CONCISE COMMUNICATION

HLA B*5701 status, disease progression, and response to antiretroviral therapy

The UK Collaborative HIV Cohort Study Steering Committee

Objective: In addition to hypersensitivity reactions to abacavir, HLA B*5701 has been associated with slow or nonprogression of HIV infection. We explored the effect of HLA B*5701 on $CD4^+$ cell count and viral load in untreated patients and on responses to nonabacavir-containing combination antiretroviral therapy (cART) in a large UK-based cohort.

Design: Analysis of a cohort of HIV-infected adults.

Methods: In untreated patients, $CD4^+$ cell count and viral load at study entry were compared in HLAB*5701-positive and HLAB*5701-negative individuals and linear regression tested for an interaction effect of viral load and HLA B*5701 on $CD4^+$ cell count. In patients starting a nonabacavir cART regimen, Cox proportional hazards models compared virological responses to cART among HLA B*5701-negative, HLA B*5701-positive, and those not tested. Six-month and 12-month changes in $CD4^+$ cell count were used as outcomes in linear regression to compare immunological response to cART in these groups.

Results: ART-naive HLA B*5701-positive individuals had higher $CD4^+$ cell count ($P<0.0001$) and lower viral load ($P<0.0001$) at study entry than negatives; however, HLA B*5701 status was not found to effect the association between viral load and $CD4^+$ cell count (interaction P value = 0.09). HLA B*5701-positive patients were more likely to achieve viral suppression than negative patients on a nonabacavir regimen [hazard ratio = 1.29, 95% confidence interval, CI (1.15–1.54)] and less likely to experience viral rebound [hazard ratio = 0.61, 95% CI (0.37–0.99)].

Conclusion: Better virological but not immunological responses to cART were seen in HLA B*5701-positive patients on nonabacavir regimens. This study provides further evidence of the potentially beneficial effect of HLA B*5701 on HIV progression.

AIDS 2013, **27**:2587–2592

Keywords: antiretroviral therapy progression, HIV, HLA B*5701

Introduction

The HLA allele B*5701 is strongly associated with hypersensitivity reactions to abacavir [1–4]. Hence, most treatment guidelines recommend that patients initiating abacavir be tested for the presence of this allele, and that those who are positive should not receive abacavir. Since the widespread introduction of HLA B*5701 testing, the incidence of hypersensitivity reactions in those receiving abacavir has dropped substantially

Research Department of Infection & Population Health, UCL, London, UK.
Correspondence to Miss Sophie Jose, HIV Epidemiology & Biostatistics Group, Research Department of Infection & Population Health, UCL, Floor 1, Royal Free Campus, London NW3 2PF, UK.
Tel: +44207 794 0500 ext. 36763; e-mail: sophie.jose@ucl.ac.uk
Received: 7 May 2013; revised: 1 July 2013; accepted: 1 July 2013.

DOI:10.1097/01.aids.0000432613.95455.71

ISSN 0269-9370

[5]. In addition to the association with hypersensitivity, the HLA B*5701 allele has also been found to be more common in HIV 'slow progressors' or 'nonprogressors' [6–8]. It is hypothesized that protection occurs through more effective HLA class I T-lymphocyte responses to HIV-1 antigens with less mutational escape leading to better control of viral replication and lower viral loads [7–12]. Previous studies exploring the influence of HLA B*5701 on disease progression have been relatively small [6–8]; none have explored the effect of this allele on the relationship between HIV viral load and $CD4^+$ cell count in untreated individuals and few have assessed its influence on the response to antiretroviral therapy (ART) [13,14]. We explored the effect of HLA B*5701 status on both of these parameters in a large UK cohort.

Methods

The UK Collaborative HIV Cohort (UK CHIC) study collates data collected routinely as part of HIV care from several large HIV centers across the UK [15]. Data items collected include demographics, $CD4^+$ cell count and HIV viral load, ART history, AIDS-defining events, laboratory markers, and HLA B*5701 testing. The current dataset contains information on patients from 15 centers, of which, four did not provide data on HLA B*5701 testing. There were two aspects to this study: to investigate the effect of a positive HLA B*5701 status on viral load and $CD4^+$ cell count in untreated individuals and to compare response to combination antiretroviral therapy (cART) in those positive and negative for the allele. Individuals tested for HLA B*5701 were included in the first aspect of this study if they were found to have been ART-naive upon entry into the UK CHIC study, regardless of when the test was performed. If, following their test, participants went on to commence a nonabacavir cART regimen, they were eligible to be included in the comparison of virological and immunological treatment responses according to HLA B*5701 status. Individuals who were not tested and who started a nonabacavir regimen after 2005 when HLA B*5701 testing became routine were also included for comparison with the HLA B*5701-negative individuals. A nonabacavir cART regimen was defined as any regimen combining at least three antiretroviral drugs, none of which were abacavir. Mono and dual-therapy regimens were not classed as cART. Analyses were performed in all patients starting a nonabacavir regimen as previously stipulated and in a subgroup of individuals who were ART-naive at the time of starting the regimen.

Continuous variables were compared using Wilcoxon rank-sum tests or *t*-tests and χ^2 tests compared categorical variables according to HLA B*5701 status. The effect of viral load and HLA B*5701 status on $CD4^+$ cell count in untreated individuals were assessed using linear regression adjusted for sex, age (per 10 years), and ethnic group (white, black African, black other, other). An interaction between viral load and HLA B*5701 status was then tested in the regression model to determine whether the effect of viral load on $CD4^+$ cell count differed in those who were positive for the allele and those negative. A subanalysis was performed only in those of white ethnicity and the analysis was repeated as a sensitivity analysis using generalized estimating equations (GEEs) to analyze all off-ART $CD4^+$ cell count and viral load pairs, taking into account within-subject correlation. Cox Proportional Hazards Models compared virological response to a nonabacavir regimen in HLA B*5701-negative individuals to that in HLA B*5701-positive individuals and those who had not been tested for the allele. Outcomes assessed were time to undetectable viral load (first viral load <50 copies/ml), viral rebound (the first of two consecutive viral loads >50 copies/ml in those who had achieved undetectable viral load), and treatment switch. Covariates adjusted for were sex; ethnicity (white, black, other); exposure (homo/bisexual, heterosexual, other); age (per 10 years); viral load at regimen start ($\log_{10}$copies/ml); $CD4^+$ cell count at regimen start (per 50 cells/μl); nonabacavir regimen class (protease inhibitor-based, non-nucleoside reverse transcriptase inhibitor-based, nucleoside reverse transcriptase inhibitor only, other); hepatitis B virus/hepatitis C virus (HCV) coinfection (no, yes, not tested); and, wherein ART-experienced patients were included, the number of previous regimens (0, 1–5, 6–10, >10) and any previous virological failures (no, yes). Linear regression assessed immunological response to cART according to HLA B*5701 status, with both 6-month and 12-month change in $CD4^+$ cell count from regimen start used as outcomes. Models were adjusted for sex, ethnicity, exposure, age, viral load, and $CD4^+$ cell count at regimen start, nonabacavir regimen class, HCV coinfection, number of previous regimens, and any previous virological failure.

Results

A total of 8246 patients in the UK CHIC study had ever received a HLA B*5701 test, of whom 426 (5.2%) were positive. There were 3258 patients ever tested who were ART-naive at study entry and who were included in the study of the effects of HLA B*5701 status and viral load on $CD4^+$ cell count; 165 (5.1%) of this group had tested positive for HLA B*5701. Characteristics of these patients are given in Table 1(i). Median (interquartile range, IQR) $CD4^+$ cell count at entry was 511 (365–663) cells/μl in HLA B*5701-positive individuals and 395 (282–540) cells/μl in HLA B*5701-negative ($P<0.0001$). Median (IQR) viral load at study entry was 4.1 (3.3–4.6) and 4.5 (3.9–5.0) $\log_{10}$ copies/ml in those positive and negative, respectively ($P<0.0001$).

Table 1. Characteristics of patients included in each aspect of study.

	(i) Patients ever tested who were untreated at study entry ($n=3258$)			(ii) Patients commencing nonabacavir regimen ($n=9565$)			
	HLA B*5701-positive	HLA B*5701-negative	*P*	HLA B*5701-positive	HLA B*5701-negative	Not tested	*P*
N (%)	165 (5.1)	3093 (94.9)		220 (2.3)	2981 (31.2)	6364 (66.5)	
ART-naive	–	–	–	89 (40.5)	1393 (46.7)	2157 (33.9)	<0.0001
Age [median (IQR)]	34 (29–40)	34 (28–40)	0.28	43 (37–50)	39 (33–46)	41 (35–47)	<0.0001
Sex							
Male	140 (84.8)	2259 (73.0)	0.001	192 (87.3)	2022 (67.8)	4538 (71.3)	<0.0001
Ethnicity							
White	127 (77.0)	1676 (54.2)	<0.0001	161 (73.2)	1407 (47.2)	3402 (53.5)	<0.0001
Black African	15 (9.1)	846 (27.4)		17 (7.7)	1044 (35.0)	1876 (29.5)	
Black other	7 (4.2)	208 (6.7)		12 (5.5)	223 (7.5)	316 (5.0)	
Other	16 (9.7)	363 (11.7)		30 (13.6)	307 (10.3)	770 (12.1)	
Exposure							
MSM	123 (74.5)	1700 (55.0)	<0.0001	161 (73.2)	1352 (45.4)	3235 (50.8)	<0.0001
Heterosexual	34 (20.6)	1217 (39.4)		47 (21.4)	1393 (46.7)	2614 (41.1)	
Other/unknown	8 (4.9)	176 (5.7)		12 (5.5)	236 (7.9)	515 (8.1)	
Hepatitis B coinfection							
No	82 (49.7)	1725 (55.8)	0.034	162 (73.6)	2134 (71.6)	3762 (59.1)	<0.0001
Yes	0 (0.0)	62 (2.0)		5 (2.3)	133 (4.5)	311 (4.9)	
No test/unknown	83 (50.3)	1306 (42.2)		53 (24.1)	714 (24.0)	2291 (36.0)	
Hepatitis C coinfection							
No	88 (53.3)	1749 (56.5)	0.53	161 (73.2)	2036 (68.3)	3788 (60.1)	<0.0001
Yes	4 (2.4)	101 (3.3)		11 (5.0)	153 (5.1)	317 (5.5)	
No test/unknown	73 (44.2)	1243 (40.2)		48 (21.8)	792 (26.6)	2259 (34.4)	
Year of entry							
Prior to 2004	69 (41.8)	1197 (38.7)	0.48	146 (66.4)	1393 (46.7)	4043 (63.5)	<0.0001
2005–2007	52 (31.5)	1119 (36.2)		48 (21.8)	879 (29.5)	1164 (18.3)	
2008–2011	44 (26.7)	777 (25.1)		26 (11.8)	709 (23.8)	1157 (18.2)	
Previous AIDS							
Yes	11 (6.7)	290 (9.4)	0.24	38 (17.2)	537 (18.0)	1468 (23.1)	<0.0001
$CD4^+$ cell count cells/μl							
[Median (IQR)]	511 (365–663)	395 (282–540)	<0.0001	319 (209–515)	300 (198–460)	350 (220–559)	<0.0001
Viral load $\log_{10}$ copies/ml							
[Median (IQR)]	4.1 (3.3–4.6)	4.5 (3.9–5.0)	<0.0001	2.9 (1.7–4.6)	3.9 (1.7–4.9)	1.8 (1.7–4.5)	<0.0001

(i) Characteristics for this patient group are calculated at study entry; (ii) characteristics for this patient group are calculated upon commencement of nonabacavir combination antiretroviral therapy (cART) regimen.

In linear regression, both HLA B*5701 status and viral load were independently associated with $CD4^+$ cell count at entry after adjustment for age, sex, and ethnicity, with a mean (95% confidence interval, CI) $CD4^+$ cell count increase of 42 (10–74) cells/μl in HLA B*5701-positive individuals over negative and an 80 (72–88) cells/μl decrease for every $\log_{10}$ copy increase in viral load (results not shown). However, a test for an interaction between HLA B*5701 status and viral load did not suggest strong evidence that viral load had a differential impact on $CD4^+$ cell count in those who were positive for the allele and those negative ($P=0.088$). Further, in linear regression models of all off-ART $CD4^+$ and viral load pairs and models restricted to those of white ethnicity, there was no evidence of an interaction between viral load and HLA B*5701 status ($P=0.76$ and $P=0.95$, respectively).

There were 3476 tested individuals who commenced a nonabacavir cART regimen following a test for HLA B*5701, 3201 of whom had follow-up of at least one $CD4^+$ cell count and viral load measurement. A further 6364 individuals who had not been tested commenced a nonabacavir regimen after 2005. Characteristics of all 9565 patients upon starting a nonabacavir regimen are shown in Table 1(ii). In the subgroup of ART-naive patients, HLA B*5701-positive individuals were more likely to achieve an undetectable viral load than negative [adjusted hazard ratio (AHR) = 1.60, 95% CI (1.28–2.01) (Table 2)]. HLA B*5701-positive patients also showed a decreased likelihood of experiencing viral rebound compared with negatives, although this result did not reach statistical significance [AHR = 0.57, 95% CI (0.23–1.39)]. There was a small reduction in the risk of treatment switch that was not significant [AHR = 0.86, 95% CI (0.60–1.22)]. Those not tested had a similar risk of viral rebound and treatment switch to HLA B*5701 negatives, but a slightly increased likelihood of achieving an undetectable viral load (hazard ratio = 1.15, 95% CI 1.06–1.24). Including ART-experienced patients in the analysis of virological response yielded similar results (Table 2). An increased likelihood of viral suppression was still present in positive patients compared with negative [AHR = 1.29, 95% CI (1.15–1.54)], as was

Table 2. Risk of achieving different virological end-points according to HLA-B*5701 status.

		HLA B*5701 status	Unadjusted hazard ratio	95% Confidence interval	*P* value	Adjusted[a] hazard ratio	95% Confidence interval	*P* value
ART-naive only	Viral load <50 copies/ml	Negative	1.00	–	–	1.00	–	–
		Positive	1.50	(1.21–1.87)	0.0003	1.60	(1.28–2.01)	<0.0001
		Not tested	0.96	(0.89–1.03)	0.29	1.15	(1.06–1.24)	0.001
	Viral load rebound	Negative	1.00	–	–	1.00	–	–
		Positive	0.44	(0.18–1.08)	0.073	0.57	(0.23–1.39)	0.22
		Not tested	0.95	(0.77–1.17)	0.63	0.90	(0.72–1.13)	0.37
	Treatment switch	Negative	1.00	–	–	1.00	–	–
		Positive	0.72	(0.51–1.02)	0.063	0.86	(0.60–1.22)	0.39
		Not tested	1.11	(0.89–1.07)	0.056	1.05	(0.94–1.17)	0.44
		HLA B*5701 status	Unadjusted hazard ratio	95% Confidence interval	*P* value	Adjusted[b] hazard ratio	95% Confidence interval	*P* value
All patients	Viral load <50 copies/ml	Negative	1.00	–	–	1.00	–	–
		Positive	1.45	(1.26–1.67)	<0.0001	1.29	(1.15–1.54)	0.0005
		Not tested	1.01	(0.97–1.06)	0.59	0.97	(0.92–1.01)	0.15
	Viral load rebound	Negative	1.00	–	–	1.00	–	–
		Positive	0.47	(0.29–0.77)	0.003	0.61	(0.37–0.99)	0.044
		Not tested	0.91	(0.81–1.04)	0.15	0.87	(0.77–1.00)	0.044
	Treatment switch	Negative	1.00	–	–	1.00	–	–
		Positive	0.80	(0.66–0.98)	0.030	0.91	(0.74–1.12)	0.38
		Not tested	1.03	(0.96–1.09)	0.43	0.98	(0.92–1.05)	0.60

ART, antiretroviral therapy.
[a]Adjusted for viral load, $CD4^+$ cell count, regimen type, age, hepatitis B and C coinfection at regimen start and sex, ethnicity, and exposure group.
[b]Adjusted for viral load, $CD4^+$ cell count, regimen type, age, hepatitis B and C coinfection, number of previous regimens and any previous virological failure at regimen start and sex, ethnicity, and exposure group.

the decreased risk of viral rebound, which was now significant [AHR = 0.61, 95% CI (0.37–0.99)] due to the larger number of individuals included in the analysis.

Immunological response to cART did not differ according to HLA B*5701 status. Being HLA B*5701-positive increased 6-month $CD4^+$ cell count change by 16.7 cells/μl [95% CI (−11.5–45.0)] on average compared with the 6-month change in negative patients. Twelve-month $CD4^+$ cell count change was in fact lower by approximately 28 cells/μl [95% CI (−62.3–5.8)] in positive patients compared with negative. There was no difference in 6-month [$\beta = -10.6$, 95% CI (−20.0–1.2)] or 12-month [$\beta = 1.2$, 95% CI (−10.5–12.9)] $CD4^+$ cell count change between those negative and those not tested for the allele.

Discussion

To our knowledge, this is the first large study of a representative HIV-infected population to assess the influence of HLA B*5701 status on virological outcomes and immunological response to cART. When treated with nonabacavir-containing cART and after adjustment for baseline viral load, HLA B*5701-positive patients were more likely to achieve an undetectable viral load, and less likely to experience viral load rebound than HLA B*5701-negative individuals. This is the first study to indicate a beneficial effect of HLA B*5701 on achieving and maintaining viral load suppression. Interestingly, the only other study assessing virological outcomes, the female WIHS Cohort (some of whom were treated with abacavir), showed poorer virological responses in those with HLA B*5701 [14]. Previous studies, like ours, failed to show any effect of HLA B*5701 on $CD4^+$ cell recovery after starting ART [13,14]. A possible mechanism for our findings may be that the allele provides a more effective immunological (cytotoxic T lymphocyte) response to augment the effect of ART in diminishing cells that support active viral replication [13,14,16]. Our finding of improved virological outcomes in HLA B*5701-positive individuals requires confirmation in other large cohorts.

Our data also demonstrate that HLA B*5701-positive individuals had a significantly higher $CD4^+$ cell count and lower viral load at presentation compared with HLA B*5701-negative patients. The observation that HLA B*5701-positive individuals had improved markers of HIV disease over HLA B*5701-negative individuals at study entry is consistent with slower HIV disease progression in this group, which has been seen in other studies [6,7,14]. However, a main limitation of this study is that this hypothesis could not be confirmed, as data on the likely date of HIV infection were not available. Another limitation of this study is the relatively small numbers of HLA B*5701-positive individuals in some analyses. We did not assess rate of $CD4^+$ cell decline

according to HLA B*5701 status as a measure of HIV disease progression in our untreated patient group. In an observational cohort such as this that utilizes only clinical data, we are unlikely to attain sufficient pre-ART $CD4^+$ cell data to achieve reliable results from an analysis of this kind. Further work to assess $CD4^+$ cell count decline from time of HIV seroconversion in untreated HLA B*5701-positive and negative individuals is needed.

In conclusion, we have found that HLA B*5701 status may affect $CD4^+$ cell count, HIV viral load, and responses to cART. This is further evidence that the HLA B*5701 allele may be beneficial in terms of slower progression of HIV infection.

Acknowledgements

Members of Writing Committee are as follows: Sophie Jose (Research Department of Infection and Population Health, University College London, UK), David Chadwick (The James Cook University Hospital, Middlesbrough, UK), Teresa Hill (Research Department of Infection and Population Health, University College London, UK), Adrian Palfreeman (University Hospitals of Leicester NHS Trust, Leicester, UK), Richard Gilson (Mortimer Market Centre, University College Medical School, London, UK), Chloe Orkin (Barts and The London NHS Trust, London, UK), Frank Post (Kings College Hospital NHS Foundation Trust, London, UK), David Dunn (MRC Clinical Trials Unit, London, UK), Jane Anderson (Homerton University Hospital NHS Trust, London, UK), Jonathan Ainsworth (North Middlesex University Hospital NHS Trust, London, UK), Martin Fisher (Brighton and Sussex University Hospital NHS Trust, Brighton, UK), Mark Gompels (North Bristol NHS Trust, Bristol, UK), Clifford Leen (Edinburgh University, Western General Hospital, Edinburgh, UK), John Walsh (Imperial College Healthcare NHS Trust, London, UK), and Caroline Sabin (Research Department of Infection and Population Health, University College London, UK) For the UK Collaborative HIV Cohort Study Steering Committee.

Members of UK CHIC Steering Committee are as follows: Jonathan Ainsworth, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Stephen Kegg, Clifford Leen, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Frank Post, Caroline Sabin (PI), Memory Sachikonye, Achim Schwenk, and John Walsh.

Central Co-ordination: UCL Research Department of Infection & Population Health, Royal Free Campus, London (Teresa Hill, Susie Huntington, Sophie Jose, Andrew Phillips, Caroline Sabin, Alicia Thornton); Medical Research Council Clinical Trials Unit (MRC CTU), London (David Dunn, Adam Glabay).

Participating centers are as follows: Barts and The London NHS Trust, London (C Orkin, N Garrett, J Lynch, J Hand, C de Souza); Brighton and Sussex University Hospitals NHS Trust (M Fisher, N Perry, S Tilbury, D Churchill); Chelsea and Westminster Hospital NHS Trust, London (B Gazzard, M Nelson, M Waxman, D Asboe, S Mandalia); Health Protection Agency – Centre for Infections London (HPA) (V Delpech); Homerton University Hospital NHS Trust, London (J Anderson, S Munshi); King's College Hospital NHS Foundation Trust, London (H Korat, M Poulton, C Taylor, Z Gleisner, L Campbell); Mortimer Market Centre, London (R Gilson, N Brima, I Williams); North Middlesex University Hospital NHS Trust, London (A Schwenk, J Ainsworth, C Wood, S Miller); Royal Free NHS Trust and UCL Medical School, London (M Johnson, M Youle, F Lampe, C Smith, H Grabowska, C Chaloner, D Puradiredja); St. Mary's Hospital, London (J Walsh, J Weber, F Ramzan, N Mackie, A Winston); The Lothian University Hospitals NHS Trust, Edinburgh (C Leen, A Wilson); North Bristol NHS Trust (M Gompels, S Allan); University of Leicester NHS Trust (A Palfreeman, A Moore); South Tees Hospitals NHS Foundation Trust (D Chadwick, K Wakeman).

C.S., S.J., and D.C. designed the study and wrote the article. S.J. did the main analyses and C.L. advised on analysis and critically reviewed the article. T.H. (study coordinator) is responsible for collecting and preparing UK CHIC data for analysis. As steering committee members for participating centers A.P., R.G., C.O., F.P., D.D., J.An., J.Ai., M.F., M.G., C.L., and J.W. advised on study concept and design and critically reviewed the article.

The UK CHIC study is funded by the Medical Research Council, UK (grant numbers G0000199, G0600337, and G0900274).

Conflicts of interest

S.J., D.C., T.H., A.P., D.D., J.Ai. and C.L. have no conflicts of interest to report. R.G. has reported receiving funding from the following in connection with conference attendance, advisory boards or speaker fees: Gilead Sciences, Roche, Janssen-Cilag, Bristol-Myers Squibb, Merck. His department has received research funds from Gilead, Viiv, and Pfizer. C.O. has reported receiving funding from the following in connection with consultancy services, project grants, speakers fees, development of educational materials or conference attendances: Viiv, GSK, Abbott, BMS, Gilead Sciences. F.P. has reported receiving funding from the following in connection with consultancy services, project grants, speakers fees, development of educational materials or

conference attendances: BMS, Gilead Sciences, Viiv, Abbott, Janssen. J.An. has reported receiving money from Pharma in connection with consultancy services, project grants, speakers fees or development of educational materials. M.F. has reported receiving funding from the following in connection with project grants, speakers fees or conference attendances: Gilead Sciences, Bristol-Myers Squibb, Janssen, Abbott, Merck, Viiv. M.G. has reported receiving funding from the following in connection with speakers fees and membership of advisory boards: Janssen, Bristol-Myers Squibb, Viiv, Viropharma, CSL Behring. J.W. has reported receiving funding from the following in connection with conference attendance: Gilead Sciences. C.S. has reported receiving funding from the following in connection with membership of data safety and monitoring boards, advisory boards, speakers panels and for the development of educational materials: Gilead Sciences, Abbott Pharmaceuticals, Janssen-Cilag, Viiv, Merck Sharp and Dohme, Bristol-Myers Squibb.

References

1. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, *et al*. **Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir.** *Lancet* 2002; **359**:727–732.
2. Hughes AR, Mosteller M, Bansal AT, Davies K, Haneline SA, Lai EH, *et al*. **Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations.** *Pharmacogenomics* 2004; **5**:203–211.
3. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, *et al*. **HLA-B*5701 screening for hypersensitivity to abacavir.** *N Engl J Med* 2008; **358**:568–579.
4. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, *et al*. **High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients.** *Clin Infect Dis* 2008; **46**:1111–1118.
5. Waters LJ, Mandalia S, Gazzard B, Nelson M. **Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience.** *AIDS* 2007; **21**:2533–2534.
6. Salgado M, Simon A, Sanz-Minguela B, Rallon NI, Lopez M, Vicario JL, *et al*. **An additive effect of protective host genetic factors correlates with HIV nonprogression status.** *J Acquir Immune Defic Syndr* 2011; **56**:300–305.
7. Gao X, O'Brien TR, Welzel TM, Marti D, Qi Y, Goedert JJ, *et al*. **HLA-B alleles associate consistently with HIV heterosexual transmission, viral load, and progression to AIDS, but not susceptibility to infection.** *AIDS* 2010; **24**:1835–1840.
8. Fellay J, Shianna KV, Ge D, Colombo S, Ledergerber B, Weale M, *et al*. **A whole-genome association study of major determinants for host control of HIV-1.** *Science* 2007; **317**: 944–947.
9. Migueles SA, Sabbaghian MS, Shupert WL, Bettinotti MP, Marincola FM, Martino L, *et al*. **HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors.** *Proc Natl Acad Sci U S A* 2000; **97**:2709–2714.
10. Carrington M, O'Brien SJ. **The influence of HLA genotype on AIDS.** *Ann Rev Med* 2003; **54**:535–551.
11. Gillespie GM, Kaul R, Dong T, Yang HB, Rostron T, Bwayo JJ, *et al*. **Cross-reactive cytotoxic T lymphocytes against a HIV-1 p24 epitope in slow progressors with B*57.** *AIDS* 2002; **16**: 961–972.
12. Yu XG, Lichterfeld M, Chetty S, Williams KL, Mui SK, Miura T, *et al*. **Mutually exclusive T-cell receptor induction and differential susceptibility to human immunodeficiency virus type 1 mutational escape associated with a two-amino-acid difference between HLA class I subtypes.** *J Virol* 2007; **81**:1619–1631.
13. Ahuja SK, Kulkarni H, Catano G, Agan BK, Camargo JF, He W, *et al*. **CCL3L1-CCR5 genotype influences durability of immune recovery during antiretroviral therapy of HIV-1-infected individuals.** *Nat Med* 2008; **14**:413–420.
14. Kuniholm MH, Gao X, Xue X, Kovacs A, Anastos K, Marti D, *et al*. **Human leukocyte antigen genotype and risk of HIV disease progression before and after initiation of antiretroviral therapy.** *J Virol* 2011; **85**:10826–10833.
15. UK Collaborative HIV Cohort Steering Committee. **The creation of a large UK-based multicentre cohort of HIV-infected individuals: the UK Collaborative HIV Cohort (UK CHIC) Study.** *HIV Med* 2004; **5**:115–124.
16. Brumme ZL, Brumme CJ, Chui C, Mo T, Wynhoven B, Woods CK, *et al*. **Effects of human leukocyte antigen class I genetic parameters on clinical outcomes and survival after initiation of highly active antiretroviral therapy.** *J Infect Dis* 2007; **195**:1694–1704.