHO) have recommended the use of CTX prophylaxis in infants, children, and adolescents with HIV to prevent opportunistic infections.[4] However, CTX is associated with severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and fixed drug eruption (FDE).[5-8] Sulfamethoxazole is metabolized to sulfamethoxazole hydroxylamine, which is further oxidized to nitrosulfamethoxazole. Nitrosulfamethoxazole binds covalently to host proteins, eliciting an IgE and/or a T cell mediated response to modified proteins manifesting in different forms of drug hypersensitivity.[9]

Human leukocyte antigen (HLA) is the human major histocompatibility complex responsible for presentation of processed peptide antigens to T cells to initiate the adaptive immune response.[10] There are three regions of the human MHC: class I region consists of *HLA-A*, *HLA-B*, and *HLA-C* genes, class II region consists of *HLA-DR*, *HLA-DQ*, and *HLA-DP* genes, and class III region, which does not encode HLA molecules, consists of genes for complement components (C2, C4, factor B), 21-hydroxylase, tumor necrosis factors (TNFs), and others.[11] Several *HLA* alleles have been reported to be associated with CTX-induced SCARs. A recent case-control study in the Thai population reported an association between CTX-induced

SJS/TEN and *HLA-B*15:02* (odds ratio [OR] = 3.91 [95% confidence interval [CI]: 1.42-10.92], *P*=0.0037), *HLA-C*06:02* (OR = 11.84 [95% CI: 1.24-566.04], *P*=0.0131) and *HLA-C*08:01* (OR = 3.53 [95% CI: 1.21-10.40], *P*=0.0108).[12] In European patients the presence of *HLA-B*38* was significantly associated with sulfamethoxazole-related SJS/TEN, but the different allelic variants of *HLA-B*38* did not show significant association with sulfamethoxazole-related SJS/TEN.[13] Additionally, a strong association between SJS/TEN and trimethoprim alone was observed. (OR = 9.44, 95%CI = 3.83-23.25)[14]. This finding suggests that not only most common culprit sulfamethoxazole but also trimethoprim induce SJS/TEN in patients. A retrospective genome-wide association study (GWAS) in European subjects did not find any single-nucleotide polymorphisms (SNPs) with genome-wide significance when CTX-induced SJS/TEN cases were compared with controls.[15] Highly polymorphic gene, CYP2C9 is a key factor in enzyme activity variation in various drug once this variant occurred. Recently, Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends guidelines for *CYP2C9* and HLA-B Genotype and Phenytoin Dosing[16]. There was the report of *CYP2C9*3* association to phenytoin-induced SCARs in Thai epileptic children with odd ratio = 14.52 (95% CI = 1.18–∞, P-value = 0.044).[17] However, no study on the association between *CYP2C9* and co-trimoxazole was performed.

Until now, although one study has reported the association of *HLA* alleles and CTX-induced SJS/TEN in the Thai population, there are no data on the association with other SCAR phenotypes such as DRESS. In the present study, our aim was to identify and compare the HLA alleles associated with CTX-induced SJS/TEN and DRESS in Thai patients.

Materials and Methods

Patient recruitment

For our study, we included a total of 30 patients with CTX-induced SCARs (18 males and 12 females). These patients were admitted to the hospital for treatment of CTX-induced SCARs between 2014 and 2017 and were prospectively enrolled in our study. The patients recruited in the present study are different from those previously reported by Kongpan *et al.*[13]

The RegiSCAR criteria were used to diagnose and classify SCARs,[18, 19] and a dermatologist and allergist confirmed the diagnoses based on the photographs, pathological slides, clinical morphology, and medical records. SJS was defined as a mucocutaneous disorder characterized by skin rash and skin detachment affecting <10% of the body surface area. TEN was defined as skin detachment >30%. SJS-TEN overlap was defined as skin detachment of 10% to 30%. DRESS was characterized by acute skin rash, fever above 38°C, enlarged lymph nodes, internal organ involvement, and hematological abnormalities, including lymphocytosis or lymphocytopenia, eosinophilia, and thrombocytopenia. We evaluated co-trimoxazole was the causative drug of SJS/TEN or DRESS using Naranjo algorithm,[20] the score of the algorithm of drug causality for epidermal necrolysis (ALDEN)[21] and DRESS score. The cases defined as possible, probable and definite were recruited in this study. In some cases, *in vitro* assay (such as ELISpot) was performed. Two groups of control were used in the present study: 91 CTX-tolerant patients (which are the same group as previously reported by Kongpan *et al*.[13]) and 150 healthy Thai subjects which obtained from five regional groups of unrelated healthy Thai individuals. The individuals lived in the abovementioned regions for more than three generations[22].

This study was approved by the Ramathibodi Hospital Ethical Review Board, and the Khon Kaen Ethics Committee for Human Research, Khon Kaen University, Thailand. Written informed consent was obtained from all the participants.

HLA-A, -B and -_C_ alleles genotyping

For all the study subjects, DNA extraction using MagNAPure Compact Nucleic Acid Isolation kits was performed based on magnetic-bead technology (Roche Applied Science, Mannheim, Germany). DNA was aliquoted and stored at -20^{O}C before HLA typing. Genotyping of *HLA-A*, *-B* and *-C* alleles were determined by the polymerase chain reaction with sequence-specific oligonucleotide probes (PCR-SSOP) hybridization method using Luminex®IS 100 system (Luminex Corporation, Austin, Texas, USA) with well-established protocols.

CYP2C9 genotyping

The *CYP2C9* variant alleles are routinely tested include CYP2C9*2 and*3 , *CYP2C9*2 (430C>T, rs1799853)* and *CYP2C9*3 (1075A>C, rs1057910)* were genotyped by pre-designed TaqMan® SNP genotyping assays using sequence primers and TaqMan MGB probes of *CYP2C9*2* (assay ID: C_25625805_10) and *CYP2C9*3* (assay ID: C_27104892_10) (Applied Biosystems, Foster City, CA).

Statistical analysis

Statistical analyses were performed using SPSS statistical software package, version 18 (SPSS Inc, Chicago, IL). To detect differences in the demographic of study population, an independent t-test was used for continuous variables. The ORs with corresponding 95% CIs were calculated to determine the association between the presence of the HLA loci and CTX-induced SCARs. Fisher's exact test was used to compare allele frequencies between cases and controls. Bonferroni correction was applied to adjust for multiple comparisons. *P*-values < 0.05 (two-sided) indicated a statistical significance.

In this study, we pooled data from a previous study by Kongpan et al.[13] and the present study and compared the frequencies of *HLA* alleles in CTX-SJS/TEN cases and tolerant controls. Haplotype association analysis was carried out using the “haplo.stats” package.

Results

The demographic data of all the case are shown in Table 1. Our cohort comprised 13 (43.33%) cases of CTX-induced SJS, 4 (13.33%) cases of CTX-induced TEN, 1 (3.33%) case of CTX-induced SJS/TEN overlap, and 12 (40.00%) cases of CTX-induced DRESS (a total of 30). The mean age of co-trimoxazole hypersensitive patients was 40.90±13.94 and 60.00% were male. Most cases received CTX for prophylactic use among HIV-infected persons. There were no significant differences in gender, age, indication of drug administration, onset of reaction and co-morbidity.

Mucosal involvement including eye, oral and genital mucosa, abnormal liver and renal function test were observed in SCARs patients (Table S1). Nine cases received monotherapy with CTX while the other 21 cases received concomitant medications. For 9 individuals, the CTX dose administered were not available in their medical records. Among 30 CTX-related SCARs, we found no *CYP2C9*2* and **3* alleles which possibly interpreted as *CYP2C9*1/*1* (extensive metabolizer; EM) base on the frequency of this genotype in study population. The genotypes of *HLA-A*, *HLA-B*, *HLA-C* and *CYP2C9* in the 30 cases with CTX-induced SCARs are shown in Table 2.

Association of all CTX-induced SCARs with *HLA* alleles

We compared the carrier frequencies of the *HLA* class I alleles in the 30 CTX-induced SCARs cases with the 91 CTX-tolerant controls and 150 healthy Thai population controls. The results are summarized in Table 3.

*HLA-B*13:01* was observed in 43.33% (13/30) of cases, 16.48% (15/91) of tolerant controls, and 15.33% (23/150) of healthy controls. *HLA-B*15:02* was observed in 30.00% (9/30)

of cases, 10.99% (10/91) of tolerant controls, and 18.00% (27/150) of healthy controls. *HLA-B*13:01* and *HLA-B*15:02* were significantly overrepresented in patients with CTX-induced SCARs as compared to CTX-tolerant controls with ORs of 3.88 (95% CI = 1.56-9.63, *P*=0.0025) and 3.47 (95% CI = 1.25-9.63, *P*=0.0201), respectively. Of the other HLA alleles, *HLA-A*11:01* allele showed the most significant association with CTX-induced SCARs cases with an OR of 3.25 (95% CI = 1.34-7.89, *P*=0.0073). The frequency of *HLA-A*02:07* allele was significantly decreased among the CTX-induced SCARs cases and was thus designated protective allele. *HLA-C*07:27* and *HLA-C*08:01* were also significantly associated with CTX-induced SCARs compared to CTX-tolerant controls with ORs of 31.08 (95% CI = 1.62-595.88, *P*=0.0032) and 3.91 (95% CI = 1.38-11.06, *P*=0.0149), respectively.

Haplotype analysis revealed that only the frequencies of the *HLA-A*11:01-B*15:02* and *HLA-B*13:01-C*03:04* haplotypes in the CTX-induced SCAR group were significantly different from those in the control groups. The OR for CTX-induced SCARs among patients with the *HLA-A*11:01-B*15:02* haplotype was 4.36 (95% CI = 1.43–13.34, *P*= 0.0108), whereas the OR among those with the *HLA-B*13:01-C*03:04* haplotype was 3.77 (95% CI = 1.27–11.19, *P*=0.0251). However, the significant associations of the HLA alleles and haplotypes disappeared after corrections for multiple testing ($P < 0.0025$).

Association of CTX-induced DRESS and *HLA* alleles

We compared the carrier frequencies of *HLA* class I alleles in the 12 CTX-induced DRESS patients, in 91 CTX-tolerant controls, and in 150 healthy Thai population controls. The results are summarized in Table 4 (only the alleles and haplotypes of *HLA* that showed a significant association when compared with the CTX-tolerant controls and/or healthy population controls) are shown.

As shown in Table 4, four alleles were significant in the CTX-induced DRESS group: *HLA-A*11:01, HLA-B*13:01, HLA-C*03:04,* and *HLA-C*07:27*. Only the *HLA-B*13:01* allele reached statistical significance after Bonferroni correction (75.00% versus 16.48%, P = 7.2×10^{-5}, OR = 15.20, 95% CI = 3.68–62.83).

Haplotype analysis revealed that the carrier rate of *HLA-B*13:01-C*03:04* haplotype was significantly higher among patients with CTX-induced DRESS as compared to the CTX-tolerant controls (OR = 14.53, 95% CI = 3.74-56.47, *P* = 1.8×10^{-4}).

Association of CTX-induced SJS/TEN and *HLA* alleles

We compared the carrier frequencies of *HLA* class I alleles in the 18 CTX-induced SJS/TEN patients, 91 CTX-tolerant controls, and 150 healthy Thai population controls. The results are summarized in Table 5 (only the alleles and haplotypes of *HLA* are shown that showed a significant association when compared with the CTX-tolerant controls and/or healthy population controls).

None of *HLA-A* alleles were significantly associated with CTX-induced SJS/TEN. Interestingly, we identified an increased frequency of *HLA-A*02:07* and *HLA-A*33:03* alleles in the controls as compared to the CTX-induced SJS/TEN cases.

A strong association between *HLA-B*15:02* and CTX-induced SJS/TEN was confirmed with an OR of 5.16 (95% CI = 1.63–16.33, *P* = 0.0075). The *HLA-B*38:02* allele which was observed in 33.33% (6/18) of CTX-induced SJS/TEN cases showed statistically significant difference. (OR = 4.05, 95% CI = 1.25-13.18, P = 0.0249).

We found that *HLA-C*08:01* allele was detected more frequently in cases, with 7 of 18 CTX-induced SJS/TEN possessing *HLA-C*08:01* allele versus 9 of 91 of the CTX-tolerant controls (OR = 5.79, 95% CI = 1.79-18.70, *P* = 0.0049). In addition, we also found a significant

association between *HLA-C*07:27* allele and CTX-induced SJS/TEN with OR of 27.73 (95% CI = 1.27-604.11, P = 0.0259).

The *HLA-A*11:01-B*15:02* haplotype was found with a higher frequency in CTX-induced SJS/TEN patient group than in CTX-tolerant control group (33.33% versus 7.69%, *P* = 0.0074, OR = 6.00, 95% CI = 1.72–20.88).

Association of CTX-induced SCARs and *HLA* alleles among the different subgroup.

In subgroup analysis of HIV patients, 23 patients in case and 61 patients in tolerant group were analyzed. The significant association between *HLA* class I and CTX-induced SCARs was shown in Table 6. For DRESS group, 9 patients in case and 61 patients in tolerant group were analyzed. The *HLA-A*11:01*, *HLA-B*13:01* and *HLA-C*07:27* were statistically associated with CTX-induced DRESS with OR of 5.78, 95% CI = 1.11-30.25, P = 0.0376, OR of 11.55, 95% CI = 2.44-54.78, P = 0.0021 and OR of 41.00, 95% CI = 2.44-54.78, P = 0.0200, respectively. Furthermore, HIV patients was carried out in 14 patients in SJS/TEN case and 61 patients in tolerant group. The *HLA-B*15:02* and *HLA-B*38:02* showed significant difference with CTX-induced SJS/TEN (OR = 5.09, 95% CI = 1.28-20.25, P = 0.0208, OR = 8.40, 95% CI = 2.07-34.03, P = 0.0029, respectively). Additionally, the association between *HLA-C*07:27* and *HLA-C*08:01* and CTX-induced SJS/TEN was also observed with OR of 24.60 (95% CI = 1.11-544.28, P = 0.0427 and OR of 10.74 (95% CI = 2.18-52.90, P = 0.0035, respectively. Whilst, there was no association between *HLA-A*, *B* and *C* alleles and CTX-induced SCARs in HIV-negative patients.

Pooled-data analysis

The allele frequencies of *HLA-A*11:02*, *HLA-B*15:02* and *C*08:01* in CTX-induced SJS/TEN and tolerant controls are shown in Table 7 after pooling our results with those obtained

by Kongpan e*t al*. The frequency of *HLA-B*15:02* and *HLA-C*08:01* in CTX-SJS/TEN were significantly higher than the frequency found in tolerant controls (OR = 4.25, 95% CI = 1.83-9.88, *P* = 0.0008 and OR = 4.12, 95% CI = 1.72-9.90, *P* = 0.0015, respectively). Nevertheless, no significant difference was observed when the frequency of *HLA-A*11:02* was compared between CTX-SJS/TEN cases and tolerant controls (OR = 1.64, 95% CI = 0.86-3.16, *P* = 0.1361).

In subgroup analysis of HIV-positive patients, two HLA alleles, *HLA-B*15:02* and *C*08:01* were significantly associated with CTX-SJS/TEN with OR of 5.77 (95%CI = 2.04-16.30, P = 0.0009) and 11.05 (95%CI = 2.97-41.07, P = 0.0003), respectively. Whilst, there was no association between *HLA-A*11:01*, *HLA-B*15:02* and *HLA-C*08:01* and CTX- induced SCARs in HIV-negative patients (data not shown).

Discussion

SJS, TEN, and DRESS are potentially fatal SCARs affecting multiple organs and systems, and CTX has been implicated as a trigger for these adverse drug reactions.[23, 24] The hypersensitivity reaction should be occurred approximately 2 to 7 weeks after first exposure. The previous studies presented the range of drug exposure time of CTX patients was 1 to 74 days.[12] However, some of our patients appear to be outside of a recognized window of drug exposure. The latency was more than 7 weeks. Several studies have provided evidences of the genetic predisposition to SCARs in various populations.[25] In this study, we examined HLA risk factors for CTX-induced SCARs among Thai patients. We identified that carriers of *HLA-B*15:02* and *HLA-C*08:01* alleles are significantly more likely to develop SJS/TEN, while the *HLA-B*13:01* allele was associated with an increased risk of developing DRESS in patients taking CTX. None of the *HLA-A* alleles showed a significant association with CTX-induced SCARs. The haplotype

297 analysis revealed a significant increase in the frequency of *HLA-A*11:01-B*15:02* and *HLA-*
298 *B*13:01-C*03:04* haplotypes in the CTX-induced SJS/TEN and DRESS cases, respectively.
299 However, the haplotype data was imputed by statistical program.

300 The association between the *HLA* class *I* and *HLA-DRB1* polymorphisms and CTX-
301 induced SJS/TEN was first reported in a Thai population by Kongpan *et al.* [12] in which they
302 demonstrated an increased frequency of *HLA-B*15:02*, *HLA-C*06:02*, and *HLA-C*08:01* in
303 CTX-induced SJS/TEN patients with risk being about 4-fold higher among patients with the
304 *HLA-B*15:02* or *HLA-C*08:01* alleles and 12 folds higher among patients with *HLA-C* 06:02*.[12]
305 In the present study, we replicated the association with *HLA-B*15:02* and *HLA-C*08:01* but not
306 with *HLA-C*06:02*. The *HLA-A*02:07* and *HLA-A*33:03* alleles were more common in the
307 controls than in cases suggesting that they may protect against the development of CTX-induced
308 SJS/TEN in Thai patients. However, these alleles did not reach statistical significance after
309 Bonferroni correction ($P > 0.0025$).

310 *HLA-B*15:02* is primarily associated with carbamazepine-induced SJS/TEN in patients of
311 certain Asian ethnicities.[26] Interestingly, our study provides evidence that same HLA allele may
312 predispose to SJS/TEN caused by either carbamazepine or CTX. It should be noted that *HLA-*
313 *C*08:01* was the only allele significantly associated with SJS/TEN after Bonferroni's correction
314 for multiple comparisons in the previous study by Kongpan et al.[12] In our present study, *HLA-*
315 *C*08:01* allele showed a significant association with SJS/TEN, suggesting that this allele may

316 also have a role in SJS/TEN induced by CTX. Whether *HLA-C*08:01* is a clinically relevant
317 marker for CTX-induced SJS/TEN need to be investigated in other populations.

318 The carrier frequency of the *HLA-B*13:01* allele in CTX-induced SCAR cases did not
319 differ significantly from the tolerant controls after corrections for multiple testing (P >0.0025).
320 However, *HLA-B*13:01* showed a significant association with CTX-induced DRESS (P
321 <0.0025). This observation suggests that *HLA-B*13:01* is a risk factor that is specific for CTX-
322 induced DRESS. It indicates that the individual phenotypes do not share the same risk locus in
323 the HLA system. The frequency of *HLA-C*03:04* allele was also significantly higher in CTX-
324 induced DRESS as compared to the healthy controls, and the haplotype analysis revealed a
325 significant increase in the frequency of the *HLA-B*13:01-C*03:04* haplotype in the DRESS
326 group. These haplotype results are different from the previous report in Thai population.[11] *HLA-*
327 *B*13:01* has convincingly been shown to be a risk factor for dapsone hypersensitivity syndrome
328 in Han Chinese and Thai populations.[27, 28] *HLA-B*13:01* has a well-defined sub-pocket within
329 the antigen-binding site which fits the dapsone molecule and potentially alters self-peptides upon
330 binding.[29] Given the structural similarities between sulfamethoxazole and dapsone, and in their
331 respective metabolic pathways, our finding of an association with *HLA-B*13:01* is thus
332 biologically plausible.

333 Nonetheless, *HLA-A* alleles; *HLA-A*11:01*, *HLA-A*11:02*, *HLA-A*31:01*, *HLA-A*33:03*,
334 *HLA-A*68:01* and *HLA-A*74:01* have shared peptide binding specificities[30] and 26 of 30 of the
335 cases carry one or more of these alleles. It is notable that immune response of drug interact to
336 HLA binding groove can be shared across HLA molecules with similar peptide binding

specificity[31]. In present study, seven patients (100%) who are reported HIV-negative carried *HLA-A*11:01*. Two of four HIV-negative patients with SJS/TEN have *HLA-B*15:02* and *HLA-C*08:01*, whereas three of three HLA-negative patients with DRESS patients also carried *HLA-B*13:01*. Interestingly, the association between *HLA* alleles and CTX-induced SCARs was found in HIV infected patients but not HIV-negative patients. It is possibly that HIV itself could be related to this association due to systemic reduction of glutathione in HIV-infected patients[32].

Pharmacological interaction of drugs with immune receptors, the so-called p-i concept has been proposed to explain how T cells can be stimulated by the interaction of sulfamethoxazole with T cell receptors (TCR), and resulting in clinical symptoms of drug hypersensitivity.[10,11] However, whether a specific T-cell function leads to a specific clinical phenotypes is unclear, and so further research is needed and should be based on well-characterized phenotypes and drug causality, considering the heterogeneity of T-cell function.[33] There is a theoretical possibility of cross-reactivity between sulfonamide antibiotics and non-antibiotic sulfonamides,[34] which has led precautionary advice in several countries.[35]

Some of the limitations of our study should be considered before interpreting the results. First, this research only studied the role of class I *HLA* alleles and *CYP2C9*, but not other HLA and drug metabolism enzyme genes and host factors. Apart from CYP2C9 enzyme, N-acetyltransferases and glutathione-S-transferases play important roles in sulfamethoxazole metabolism to reactive metabolites and toxicity detoxification, respectively[36,37]. Chang et al. reported that high daily doses of CTX were an independent risk factor for cutaneous and other ADRs.[38] We did not measure the serum concentrations of CTX, so it is possible that plasma and tissue concentrations of CTX might have influenced the adverse outcomes in our study. However, a previous case-control study by Pirmohamed et al. failed to demonstrate an

association between genetic polymorphisms in drug metabolizing enzymes with CTX hypersensitivity in HIV patients[39]. Nonetheless, the in vitro study on sulfamethoxazole hypersensitive patients demonstrated *HLA-DQ* plays a critical role in the activation of drug metabolite (SMX-NO)-specific CD4+ T cells. Further validation of other HLA and genetic polymorphisms in drug metabolism enzyme genes and host factors, or even *in vitro* study on drug specific T cells should be conducted. Second, there were few cases of CTX-induced SJS/TEN and DRESS. Nevertheless, despite limited power, we have identified phenotype-specific HLA associations, and present patient-level data for the SJS/TEN and DRESS cases in our study to allow for further replication. Third, there was evidence that a strong association between SJS/TEN and trimethoprim alone was found[14]. However, no *in vitro* or *in vivo* patch test was not performed to validate the culprit drug as sulfamethoxazole or trimethoprim in this study. The number needed to test to prevent one case of co-trimoxazole induced SCARs have been done in the study. The estimated number needed to test of *HLA-B*13:01*-induced CTX-DRESS and *HLA-B*15:02*-induced CTX-SJS/TEN was 23 and 31, respectively.

In conclusion, this study has highlighted the importance of HLA class I alleles or haplotypes in predisposing to evaluating their influence on the susceptibility to CTX-induced SCAR in Thai patients. Most importantly, our data indicates that the association with HLA class I alleles may be phenotype-specific. Of course, our data need further replication in larger numbers of patients and in different ethnic groups. Given the public health drive to prevent SCAR caused by drugs in Thailand through the use of genotyping, we need to consider whether the alleles identified in this study should be utilized in the future to prevent SCAR from CTX.

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Study Highlights

1. What is the current knowledge on the topic?
    - Until now, only one study reported the association of HLA alleles and CTX-induced SJS/TEN in Thai population.
    - The relationship between HLA alleles and CTX-induced SCARs remains unclear.
    - There is no published data on the genetic association with other SCAR phenotypes such as DRESS in Thai population.
2. What questions did this study address?
    - Which HLA genes are associate with CTX-induced SJS/TEN and DRESS?
    - Do they have different biomarkers in different CTX-induced manifestation?
3. What does this study add to our knowledge?
    - HLA-B*15:02 and HLA-C*08:01 alleles were significantly associated with CTX-induced SJS/TEN
    - The HLA-B*13:01 allele was significantly associated with CTX-induced DRESS.
    - In addition, a significant higher frequency of HLA-A*11:01-B*15:02 and HLA-B*13:01-C*03:04 haplotypes were detected in the group of CTX-induced SJS/TEN and DRESS cases, respectively
4. How might this change clinical pharmacology or translational science?
    - Genetic association of co-trimoxazole-induced severe cutaneous adverse reactions is phenotype-specific.

- Screening of the risk alleles is recommended for Thai patients before initiating CTX therapy.

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Supplementary Information

1. Table S1
2. Table S2

Table 1. Study population's demographics

	Co-trimoxazole hypersensitive patients (n=30)	Co-trimoxazole tolerant patients (n=91)
Type of SCARs n (%)		
SJS	13 (43.33)	0
TEN	4 (13.33)	0
SJS/TEN overlap	1 (3.33)	0
DRESS	12 (40.00)	0
Gender n (%)		
Male	18 (60.00)	54 (59.34)
Female	12 (40)	37 (40.66)
Age		
Mean±SD	40.90±13.94	45.31±12.28
Median (range)	41 (19-69)	45 (13-74)
Indication of drug administration n (%)		
HIV	23 (76.67)	61 (67.03)
Other diseases	7 (23.33)	30 (32.97)
Onset of reaction		
Mean±SD	23.88±15.82	0
Median (range)	17 (3-65)	0
Co-morbidity n (%)		
HIV	23 (76.67)	61 (67.03)
TB	3 (10.00)	2 (2.20)
Other diseases	4 (13.33)	19 (20.88)
No co-morbidity	3 (10.00)	17 (18.68)

SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; HIV, Human Immunodeficiency Virus; TB, tuberculosis.

Table 2. ***HLA class I*** **genotyping,** ***CYP2C9*** **and clinical data of Thai patients with co-trimoxazole-induced SCARs.**

No.	Sex/Age*	Type of SCAR	Indication for co-trimoxazole	*HLA class I* genotyping			*CYP2C9*
				HLA-A	*HLA-B*	*HLA-C*	
1	M/57	DRESS	HIV	*02:07/**11:01***	***13:01**/46:01*	*01:02/**03:04***	**1/*1*
2	F/21	DRESS	HIV	*24:02/24:02*	***13:01**/40:01*	***03:04/07:27***	**1/*1*
3	M/21	SJS	HIV	***11:01**/24:07*	***15:02/38:02***	***07:27**/08:01*	**1/*1*
4	M/29	SJS	HIV	***11:01**/32:01*	***15:02**/44:02*	*05:01/08:01*	**1/*1*
5	M/39	SJS	HIV	*02:03/74:01*	***13:01**/51:01*	*04:06/14:02*	**1/*1*
6	M/63	DRESS	HIV	***11:01**/11:01*	*07:05/**38:02***	*07:02/07:02*	**1/*1*
7	F/19	DRESS	N/A	***11:01**/33:03*	***13:01**/58:01*	*03:02/**03:04***	**1/*1*
8	F/30	SJS	HIV, Disseminated TB	***11:01**/33:01*	*44:03/58:01*	*03:02/07:01*	**1/*1*
9	M/52	SJS	HIV, HCV infection	***11:01**/31:01*	*35:03/**38:02***	*04:01/18:01*	**1/*1*
10	M/33	SJS	HIV, pulmonary TB	*02:02/24:02*	*46:01/48:01*	*01:02/08:03*	**1/*1*
11	M/48	TEN	HIV	*02:01/02:03*	***13:01/38:02***	***03:04/07:27***	**1/*1*
12	F/32	DRESS	HIV	***11:01**/24:02*	*15:01/40:01*	*04:01/04:03*	**1/*1*
13	F/23	SJS	HIV, pulmonary TB	***11:01/11:01***	*15:25/**38:02***	*04:03/07:02*	**1/*1*
14	M/20	DRESS	HIV	***11:01**/24:10*	***13:01**/18:02*	***03:04**/07:04*	**1/*1*
15	M/36	SJS	HIV	***11:01/11:01***	*07:05/**15:02***	*07:02/08:01*	**1/*1*
16	F/69	DRESS	HIV	*02:07/11:02*	***13:01**/46:01*	*01:02/**03:04***	**1/*1*
17	F/31	DRESS	PCP in HIV	***11:01**/24:02*	***13:01/15:02***	***03:04**/08:01*	**1/*1*
18	M/47	SJS	PCP in HIV	*02:03/33:03*	*18:01/44:03*	*07:01/07:04*	**1/*1*
19	M/48	DRESS	PCP in HIV	***11:01/11:01***	***13:01**/46:01*	*01:02/04:03*	**1/*1*
20	F/59	DRESS	Melioidosis	***11:01**/68:01*	*08:01/**13:01***	*04:03/07:02*	**1/*1*
21	M/46	DRESS	Melioidosis	*02:07/**11:01***	***13:01**/46:01*	*01:02/**03:04***	**1/*1*
22	M/57	DRESS	PCP in HIV	***11:01**/24:07*	*07:05/**15:02***	***07:27**/08:01*	**1/*1*
23	F/	SJS	N/A	***11:01/11:01***	***15:02**/15:13*	*08:01/08:01*	**1/*1*

No.	Sex/Age*	Type of SCAR	Indication for co-trimoxazole	*HLA class I* genotyping			*CYP2C9*
				HLA-A	***HLA-B***	***HLA-C***	
24	F/30	SJS/TEN overlap	N/A	*02:03/**11:01***	***15:02**/18:01*	*07:04/08:01*	**1/*1*
25	F/46	TEN	Melioidosis	***11:01**/26:01*	*08:01/51:01*	*07:02/14:02*	**1/*1*
26	M/50	SJS	PCP in HIV	*24:02/74:01*	*07:05/38:02*	*07:02/07:02*	**1/*1*
27	M/33	SJS	PCP in HIV	*24:02/29:01*	*07:05/**15:02***	*08:01/15:05*	**1/*1*
28	F/57	TEN	Melioidosis	***11:01/11:01***	***13:01**/40:02*	*04:06/15:02*	**1/*1*
29	M/37	TEN	PCP in HIV	*02:03/31:01*	***13:01**/38:02*	*04:06/07:02*	**1/*1*
30	M/43	SJS	PCP in HIV	***11:01**/26:01*	***15:02**/27:07*	*08:01/15:02*	**1/*1*

* Age at the development of co-trimoxazole-induced SCARs; *CYP2C9*, cytochrome P450 2C9; DRESS, drug reaction with eosinophilia and systemic symptoms; F, Female; HCV, hepatitis C virus; HIV, Human Immunodeficiency Virus; *HLA-A*, human leucocyte antigen-A; *HLA-B*, human leucocyte antigen-B; *HLA-C*, human leucocyte antigen-C; M, Male; N/A, not available; PCP, Pneumocystis carinii pneumonia; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TB, tuberculosis; TEN, toxic epidermal necrolysis.

Table 3. The association of *HLA class I* alleles with co-trimoxazole-induced SCARs (n = 30)

HLA class I alleles	co-trimoxazole-induced SCARs (n = 30)	Tolerant controls (n=91)	Thai population (n = 150)	co-trimoxazole-induced SCARs cases versus Tolerant controls		co-trimoxazole-induced SCARs cases versus Thai population	
				Odd ratio (95% CI)	*p*-value < 0.05	Odd ratio (95% CI)	*p*-value < 0.05
HLA-A							
02:03	5 (16.67%)	19 (20.88%)	32 (21.33%)	0.76 (0.26 - 2.24)	0.6158	0.74 (0.26 - 2.08)	0.5637
02:07	**3 (10.00%)**	**28 (30.77%)**	26 (17.33%)	**0.25 (0.07 - 0.89)**	**0.0238**	0.53 (0.15 - 1.88)	0.4209
11:01	**21 (70.00%)**	**38 (41.76%)**	**68 (45.33%)**	**3.25 (1.34 - 7.89)**	**0.0073**	**2.81 (1.21 - 6.55)**	**0.0136**
24:02	6 (20.00%)	17 (18.68%)	32 (21.33%)	1.09 (0.39 - 3.07)	0.8732	0.92 (0.35 - 2.45)	0.8702
24:07	2 (6.67%)	5 (5.49%)	14 (9.33%)	1.23 (0.23 - 6.69)	1.0000	0.69 (0.15 - 3.23)	1.0000
33:03	2 (6.67%)	18 (19.78%)	32 (21.33%)	0.29 (0.06 - 1.33)	0.1539	0.26 (0.06 - 1.17)	0.0609
HLA-B							
07:05	**5 (16.67%)**	6 (6.59%)	**8 (5.33%)**	2.83 (0.79 - 10.07)	0.1379	**3.55 (1.07 - 11.73)**	**0.0446**
13:01	**13 (43.33%)**	**15 (16.48%)**	**23 (15.33%)**	**3.88 (1.56 - 9.63)**	**0.0025**	**4.22 (1.81 - 9.86)**	**$4.7x10^{-4}$***
15:02	**9 (30.00%)**	**10 (10.99%)**	27 (18.00%)	**3.47 (1.25 - 9.63)**	**0.0201**	1.95 (0.81 - 4.73)	0.1336
38:02	**7 (23.33%)**	10 (10.99%)	**12 (8.00%)**	2.47 (0.85 - 7.19)	0.1273	**3.50 (1.25 - 9.82)**	**0.0210**
40:01	2 (6.67%)	13 (14.29%)	18 (12.00%)	0.43 (0.09 - 2.02)	0.3529	0.52 (0.12 - 2.39)	0.5352
46:01	5 (16.67%)	23 (25.27%)	40 (26.67%)	0.59 (0.20 - 1.72)	0.3323	0.55 (0.19 - 1.54)	0.2482
58:01	2 (6.67%)	11 (12.09%)	12 (8.00%)	0.52 (0.11 - 2.49)	0.5152	0.82 (0.17 - 3.87)	1.0000
HLA-C							
01:02	5 (16.67%)	23 (25.27%)	48 (32.00%)	0.59 (0.20 - 1.72)	0.3323	0.43 (0.15 - 1.18)	0.0926
03:02	2 (6.67%)	13 (14.29%)	23 (15.33%)	0.43 (0.09 - 2.02)	0.3529	0.39 (0.09 - 1.77)	0.2612
03:04	8 (26.67%)	21 (23.08%)	21 (14.00%)	1.21 (0.47 - 3.12)	0.6896	2.23 (0.88 - 5.67)	0.1027
04:01	2 (6.67%)	5 (5.49%)	20 (13.33%)	1.23 (0.23 - 6.69)	1.0000	0.46 (0.10 - 2.10)	0.5398
04:03	4 (13.33%)	13 (14.29%)	11 (7.33%)	0.92 (0.28 - 3.08)	1.0000	1.94 (0.58 - 6.58)	0.2821
07:02	7 (23.33%)	26 (28.57%)	26 (17.33%)	0.76 (0.29 - 1.99)	0.5764	1.45 (0.56 - 3.74)	0.4382
07:27	**4 (13.33%)**	**0 (0%)**	**2 (1.33%)**	**31.08 (1.62 - 595.88)**	**0.0032**	**11.39 (1.98 - 65.37)**	**0.0076**
08:01	**9 (30.00%)**	**9 (9.89%)**	33 (22.00%)	**3.91 (1.38 - 11.06)**	**0.0149**	1.52 (0.64 - 3.63)	0.3443
Haplotype							
*HLA-A*11:01/-B*15:02*	**8 (26.67%)**	**7 (7.69%)**	**16 (10.67%)**	**4.36 (1.43 - 13.34)**	**0.0108**	**3.05 (1.17 - 7.96)**	**0.0343**
*HLA-B*13:01/-C*03:04*	**8 (26.67%)**	**8 (8.79%)**	**10 (6.67%)**	**3.77 (1.27 - 11.19)**	**0.0251**	**5.09 (1.81 - 14.29)**	**0.0032**

HLA-A, human leucocyte antigen-A; *HLA-B*, human leucocyte antigen-B; *HLA-C*, human leucocyte antigen-C; SCARs, severe cutaneous adverse reactions; Significant different *p*-value < 0.05. *P*-values were calculated by Fisher's exact test. Statistically significant values are highlighted in bold.

*Corrected *P*- value was obtained after Bonferroni correction ($P_c < 0.0025$).

Table 4. The association of *HLA class I* alleles with co-trimoxazole-induced DRESS (n = 12)

HLA class I alleles	co-trimoxazole-induced DRESS (n = 12)	Tolerant controls (n=91)	Thai population (n = 150)	co-trimoxazole-induced DRESS cases versus Tolerant controls		co-trimoxazole-induced DRESS cases versus Thai population	
				Odd ratio (95% CI)	*p*-value < 0.05	Odd ratio (95% CI)	*p*-value < 0.05
HLA-A							
02:03	0	19 (20.88%)	32 (21.33%)	0.15 (0.01 - 2.62)	0.1167	0.15 (0.01 - 2.53)	0.1259
02:07	3 (25.00%)	28 (30.77%)	26 (17.33%)	0.75 (0.19 - 2.98)	1.0000	1.59 (0.40 - 6.28)	0.4516
11:01	**10 (83.33%)**	**38 (41.76%)**	**68 (45.33%)**	**6.97 (1.45 - 33.67)**	**0.0067**	**6.03 (1.28 - 28.46)**	**0.0112**
24:02	3 (25.00%)	17 (18.68%)	32 (21.33%)	1.45 (0.36 - 5.94)	0.6978	1.23 (0.31 - 4.81)	0.7231
24:07	1 (8.33%)	5 (5.49%)	14 (9.33%)	1.56 (0.17 - 14.64)	0.5338	0.88 (0.11 - 7.36)	1.0000
33:03	1 (8.33%)	18 (19.78%)	32 (21.33%)	0.37 (0.05 - 3.04)	0.4579	0.34 (0.04 - 2.69)	0.4622
HLA-B							
07:05	2 (16.67%)	6 (6.59%)	8 (5.33%)	2.83 (0.50 - 15.97)	0.2341	3.55 (0.66 - 18.99)	0.1622
13:01	**9 (75.00%)**	**15 (16.48%)**	**23 (15.33%)**	**15.20 (3.68 - 62.83)**	**7.2×10^{-5}***	**16.57 (4.17 - 65.85)**	**2.4×10^{-5}***
15:02	2 (16.67%)	10 (10.99%)	27 (18.00%)	1.62 (0.31 - 8.47)	0.6286	0.91 (0.19 - 4.39)	1.0000
38:02	1 (8.33%)	10 (10.99%)	12 (8.00%)	0.74 (0.09 - 6.32)	1.0000	1.05 (0.12 - 8.80)	1.0000
40:01	2 (16.67%)	13 (14.29%)	18 (12.00%)	1.20 (0.24 - 6.11)	0.6860	1.47 (0.29 - 7.24)	0.6452
46:01	4 (33.33%)	23 (25.27%)	40 (26.67%)	1.48 (0.41 - 5.37)	0.5084	1.38 (0.39 - 4.82)	0.7365
58:01	1 (8.33%)	11 (12.09%)	12 (8.00%)	0.66 (0.08 - 5.63)	1.0000	1.05 (0.12 - 8.80)	1.0000
HLA-C							
01:02	4 (33.33%)	23 (25.27%)	48 (32.00%)	1.48 (0.41 - 5.37)	0.5084	1.06 (0.31 - 3.70)	1.0000
03:02	1 (8.33%)	13 (14.29%)	23 (15.33%)	0.55 (0.07 - 4.59)	1.0000	0.50 (0.06 - 4.08)	1.0000
03:04	**7 (58.33%)**	**21 (23.08%)**	**21 (14.00%)**	**4.67 (1.34 - 16.24)**	**0.0162**	**8.60 (2.49 - 29.63)**	**9.7×10^{-4}***
04:01	1 (8.33%)	5 (5.49%)	20 (13.33%)	1.56 (0.17 - 14.64)	0.5338	0.59 (0.07 - 4.83)	1.0000
04:03	3 (25.00%)	13 (14.29%)	11 (7.33%)	2.00 (0.48 - 8.38)	0.3930	4.21 (0.99 - 17.84)	0.0711
07:02	2 (16.67%)	26 (28.57%)	26 (17.33%)	0.50 (0.10 - 2.44)	0.5050	0.95 (0.19 - 4.61)	1.0000
07:27	**2 (16.67%)**	**0 (0%)**	**2 (1.33%)**	**43.57 (1.96 - 969.96)**	**0.0126**	**14.80 (1.88 - 116.35)**	**0.0279**
08:01	2 (16.67%)	9 (9.89%)	33 (22.00%)	1.82 (0.34 - 9.65)	0.6133	0.71 (0.15 - 3.39)	1.0000
Haplotype							
*HLA-A*11:01/-B*15:02*	2 (16.67%)	7 (7.69%)	16 (10.67%)	2.40 (0.44 - 13.17)	0.2813	1.68 (0.34 - 8.33)	0.6255
*HLA-B*13:01/-C*03:04*	**7 (58.33%)**	**8 (8.79%)**	**10 (6.67%)**	**14.53 (3.74 - 56.47)**	**1.8×10^{-4}***	**19.60 (5.26 - 72.99)**	**2.3×10^{-5}***

HLA-A, human leucocyte antigen-A; *HLA-B*, human leucocyte antigen-B; *HLA-C*, human leucocyte antigen-C; DRESS, drug reaction with eosinophilia and systemic symptoms; Significant different *p*-value < 0.05. *P*-values were calculated by Fisher's exact test. Statistically significant values are highlighted in bold.

*Corrected *P*- value was obtained after Bonferroni correction ($P_c < 0.0025$).

Table 5. The association of *HLA class I* alleles with co-trimoxazole-induced SJS-TEN (n = 18)

HLA class I alleles	co-trimoxazole-induced SJS-TEN (n = 18)	Tolerant controls (n=91)	Thai population (n = 150)	co-trimoxazole-induced SJS-TEN cases versus Tolerant controls		co-trimoxazole-induced SJS-TEN cases versus Thai population	
				Odd ratio (95% CI)	*p*-value < 0.05	Odd ratio (95% CI)	*p*-value < 0.05
HLA-A							
02:03	5 (27.78%)	19 (20.88%)	32 (21.33%)	1.46 (0.46 - 4.59)	0.5397	1.42 (0.47 - 4.27)	0.5511
02:07	0	28 (30.77%)	26 (17.33%)	0.06 (0.01 - 1.03)	0.0058	0.13 (0.01 - 2.17)	0.0788
11:01	11 (61.11%)	38 (41.76%)	68 (45.33%)	2.19 (0.78 - 6.17)	0.1315	1.89 (0.69 - 5.15)	0.2051
24:02	3 (16.67%)	17 (18.68%)	32 (21.33%)	0.87 (0.23 - 3.35)	1.0000	0.74 (0.20 - 2.71)	0.7679
24:07	1 (5.56%)	5 (5.49%)	14 (9.33%)	1.01 (0.11 - 9.22)	1.0000	0.57 (0.07 - 4.62)	1.0000
33:03	1 (5.56%)	18 (19.78%)	32 (21.33%)	0.24 (0.03 - 1.91)	0.1893	0.22 (0.03 - 1.69)	0.2043
HLA-B							
07:05	3 (16.67%)	6 (6.59%)	8 (5.33%)	2.83 (0.64 - 12.58)	0.1669	3.55 (0.85 - 14.83)	0.0987
13:01	4 (22.22%)	15 (16.48%)	23 (15.33%)	1.45 (0.42 - 5.01)	0.5139	1.58 (0.48 - 5.22)	0.4959
15:02	**7 (38.89%)**	**10 (10.99%)**	**27 (18.00%)**	**5.16 (1.63 - 16.33)**	**0.0075**	2.89 (1.03 - 8.16)	0.0576
38:02	**6 (33.33%)**	**10 (10.99%)**	**12 (8.00%)**	**4.05 (1.25 - 13.18)**	**0.0249**	**5.75 (1.83 - 18.05)**	**0.0054**
40:01	0	13 (14.29%)	18 (12.00%)	0.16 (0.01 - 2.77)	0.1206	0.19 (0.01 - 3.35)	0.2230
46:01	1 (5.56%)	23 (25.27%)	40 (26.67%)	0.17 (0.02 - 1.38)	0.1151	0.16 (0.02 - 1.26)	0.0769
58:01	1 (5.56%)	11 (12.09%)	12 (8.00%)	0.43 (0.05 - 3.54)	0.6862	0.68 (0.08 - 5.53)	1.0000
HLA-C							
01:02	**1 (5.56%)**	23 (25.27%)	**48 (32.00%)**	0.17 (0.02 - 1.38)	0.1151	**0.13 (0.02 - 0.97)**	**0.0197**
03:02	1 (5.56%)	13 (14.29%)	23 (15.33%)	0.35 (0.04 - 2.88)	0.4581	0.33 (0.04 - 2.56)	0.4749
03:04	1 (5.56%)	21 (23.08%)	21 (14.00%)	0.19 (0.03 - 1.56)	0.1149	0.36 (0.05 - 2.86)	0.4729
04:01	1 (5.56%)	5 (5.49%)	20 (13.33%)	1.01 (0.11 - 9.22)	1.0000	0.38 (0.05 - 3.03)	0.7037
04:03	1 (5.56%)	13 (14.29%)	11 (7.33%)	0.35 (0.04 - 2.88)	0.4581	0.74 (0.09 - 6.12)	1.0000
07:02	5 (27.78%)	26 (28.57%)	26 (17.33%)	0.96 (0.31 - 2.97)	0.9456	1.83 (0.60 - 5.59)	0.3323
07:27	**2 (11.11%)**	**0 (0%)**	2 (1.33%)	**27.73 (1.27 - 604.11)**	**0.0259**	9.25 (1.22 - 70.19)	0.0573
08:01	**7 (38.89%)**	**9 (9.89%)**	33 (22.00%)	**5.79 (1.79 - 18.70)**	**0.0049**	2.26 (0.81 - 6.28)	0.1417
Haplotype							
*HLA-A*11:01/-B*15:02*	**6 (33.33%)**	**7 (7.69%)**	**16 (10.67%)**	**6.00 (1.72 - 20.88)**	**0.0074**	**4.19 (1.38 - 12.69)**	**0.0165**
*HLA-B*13:01/-C*03:04*	1 (5.56%)	8 (8.79%)	10 (6.67%)	0.61 (0.07 - 5.20)	1.0000	0.82 (0.09 - 6.84)	1.0000

HLA-A, human leucocyte antigen-A; *HLA-B*, human leucocyte antigen-B; *HLA-C*, human leucocyte antigen-C; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Significant different *p*-value < 0.05. *P*-values were calculated by Fisher's exact test. Statistically significant values are highlighted in bold.
*Corrected *P*- value was obtained after Bonferroni correction ($P_c < 0.0025$).

Table 6. List of HLA alleles that showed a significant association with Co-trimoxazole-induced SCARs among the different subgroup.

HLA class I alleles	HIV-positive patients				HIV-negative patients			
	co-trimoxazole-induced SCARs +/Total	Tolerant controls +/Total	Odd ratio (95% CI)	*p*-value	co-trimoxazole-induced SCARs +/Total	Tolerant controls +/Total	Odd ratio (95% CI)	*p*-value
SCAR								
HLA-A*02:07	**2/23**	**21/61**	**0.18 (0.04-0.85)**	**0.0302**	1/7	7/30	0.54 (0.06-5.35)	0.6047
*HLA-A*11:01*	14/23	23/61	2.57 (0.96-6.88)	0.0602	7/7	17/30	11.57 (0.61-220.97)	0.1037
HLA-B*07:05	**5/23**	**3/61**	**5.37 (1.17-24.70)**	**0.0308**	0/7	3/30	0.52 (0.02-11.30)	0.6799
HLA-B*13:01	**9/23**	**9/61**	**3.71 (1.24-11.12)**	**0.019**	4/7	6/30	5.33 (0.93-31.51)	0.0599
HLA-B*15:02	**7/23**	**6/61**	**4.01 (1.18-13.64)**	**0.0262**	2/7	4/30	2.60 (0.37-18.25)	0.3365
HLA-B*38:02	**7/23**	**5/61**	**4.90 (1.37-17.54)**	**0.0146**	0/7	5/30	0.31 (0.02-6.25)	0.4442
HLA-C*07:27	**4/23**	**0/61**	**28.38 (1.46-550.99)**	**0.0270**	0/7	0/30	N/A	N/A
HLA-C*08:01	**7/23**	**3/61**	**8.46 (1.96-36.47)**	**0.0042**	2/7	6/30	1.60 (0.24-10.36)	0.6219
DRESS								
HLA-A*11:01	**7/9**	**23/61**	**5.78 (1.11-30.25)**	**0.0376**	3/3	17/30	N/A	N/A
HLA-B*13:01	**6/9**	**9/61**	**11.55 (2.44-54.78)**	**0.0021**	3/3	6/30	N/A	N/A
HLA-C*07:27	**2/9**	**0/61**	**41.00 (1.79-937.48)**	**0.0200**	0/3	0/30	N/A	N/A
SJS/TEN								
*HLA-A*11:01*	7/14	23/61	1.65 (0.51-5.32)	0.3997	4/4	17/30	N/A	N/A
HLA-B*15:02	**5/14**	**6/61**	**5.09 (1.28-20.25)**	**0.0208**	2/4	4/30	N/A	N/A
HLA-B*38:02	**6/14**	**5/61**	**8.40 (2.07-34.03)**	**0.0029**	0/4	5/30	N/A	N/A
HLA-C*07:27	**2/14**	**0/61**	**24.60 (1.11-544.28)**	**0.0427**	0/4	0/30	N/A	N/A
HLA-C*08:01	**5/14**	**3/61**	**10.74 (2.18-52.90)**	**0.0035**	2/4	6/30	N/A	N/A

DRESS, drug reaction with eosinophilia and systemic symptoms; *HLA-A*, human leucocyte antigen-A; *HLA-B*, human leucocyte antigen-B; *HLA-C*, human leucocyte antigen-C; N/A, not available; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Significant different *p*-value < 0.05.
P-values were calculated by Fisher's exact test. Statistically significant values are highlighted in bold.

Table 7. Pooled-data analysis comparing the frequencies of *HLA-A*11:01*, *HLA-B*15:02* and *C*08:01* in co-trimoxazole induced SJS/TEN and tolerant controls. Data were obtained from two studies with high-resolution *HLA-B* typing results.

	All patients				HIV-positive patients			
HLA genotype	**CTX-SJS/TEN cases (n=61)**	**Tolerant controls (n=91)**	**Odds ratio (95% CI)**	***P*-value**	**CTX-SJS/TEN cases (n=44)**	**Tolerant controls (n=61)**	**Odds ratio (95% CI)**	***P*-value**
A*11:01	33	38	1.64 (0.86-3.16)	0.1361	23	22	1.94 (0.88-4.28)	0.0995
Without *A*11:01*	28	53			21	39		
B*15:02	21	10	**4.25 (1.83-9.88)**	**0.0008**	17	6	**5.77 (2.04-16.30)**	**0.0009**
Without *B*15:02*	40	81			27	55		
C*08:01	19	9	**4.12 (1.72-9.90)**	**0.0015**	16	3	**11.05 (2.97-41.07)**	**0.0003**
Without *C*08:01*	42	82			28	58		

HLA-A, human leucocyte antigen-A; *HLA-B*, human leucocyte antigen-B; *HLA-C*, human leucocyte antigen-C; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Significant different *p*-value < 0.05. *P*-values were calculated by Fisher's exact test. Statistically significant values are highlighted in bold.