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The association of HLA alleles with clinical disease progression in HIV-positive cohorts with varied treatment strategies.

Christina EKENBERG[1], **Joanne REEKIE**[1], **Adrian G. ZUCCO**[1], **Daniel D. MURRAY**[1,2], **Shweta SHARMA**[3], **Cameron R. MACPHERSON**[1], **Abdel BABIKER**[4], **Virginia KAN**[5], **H. Clifford LANE**[6], **James D. NEATON**[3], **Jens D. LUNDGREN**[1], **INSIGHT START and SMART Study Groups**

[1]Centre of Excellence for Health, Immunity and Infections (CHIP), Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

[2]Kirby Institute, UNSW Sydney, Sydney, New South Wales, Australia.

[3]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA.

[4]Medical Research Council, Clinical Trials Unit in University College London, London, United Kingdom.

[5]Veterans Affairs Medical Center and George Washington University, Washington D.C., USA.

[6]National Institute of Allergy and Infectious Diseases, Division of Clinical Research, Bethesda, Maryland, USA.

Abstract

Objectives: The Strategic Timing of AntiRetroviral Treatment (START) and Strategies for Management of Antiretroviral Therapy (SMART) trials demonstrated that ART can partly reverse clinically defined immune dysfunction induced by HIV replication. As control of HIV replication is influenced by the HLA region, we explored whether HLA alleles independently influence the risk of clinical events in HIV+ individuals.

Design: Cohort study.

Methods: In START and SMART participants, associations between imputed HLA alleles and AIDS, infection-related cancer, herpes virus-related AIDS events, chronic inflammation-related

Corresponding author: Christina Ekenberg, MD, CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, Phone: +45 35455757 / +45 35455894, christina.ekenberg@regionh.dk.

Author contributions

CE, JDN and JDL conceived the study. CE, AGZ and JR performed the statistical analyses. CE drafted the manuscript. All authors contributed to data interpretation, critically revised the manuscript, and approved the final version.

Conflicts of Interest

No reported conflicts of interest relevant to the content of this manuscript.

Ethics:

Samples included in this study were derived from consenting participants of the clinical trials, The Strategic Timing of AntiRetroviral Treatment (START) (NCT00867048)[1] and The Strategies for Management of Antiretroviral Therapy (SMART) (NCT00027352)[2], run by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). The trials were approved by the institutional review board or ethics committee at each contributing center, and written informed consent was obtained from all participants. All informed consents were reviewed and approved by participant site ethics review committees.

conditions and bacterial pneumonia were assessed. Cox regression was used to estimate hazard ratios (HRs) for the risk of events among allele carriers versus non-carriers. Models were adjusted for sex, age, geography, race, time-updated CD4+ T-cell counts and HIV viral load (VL) and stratified by treatment group within trials. HLA class I and II alleles were analyzed separately. The Benjamini-Hochberg procedure was used to limit the false discovery rate to <5% (i.e. q-value<0.05).

Results: Among 4,829 participants, there were 132 AIDS events, 136 chronic inflammation-related conditions, 167 bacterial pneumonias, 45 infection-related cancers and 49 herpes virus-related AIDS events. Several associations with q-value <0.05 were found: HLA-DQB1*06:04 and HLA-DRB1*13:02 with AIDS (adjusted HR [95%CI] 2.63 [1.5–4.6] and 2.25 [1.4–3.7], respectively), HLA-B*15:17 and HLA-DPB1*15:01 with bacterial pneumonia (4.93 [2.3–10.7] and 4.33 [2.0–9.3], respectively), and HLA-A*69:01 with infection-related cancer (15.26 [3.5–66.7]). The carriage frequencies of these alleles were ≤10%.

Conclusions: This hypothesis-generating study suggests that certain HLA alleles may influence the risk of immune dysfunction-related events irrespective of VL and CD4+ T-cell count.

Keywords

HLA; HIV-1; disease progression; host genetics; immune dysfunction

Introduction

The interplay between pathogen and host genetic variation influences susceptibility and progression of infectious diseases. Playing a crucial role in the regulation of immune response, the human leukocyte antigen (HLA) region has consistently been associated with a wide range of cancer, autoimmune diseases and infections[3–8], including HIV-1 control. Several studies have identified associations between genetic variants in the HLA region and HIV-1 viral load (VL) and disease progression[5, 9–16]. Set-point VL (spVL) is a prognostic marker of disease progression in HIV-positive (HIV+) individuals[17], hence, reported variants associated with VL have also been associated with disease progression[5, 18–20]. However, these studies included only antiretroviral therapy (ART)-naive persons, whereas the current treatment guidelines[21] recommend initiation of ART upon HIV diagnosis regardless of CD4+ T-cell count.

The Strategic Timing of AntiRetroviral Treatment (START)[1] and The Strategies for Management of Antiretroviral Therapy (SMART)[2] trials demonstrated that ART partly reverses clinically defined immune dysfunction induced by HIV replication. In prior pooled analyses of these trials, participants treated with deferred/intermittent ART had higher risk of infectious complications compared to participants receiving immediate/continuous ART[22]. This HIV-induced immune dysfunction was observed even at relatively high CD4+ T-cell counts. Hence, predisposition for infectious complications among HIV+ individuals is currently only partly explained. Therefore, we explored whether HLA alleles influenced the risk of immune dysfunction-related clinical events independently of HIV replication in a pooled analysis of data from START and SMART.

Methods

Study participants

Samples included in this study were derived from START (NCT00867048)[1] and SMART (NCT00027352)[2] participants consenting to genetic analyses. START and SMART were international, randomized controlled trials comparing different ART strategies in HIV+ individuals regarding serious morbidity and mortality[1, 2, 22].

Definition of clinical events

The following clinical events were ascertained in START and SMART with definitions standardized before analysis: (1) AIDS; (2) infection-related cancer; (3) herpes virus-related AIDS events; (4) bacterial pneumonia and (5) chronic inflammation-related conditions. Infection-related cancer was defined as cancer associated with human herpesvirus 8 (Kaposi sarcoma), Epstein-Barr virus (non-Hodgkin lymphoma, Hodgkin lymphoma), or human papilloma virus (anal cancer, cervical cancer). AIDS and chronic inflammation-related conditions were defined per Lifson *et al*[23] and Hart *et al*[24], respectively.

Imputation of HLA alleles

Following genotyping using a custom content Affymetrix Axiom SNP array, imputation of classical HLA alleles per locus (i.e. class I: HLA-A, HLA-B, HLA-C and class II: HLA-DP, HLA-DQ, HLA-DR) at four-digit resolution was performed with HIBAG[25]. The genotyping and HLA imputation have been described previously[15]. As part of the exploratory nature of these analyses, we aimed to explore associations with HLA alleles carried by ≥10 participants including those observed at low frequencies.

Statistics

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for the risk of clinical events among allele carriers versus non-carriers. Event-specific time-to-event was computed as the time from trial enrollment until date of first event, death, withdrawal, last known alive date, or trial unblinding (START) or study closure (SMART), whichever occurred first. To assess the effect of HLA alleles on risk of clinical events independently of HIV-induced immune dysfunction, models were adjusted for time-updated HIV VL and CD4+ T-cell counts in addition to sex, age at trial entry, self-reported race and geographical region, and stratified by the two randomized treatment groups in SMART and START (4 strata in total). Since HLA homozygosity was rare in our population and HLA is co-dominantly expressed, HLA carriers carrying one or two alleles were combined (i.e. the dominant model). HLA class I and II alleles were analyzed separately. The Benjamini-Hochberg procedure was used to limit the false discovery rate (FDR) to <5% (q-value <0.05).

Analyses were performed using Stata version 15.

Results

Study participants

This analysis was comprised of 4,829 participants from START (n=2,546) and SMART (n=2,283) who consented to genetic analyses (characteristics in Table 1). Per design, START and SMART participants differed significantly regarding HIV-specific factors. There were also differences in demographics. Median follow-up time (IQR) was 3.4 years (2.3–4.5) for START participants, 3.3 years (2.3–4.5) for SMART participants and 3.4 years (2.4–4.5) for all participants.

Imputation of HLA alleles

The percentage of participants with predicted, high accuracy, alleles per locus were: HLA-A: 4,598 (95.2%), HLA-B 3,963 (82.1%), HLA-C 4,659 (96.5%), HLA-DPB1 4,479 (92.8%), HLA-DQA1 4,607 (95.4%), HLA-DQB1 4,671 (96.7%), HLA-DRB1 3,800 (78.7%).

Following exclusion of HLA alleles present in <10 participants, 102 class I and 83 class II alleles were assessed.

Associations between HLA alleles and clinical events

There were 132 AIDS events, 136 chronic inflammation-related conditions, 167 bacterial pneumonias, 45 infection-related cancers and 49 herpes virus-related AIDS events during follow-up. We observed several associations with a q-value <0.05 between HLA alleles and immune dysfunction-related events (Table 2). HLA-DQB1*06:04 and HLA-DRB1*13:02 were associated with AIDS (adjusted HRs [95%CI] 2.63 [1.5–4.6] and 2.25 [1.4–3.7], respectively). Among participants who were called for both alleles (n=3,734), 370 were carriers of HLA-DRB1*13:02 of whom 202 (55%) also carried the HLA-DQB1:06:04 allele, whereas almost all (99.5%) HLA-DQB1*06:04 carriers (n=203) were also HLA-DRB1*13:02 carriers (n=202). HLA-B*15:17 and HLA-DPB1*15:01 showed associations with bacterial pneumonia (4.93 [2.3–10.7] and 4.33 [2.0–9.3], respectively), while an association was also observed between HLA-A*69:01 and infection-related cancer (15.26 [3.5–66.7]). No associations with herpes virus-related AIDS events or chronic inflammation-related condition reached the threshold of a q-value <0.05. Several of the reported alleles with a q-value <0.05 were observed at low frequencies with carrier frequencies as low as 0.3% among HLA predicted participants (Table 2). Kaplan-Meier plots of events according to allele carrier status are shown in Supplemental Figure S1.

Discussion

In this study, associations were detected between specific HLA alleles and AIDS, bacterial pneumonia and infection-related cancer, suggesting that HLA alleles may affect disease progression irrespective of the effect of HIV VL and CD4+ T-cell counts. Importantly, none of the identified HLA alleles have previously been associated with control of HIV replication, including a previous study of START participants[15], making the associations more likely due to a direct interaction with the pathology of the event per se.

Studies on spVL and disease progression in ART-naïve cohorts have identified the HLA class I region as the major host determinant of HIV control[5, 9, 16, 18–20, 26, 27]. This is consistent with previous knowledge on antigen presentation with class I and II molecules primarily presenting endogenously and exogenously produced antigens, respectively[28]. As we assessed a broad variety of events and aimed to explore the role of HLA alleles independently of HIV-associated immune dysfunction, we included both class I and II alleles to capture associations with different pathways of antigen presentation.

To the best of our knowledge, this is the first study exploring associations between HLA alleles and various immune dysfunction-related events in HIV+ cohorts with varied treatment strategies. Several of the components of the composite outcomes included in this study have been investigated previously in the general population[3, 29, 30] and in HIV+ individuals[31–34], however, results have been divergent and are also inconsistent with our findings. We identified associations between AIDS and DQB1*06:04 and HLA-DRB1*13:02 which have not previously been reported. AIDS is a composite outcome, including a variety of pathogens, making it difficult to delineate the exact components or pathogens driving the allele associations identified in our study. Investigation of specific AIDS events has revealed interesting HLA associations and underlined the complexities of genetic studies which could explain the discordant observations. Castro *et al.* found an association between HLA-B*14:01 and increased risk of Kaposi sarcoma in HIV+ individuals[33], but not in the control group of HIV-negative individuals with endemic Kaposi sarcoma, suggesting altered HLA function in the setting of HIV. This potential, HIV-induced modification was also suggested in studies examining the role of HLA variation in tuberculosis/HIV-1 coinfection[32] and cervical cancer in HPV/HIV-1 coinfection[31]. Across HIV+ cohorts, divergent findings are likely to be caused by different racial and geographical composition of the study populations or different antiretroviral treatment regimens. In our study, we controlled for time-updated CD4+ T-cell counts and VL aiming to remove the HIV-induced immune dysfunction, however, our results showed that this adjustment did not change effect sizes markedly. Whether this could be due to a residual HIV-effect regardless of HIV-control has not been studied and remains uncertain.

Bacterial pneumonia was associated with HLA-B*15:17 and HLA-DPB1*15:01. A previous study[3] found an association between pneumonia and HLA-B in the general population, whereas the HLA region's impact on risk of HIV-related bacterial pneumonia has not been investigated. The finding of both a class I and II association could be due to the diverse microbial etiology of the assessed bacterial pneumonias, or the events may represent secondary bacterial pneumonias succeeding viral respiratory infections.

Comparison of results across genetic studies remains challenging. Studies are often restricted to sub-populations, yielding population-specific associations due to varying allele frequencies across races and regions. As a result, certain associations cannot be replicated. We included and observed associations with alleles observed at low frequencies which may explain why these associations have not been reported previously. Moreover, statistical methodologies vary across studies with the primary method being logistic regression in a case-control design, whereas we used time-to-event methods.

The exact mechanisms accounting for the associations observed in this study remain unclear, and additional studies investigating the functional amino acid variants are required. Previous studies have reported linkage between alleles of the HLA-DQ and HLA-DR loci[35–38], challenging the delineation of causal alleles. We observed a correlation between HLA-DQB1*06:04 and HLA-DRB1*13:02 which were both associated with AIDS. As there was only one participant carrying HLA-DQB1*06:04 without the co-occurrence of HLA-DRB1*13:02, we were not able to outline whether the observed associations were driven by the co-occurrence of the alleles or an individual allele.

A main strength of this study is the careful, standardized ascertainment of events across the studies. This study also has some limitations. We pooled data from two separate trials, however, due to careful ascertainment of clinical events in both trials, we could analyze harmonized event data justifying the data pooling. Despite event pooling, there were still relatively few clinical events, limiting the power to detect associations. We used imputed HLA alleles and did not have a reference population that was identical to the unique geographic and racial composition of our population. This may have reduced the imputation accuracy, particularly among individuals of non-European descent. Furthermore, the lower call rate at HLA-B and HLA-DRB1 would most likely reduce the ability to predict low-frequency alleles at these loci compared with other loci. The study did not include HIV-1 subtypes which influence disease progression independently of host factors[39]. However, we adjusted for race and geography which are likely to capture at least part of the viral diversity.

In conclusion, this hypothesis-generating study suggests that HLA alleles may affect disease progression independently of HIV-related immune dysfunction. The allele frequency of several of these alleles was low and with likely variation across race; validation of our findings in other demographically diverse cohorts is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics at trial entry of study participants.

Characteristics	START participants n=2,546	SMART participants n=2,283	All participants n=4,829
Median age (IQR), years	36 (29–45)	44 (38–50)	41 (33–48)
Sex, n(%)			
Female	511 (20.1)	602 (26.4)	1,113 (23.1)
Male	2,035 (79.9)	1,681 (73.6)	3,716 (77.0)
Race/ethnic group, n(%)			
Black	577 (22.7)	876 (38.4)	1,453 (30.1)
Hispanic	498 (19.6)	396 (17.4)	894 (18.5)
Asian	26 (1.0)	32 (1.4)	58 (1.2)
White	1,404 (55.2)	948 (41.5)	2,352 (48.7)
Other	41 (1.6)	31 (1.4)	72 (1.5)
Geographical region, n(%)			
Africa	343 (13.5)	56 (2.5)	399 (8.3)
Asia	0 (0)	10 (0.4)	10 (0.2)
Australia & New Zealand	96 (3.8)	132 (5.8)	228 (4.7)
Europe and Israel	1,148 (45.1)	124 (5.4)	1,272 (26.3)
Latin America	499 (19.6)	126 (5.5)	625 (12.9)
United States & Canada	460 (18.1)	1,835 (80.4)	2,295 (47.5)
Mode of HIV-infection, n(%)			
Sexual contact			
Men having sex with men	1,633 (64.1)	1,096 (48.0)	2,729 (56.5)
With person of opposite sex	751 (29.5)	813 (35.6)	1,564 (32.4)
Injection-drug use	45 (1.8)	264 (11.6)	309 (6.4)
Other	117 (4.6)	110 (4.8)	227 (4.7)
Median time since HIV diagnosis (IQR), years	1 (0–3)	8 (5–12)	3 (1–8)
On ART, n(%)	0 (0)	1,815 (79.5)	1,815 (37.6)
ART-naïve, n(%)	2,546 (100)	137 (6.0)	2,683 (55.6)
Median CD4+ T-cell count (IQR), cells/mm^3	651 (585–759)	572 (455–773)	631 (540–762)
Median HIV viral load (IQR), copies/mL	14,833 (3,503–46,000)	400 (50–2,789)	3,810 (310–26,104)

Table 2.

Unadjusted and adjusted hazard ratios for HLA class I and II alleles associated with clinical events in HIV-positive individuals (n=4,829) from the START and SMART pooled cohorts who provided consent for genetic analyses.

All associations with a *q*-value <0.05 in the multivariable model are shown.

Clinical event (no. of events[a])	Allele	Participants with predicted HLA, n(% of cohort)	HLA allele carrier status, n(% with predicted HLA)		Events by allele carrier status[b], n(%)	Univariable	Multivariable[c]	
						HR (95% CI)	HR (95% CI)	*q*-value
AIDS (n=132)	HLA-DQB1*06:04	4,671 (96.7)	Non-carriers	4,452 (95.3)	108 (2.4)	1	1	
			Carriers	219 (4.7)	15 (6.8)	2.75 (1.6–4.7)	2.63 (1.5–4.6)	0.041
	HLA-DRB1*13:02	3,800 (78.7)	Non-carriers	3,410 (89.7)	79 (2.3)	1	1	
			Carriers	390 (10.3)	22 (5.6)	2.50 (1.6–4.0)	2.25 (1.4–3.7)	0.041
Bacterial pneumonia (n=167)	HLA-B*15:17	3,963 (82.1)	Non-carriers	3,921 (98.9)	127 (3.2)	1	1	
			Carriers	42 (1.1)	7 (16.7)	5.57 (2.6–11.9)	4.93 (2.3–10.7)	0.005
	HLA-DPB1*15:01	4,479 (92.8)	Non-carriers	4,423 (98.7)	142 (3.2)	1	1	
			Carriers	56 (1.3)	7 (12.5)	4.08 (1.9–8.7)	4.33 (2.0–9.3)	0.015
Infection-related cancer (n=45)	HLA-A*69:01	4,598 (95.2)	Non-carriers	4,585 (99.7)	42 (0.9)	1	1	
			Carriers	13 (0.3)	2 (15.4)	19.06 (4.6–78.8)	15.26 (3.5–66.7)	0.027

[a] Total number of events in the pooled cohort.

[b] The total number of events among allele carriers and non-carriers will vary depending on the number of participants with predicted HLA at each HLA locus.

[c] Time to first event adjusted for time-updated $\log_2$CD4+ T-cell count, time-updated $\log_{10}$viral load, race, geographical region, sex and age at baseline and stratified by treatment group within trial.

HR: hazard ratio, CI: confidence interval.

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