

Progression of HIV to AIDS: a Protective Role for HLA-B27?

Debby den Uyl¹, Irene E. van der Horst-Bruinsma¹ and Michiel van Agtmael²

¹Departments of Rheumatology and ²Internal Medicine, VU University Medical Centre Amsterdam, The Netherlands

Abstract

HLA-B27 is known for its strong association with inflammatory spondyloarthropathies (SpA), a group of rheumatic diseases. Apart from playing its role in the onset of these inflammatory diseases, HLA-B27 is so ubiquitous in the world that the carrying of this gene must have also have an advantage. There are some indications that a beneficial effect can be found as a less severe course of viral infections among B27-carriers. The literature on this subject was reviewed and revealed a favorable course of infection with influenza virus, herpes simplex type 2 virus, Epstein-Barr virus and, even more interesting, a protective effect of HLA-B27 in the progression of HIV infections. The course of HIV infection differs among individuals and is thought to be partly related to host-factor variability, reflecting broad genetic heterogeneity. The polymorphic human leukocyte antigens (HLA) are herein analyzed intensively with respect to this relationship.

Cytotoxic T lymphocyte (CTL) responses, activated by HLA antigen presentation, are implicated in the control of HIV replication. An immunological explanation for the protective role for HLA B27 in HIV disease is that B27+ patients have a specific and strong CTL response against the p24 epitope, a conservative HIV protein that does not easily mutate. Some HLA genes seen in long-term non-progressors (LTNP) (>10 years disease free) are associated with a favorable prognosis. One of the alleles found predominantly in LTNPs is HLA-B27. More genetic factors seem to influence disease progression in HIV infections. Therefore, it would be interesting to further explore the influence of the genetic make up of these HIV-infected individuals. Knowledge of the immunogenetic profile might give clues for the individual course of the HIV infection, may influence the development of drug-resistant viruses and will possibly lead to a tailored therapeutic strategy in HIV-infected persons. (AIDS Reviews 2004;6:89-96)

Key words

HLA-B27. HIV. AIDS. Spondyloarthropathy. Disease progression.

Introduction

The natural course of HIV infection is characterized by considerable variations among infected individuals. The time between infection and progression to AIDS

varies per individual from 5-20 years and is believed to be related to both viral and host factors, including genetic differences. Prognostic viral factors for fast progression are the level of the viral load and the presence of certain mutants. For instance, SI (syncytium-inducer, or X4) viruses accelerate the immune decay more than NSI (non-syncytium-inducer, or R5) viruses. The intriguing relationship between viral and host factors has led to many studies to unravel the extent of their respective roles.

Host factors are, among others, a strong cytotoxic T lymphocyte (CTL) response against HIV, which is generally believed to play an important role in controlling virus replication¹. CTLs are activated by binding to antigenic peptides, presented by human leukocyte antigens (HLA), thereby initiating the immune response.

Correspondence to:

Irene E. van der Horst-Bruinsma
Department of Rheumatology, room 4A-42
PO Box 7057
1007 MB Amsterdam
The Netherlands
Phone: +0031 204443432
Fax: +0031 204442138
E-mail: IE.vanderHorst@vumc.nl

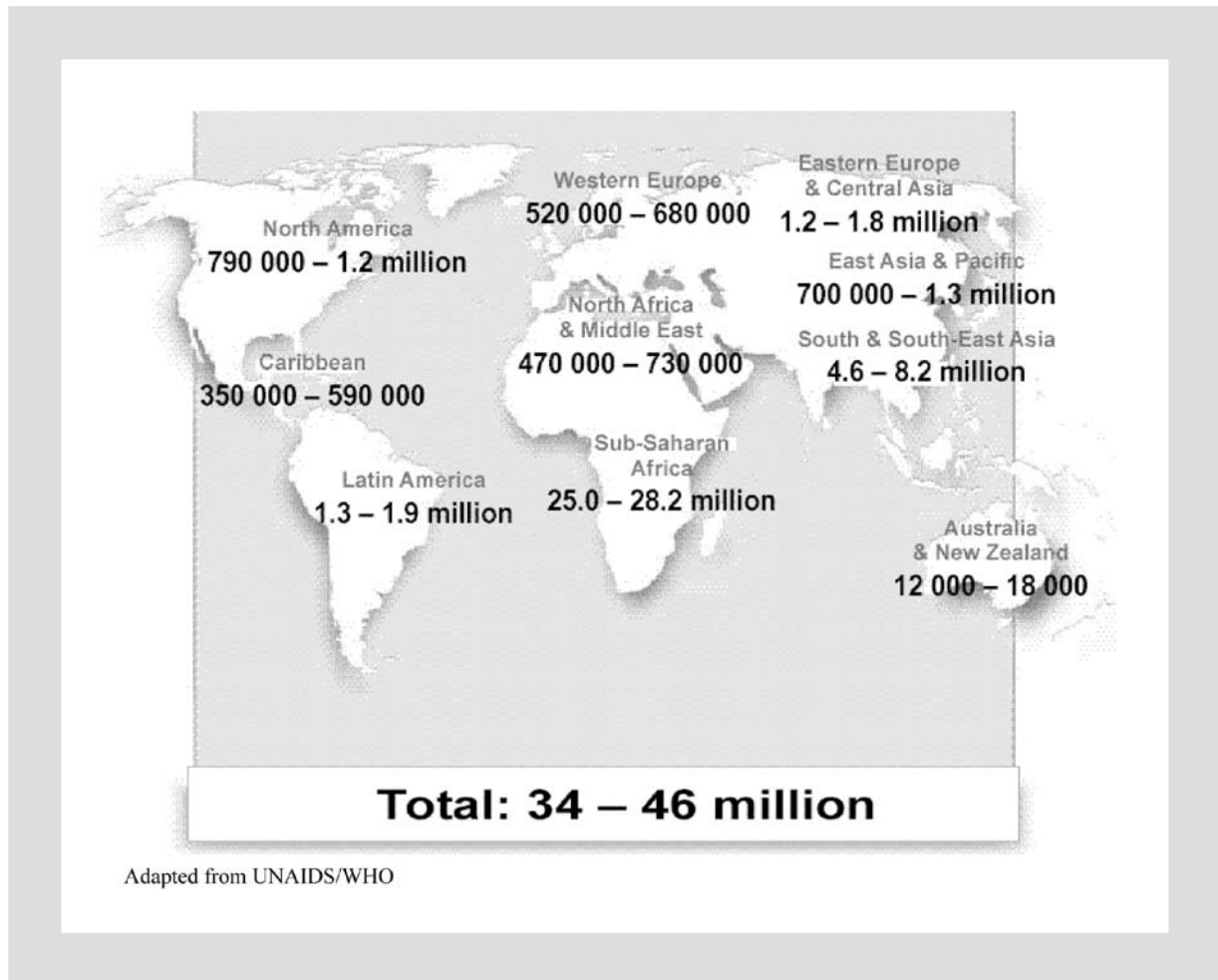


Figure 2. Number of children and adults with HIV/AIDS at the end of year 2003.

monella, *Shigella*, *Campylobacter* and *Klebsiella*, triggers the local chronic inflammation causing reactive arthritis¹⁶.

Animal models support the importance of an infectious agent triggering disease. Rats maintained in germ-free environments did not develop arthritis; however after being transferred out of the pathogen-free colony, arthritic changes were seen within several weeks¹⁷. Different bacteria involved in SpA pathology were found to have sequence homology with certain regions of the B27 molecule¹⁸.

The “molecular mimicry” hypothesis explains that bacteria would cause SpA as antibodies cross-react with self-peptides. Another theory suggested that bacteria bind to an empty HLA-B27 molecule, thereby activating autoreactive T-cells¹⁴. Empty HLA-B27 molecules are relatively stable compared to other HLA subtypes, and are able to bind to several peptides¹⁹.

Finally, the role of CD4+ T-cells is believed to be of importance. MHC class II-, HLA-B27+ transgenic mice still develop spontaneous disease²⁰. This can be explained by the hypothesis that CD4+ T-cells can recognize MHC class I molecules¹⁵. Some investigators believe that the empty B27 molecule forms an abnormal complex with itself, causing a local autoimmune response by activating CD4+ cells^{14,15}. The enhanced CTL response in B27+ HIV-infected patients should explain their better prognosis.

Twenty subtypes of HLA-B27 exist, but not all are associated with human disease. B2706 and B2709 are not disease-associated, while B2702, B2703, B2705 (the most common subtypes) and B2707 are clearly associated with disease²¹. It is believed that the diversity of the HLA antigens is maintained through natural selection by local infectious diseases²². But if HLA-B27 is strongly associated with SpA, why is it more common in the northern than in the southern hemisphere (Fig. 1)?

Could there be advantages of having HLA-B27, thereby causing an evolutionary selection?

HLA-B27 viral infections

Demographic data indicate that the incidence of some viral infections is higher in the northern hemisphere. Hepatitis C is found predominantly in countries of the northern hemisphere²³ and outbreaks of influenza viruses and SARS are also mainly associated with countries of the northern hemisphere where HLA-B27 is more prevalent²⁴. Could there be an evolutionary connection?

HLA-B27 is thought to positively influence the outcome of viral infections like influenza, herpes simplex virus type 2 (HSV-2) and Epstein-Barr virus (EBV)^{12,25-27}. The importance of HLA B27 in influenza is clear from the recent description of a new escape mutant influenza A virus with a mutation of a HLA B27 specific epitope²⁵. Also B27+ individuals infected with EBV show high, specific CTL responses against viral epitopes, suggesting a protective role^{26,27}. The evaluation of three cohorts showed an association of B27 with asymptomatic infection of HSV-2²⁷. B27 is associated with a benign clinical course of hantavirus infection²⁸. In addition progression of HIV infection in particular appears to be positively effected by presence of HLA-B27^{12,14}.

Definition of HIV progression

HIV progression can be measured in two ways: by the level of viral antigens (viral load) and by the decrease in CD4+ cells (CD4 count).

Viral load and viral escape

AIDS is the result of an ongoing infection of the immune system. CTLs have been implicated in the control of HIV infection by several mechanisms, including direct killing through lysis, or by inhibiting viral replication by production of cytokines and chemokines². Infected patients produce strong CTL responses to HIV²⁹. Ogg, et al.¹ observed an inverse correlation between HIV-specific CTL frequency and plasma RNA viral load. Characteristic of HIV is its ability to escape CTL responses. This is due to the high mis-incorporation rate of HIV and its transcriptase, which lacks proof-reading activity^{29,30}.

In longstanding, progressed, HIV infection not just one HIV-epitope but a cloud of mutated epitopes was found in patients with increasing viral load levels^{29,31,32}. This mechanism seems an effective survival strategy of the virus. CTLs exert a selective force on HIV, giving an advantage to epitopes mutated in critical amino acids in the dominant epitopes. This viral escape causes an increase in viral load^{29,32,33}. An epitope which escapes from CTLs has a selective advantage and this escape mutant will eventually dominate the virus population^{29,32,33}. The consequence of this antigenic variation is a shift of immunodominance of CTL response to other epitopes, resulting in an irreversible immunodeficiency. Thus, high levels of plasma HIV-RNA levels are associated with rapid disease progression. Effective therapy will prevent viral escape because a high viral replication is needed for HIV to mutate. However, suboptimal therapy will lead to escape variants, which can be transmitted sexually, theoretically leading to a spread of non-responsive epitopes over the world³⁴ (Fig. 2).

CD4 count and CTL response

Failure to control the virus will cause CTL escape. Moreover, CD4+ T-cells have direct antiviral effects³⁵ and because of their antigen-presenting role, T-helper cells are important in the priming of CTLs, maintaining CTL memory, and for maturing CTLs³⁶. T-helper cells are needed to initiate new CTL responses against the mutated epitopes³. However, with ongoing HIV infection there is a gradual loss of these CD4+ T-helper cells, as they are the main targets of the HIV virus. The decline in the CD4+ count will weaken the CTL response and is therefore a second cause for viral escape. An effective suppression of the virus with antiretroviral therapy will protect CD4+ cells, resulting in a better control of HIV³⁶. By reducing the replication of the virus to a minimum, thus halting the destruction of CD4+ T-cells, a strong CTL response is maintained.

HLA B27 and slow HIV progression

With the HIV pandemic evolving in low-resource countries with limited access to antiretroviral drugs, there is growing interest in identifying the 5-10% of patients with a relatively natural course being called "long-term survivors" (10-20 years). A number of studies have shown a higher frequency of the B27 haplo-

Table 1. Results of studies associating HLA-B27 with slow progression of HIV-1 infection

Reference	Study design	Risk group	Race	Cohort size (% B27)	Definition of disease progression	Antiretroviral treatment	RR B27
Kaslow '96 ⁴	Cohort*	Homosexual	Caucasian	241 (7%)	AIDS-free interval	(50%)	0.23
McNeil '96 ⁵	Cohort	IDU	?	313 (8%)	Rate CD4+ decline in time	AZT (66%)	0.3
Carrington '99 ³⁷	Cohort	IDU	African-American	144 (?)	AIDS-free time Time till death	?	6.86
Keet '99 ¹⁰	Cohort	Homosexual	Caucasian	375 (8%)	Rate CD4+ decline in time AIDS-free interval	Single or combination	0.4
Magierowska '99 ⁶	Extremes [†]	Homosexual IDU	Caucasian	153 (11%)	LTNP: asymptomatic ≥ 8 years + CD4 > 600 µl last 5 years	LTNP: no therapy	0.2
Hendel '99 ¹¹	Extremes	?	Caucasian	276 (13%)	LTNP: asymptomatic ≥ 8 years + CD4 > 500 cells/mm ³	LTNP: no therapy	0.34
Trachtenberg '03 ³⁰	Cohort	Homosexual	?	481 (2%)	Rate CD4+ decline in time Viral load level	HAART (guidelines)	?

*Cohort: prospective follow-up cohort with known seroconversion date; †extremes = extreme patient study: comparing the extremes of disease progression (slow progressors and fast progressors); IDU: injection drug users; RR = relative risk; >1 = short AIDS-free interval; <1 = prolonged AIDS-free interval.

type in this subgroup of patients. Table 1 summarizes the associations between B27 and HIV progression resulting from several observational cohorts and so-called “extreme patient” studies^{4-6,8,9,30}. These studies suggest that HLA-B27 is involved in the pathogenesis of HIV.

Kaslow, et al.⁴ correlated in 1996 one of the first individual HLA-B27 profiles with slow progression. This observation was confirmed by Magierowska, et al.⁶. McNeil, et al.⁵ showed a significant association of B27 with a delayed progression to AIDS. Hendel, et al.⁹ studied a cohort of individuals representing extremes of fast progressors and non-progressors and they also found a protective effect of B27 on the progression to AIDS. In contrast, the results of Carrington, et al.³⁷ showed an association of B27 with rapid progression. This was found among the 144 African-Americans studied, whereas the positive effect of B27 in other studies had been seen among Caucasians. Smith, et al.³⁸ found an overall lower CD4 count among black HIV-infected persons compared with white HIV-infected persons, while Trachtenberg, et al.³⁰ found that black men had lower viral loads than white men. These

data suggest an influence of ethnic background on HIV progression; therefore the association of B27 with rapid progression among African-Americans could be a result of selection bias.

Although most studies implicated B27 prevalence with slow progression, some associations of B27 with HIV progression only indicate a trend^{10,30,39}. The inconsistencies seen in B27 data could be explained by the study design or by the fact that B27 is a rare HLA subtype in these research-groups. To study HLA influence on HIV progression it is important to know the date of seroconversion and to choose an exact endpoint (death, AIDS or CD4+ decline)⁷. Also, a short interval of HLA-typing is important to ensure that no HLA types are missed because of early death⁷. The effects of multi-allelic associations may be difficult to interpret. The extensive polymorphism of HLA, linkage disequilibrium and cohort size can complicate the interpretation of results^{7,8,40}. For example, small numbers of patients in a study lead to weaker associations because of the multiplicity of the HLA alleles, while large numbers of alleles need multiple-comparison correction (Bonferroni) to consider other HLA effects that

Table 2. Genetic factors involved in HIV-1 disease progression

Genetic factors	Function	Influence on HIV progression
HLA homozygosity	MHC	Rapid progression
HLA-B35	MHC	Rapid progression
HLA-Cw04	MHC	Rapid progression
HLA-B27	MHC	Slow progression
HLA-B57	MHC	Slow progression
CCR2-64I	Chemokine receptor	Slow progression
CCR5-Δ32	Chemokine receptor	Slow progression
CX3CR1	Chemokine receptor	Rapid progression
SDF1-3'A	Chemokine	Slow progression
RANTES	Chemokine	Slow progression
IL10-5'A	Cytokine	Rapid progression
MBL	Mannose-binding lectin	Rapid progression

CCR2 and CCR5 are coreceptors for HIV-1. CX3CR1 is rarely used as coreceptor for HIV; a mutated form was associated with rapid progression in one study. SDF1 is the chemokine receptor for CXCR4, an important coreceptor for HIV-1 in the late disease course. RANTES is the CCR5 chemokine ligand and could suppress HIV-1 infection by blocking CCR5. IL10 is a TH-2 cell cytokine that is shown to inhibit HIV-1 replication in macrophages. MBL activates complement and phagocytosis and a genetic variant is associated with rapid progression to AIDS.

could mask the influence^{7,40}. Ideally a study is performed in hundreds of HLA-characterized patients, but this is difficult to establish in practice.

Mechanism of Gag-specific CTL response

Although not all results of the role of B27 in HIV progression seen in cohort and cross-sectional studies are consistent, there is a molecular basis to explain the protective role of B27 in HIV progression. It is believed that HIV-infected patients carrying HLA-B27 control the virus better due to their strong immune response. Studies show that patients with HLA-B27 maintain stable CD4 counts for many years and present high levels of HIV-specific CD8+ T-cells during the asymptomatic phase. It is known that HIV can escape from selective pressure of CTLs. Patients with HLA-B27 have CTLs specifically selected for a Gag p24 epitope (amino acids 263-272, sequence KRWILGLNK), a core protein of HIV^{31,41}. This Gag p24 epitope is strongly immunodominant³². Although oligoclonal T-cell responses are believed to give a better protection against viral escape³⁵, B27+ patients clearly show an immune response against one epitope. How can this be explained?

Results from several studies have shown that Gag p24 does not mutate easily and therefore it is believed to represent a conservative HIV protein^{31,42,43}. Most mutations lead to a non-viable virus, because they result in a changed conformation, causing the peptide

to lose its function³¹. But even when a mutation variant survives, peptide-binding experiments have shown that B27-specific CTLs still recognize these mutated Gag p24^{31,42}. Crystallographic analysis showed the importance of arginine at position 2, which binds strongly with the B-pocket of the B27 molecule, creating a stable complex⁴⁴. An amino acid substitution from arginine (R) to lysine (K) or glycine (G) leads to a peptide that binds poorly to B27^{31,42}. Kelleher, et al.³¹ proved that Gag p24 escapes from HLA-B27 only after a particular array of mutations. The functional importance of p24 and the genetic tolerance of B27 explain why HIV escape from B27-specific CTLs occurs late in the course of infection.

Unfortunately, the mutational escape variant is found to be sexually transmittable⁴⁵. Children sharing the HLA-B27 with their mother failed to control HIV replication. These children showed a rapid disease progression because they targeted an epitope that had already escaped from B27-specific CTLs. Other studies support the theory that advantageous mutated epitopes may be transmitted frequently to other individuals with the same HLA type^{30,45,46}.

Other genetic factors and progression to AIDS

HIV is found to progress faster in individuals homozygous for HLA loci, because CTL escape occurs easier^{10,37}. Patients heterozygous at the HLA loci are able to present a higher variety of antigenic epitopes

to CTLs and studies suggest that this results in a more productive immune response^{30,37}.

A fast growing number of host genetic associations have been identified as correlating with HIV disease progression (Table 2). The role of chemokine receptors CCR2 and CCR5 especially have been studied intensively. These receptors are found to be used as coreceptors for HIV-1 together with CD4⁴⁷. A mutation in these genes, CCR5-Δ32 and CCR2-64I, has been shown to provide strong protection and is found more frequently in LTNPs than in rapid progressors. Both are found to be associated with slow progression in many cohorts^{6,9,40,47,48}. Altogether, the results of many association studies illustrate the complexity of host genetic interactions with the HIV pathogen.

Conclusion

The role of HLA in HIV disease progression should be further elucidated to identify those patients with either a mild or aggressive course of their natural HIV-1 infection. HLA genotyping might influence the timing to start HIV therapy, for example postponing therapy in the long-term survivor group. This risk stratification could be relevant in countries with limited access to antiviral drugs. Under antiretroviral therapy, HLA type (like drug levels) may influence the risk for developing drug-resistant viruses. Thus, HLA typing could play a role in the choice of antiretroviral regimens, mainly in drug-naive patients. Knowledge of the immunogenetic background may enable us to calculate a composite genetic risk, which will be of increasing importance in the tailored management of HIV-infected patients. Moreover, since HLA loci vary by ethnic group and region, it may affect the response to specific vaccines in different parts of the world.

References

- Ogg G, Jin X, Bonhoeffer S, et al. Quantitation of HIV-1-specific cytotoxic T lymphocytes and plasma load of viral RNA. *Science* 1998;279:2103-6.
- McMichael A, Rowland-Jones S. Cellular immune responses to HIV. *Nature* 2001;410:980-7.
- McMichael A. T-cell responses and viral escape. *Cell* 1998;93:673-6.
- Kaslow R, Carrington M, Apple R, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med* 1996;2:405-11.
- McNeil A, Yap P, Gore S, et al. Association of HLA types A1-B8-DR3 and B27 with rapid and slow progression of HIV disease. *Q J Med* 1996;89:177-85.
- Magierowska M, Theodorou I, Debré P, et al. Combined genotypes of CCR5, CCR2, SDF1 and HLA genes can predict the long-term non-progressor status in HIV-1-infected individuals. *Blood* 1999;93:936-41.
- Gore S, Hutchinson S, Brettle R. Study requirements for investigating HLA-associated progression of HIV-disease, and review. *Q J Med* 1999;92:609-17.
- Buchbinder S, Katz M, Hessel N, O'Malley P, Holmberg S. Long-term HIV-1 infection without immunological progression. *AIDS* 1994;8:1123-82.
- Easterbrook P. Long-term non-progression in HIV infection: definitions and epidemiological issues. *J Infect* 1999;38:71-3.
- Keet I, Tang J, Klein M, et al. Consistent associations of HLA Class I and II and transporter gene products with progression of HIV-1 infection in homosexual men. *J Infect Dis* 1999; 180:299-309.
- Hendel H, Caillat-Zucman S, Lebeanec H, et al. New Class I and II HLA alleles strongly associated with opposite patterns of progression to AIDS. *J Immunol* 1999;162:6942-6.
- McMichael A, Bowness P. HLA-B27: natural function and pathogenic role in spondylarthritis. *Arthritis Res* 2002;4(Suppl 3):153-8.
- Khan M. Epidemiology of HLA-B27 and arthritis. *Clin Rheumatol* 1996;15(Suppl 1):0-2.
- Khare S, Luthra H, David C. HLA-B27 and other predisposing factors in spondyloarthropathies. *Curr Opin Rheumatol* 1998;10:282-91.
- Boyle L, Hill-Gaston J. Breaking the rules: the unconventional recognition of HLA-B27 by CD4+ T lymphocytes as an insight into the pathogenesis of the spondyloarthropathies. *Rheumatol* 2003;42:404-12.
- Kvien T, Glennas A, Melby K, et al. Reactive arthritis: incidence, triggering agents and clinical presentation. *J Rheumatol* 1994; 21:115-22.
- Taurog J, Maika A, Satumtira N, et al. Inflammatory disease in HLA-B27 transgenic rats. *Immunol Rev* 1999;169:209-23.
- Lahesmaa R, Skurnik M, Vaara M, Leirisalo-Repo M, Nissila M, Granfors K. Molecular mimicry between HLA-B27 and *Yersinia*, *Salmonella*, *Shigella* and *Klebsiella* within the same region of HLA alpha 1-helix. *Clin Exp Immunol* 1991;86:399-404.
- Benjamin R, Madrigal J, Parham P. Peptide binding to empty HLA-B27 molecules of viable human cells. *Nature* 1991;351:74-7.
- Khare S, Bull M, Hanson J, Luthra H, David C. Spontaneous inflammatory disease in HLA-B27 transgenic mice is independent of MHC class II molecules: a direct role for B27 heavy chains and not B27-derived peptides. *J Immunol* 1998;160:101-6.
- Khan M. Update: the twenty subtypes of HLA-B27. *Curr Opin Rheumatol* 2000;12:235-8.
- Parham P, Ohta T. Population biology of antigen presentation by MHC Class I molecules. *Science* 1996;272:67-74.
- Brown R Jr, Gaglio P. Scope of Worldwide Hepatitis C problem. *Liver Transpl* 2003;9(Suppl):10-3.
- WHO. Communicable Disease Surveillance & Response (Available from URL: www.who.int/csr/disease/en/).
- Voeten J, Bestebroer T, Nieuwkoop N, Fouchier R, Osterhaus A, Rimmelzwaan G. Antigenic drift in the influenza A virus (H3N2) nucleoprotein and escape from recognition by cytotoxic T lymphocytes. *J Virol*. 2000 Aug;74(15):6800-7.
- Brooks J, Colbert R, Mear J, Leese A, Rickinson A. HLA-B27 subtype polymorphism and CTL epitope choice: studies with EBV peptides link immunogenicity with stability of the B27-peptide complex. *J Immunol* 1998;161:5252-9.
- Lekstrom-Himes J, Hohman P, Warren T. Association of major histocompatibility complex determinants with the development of symptomatic and asymptomatic genital herpes simplex virus type 2 infections. *J Infect Dis* 1999;179:1077-85.
- Mustonen J, Partanen J, Kanerva M, Pietila K, Vapalahti O. Association of HLA-B27 with benign clinical course of nephropathia epidemica caused by Puumala Hantavirus. *Scand J Immunol* 1998;47:277-9.
- Borrow P, Lewicki H, Wei X, et al. Antiviral pressure exerted by HIV-1-specific cytotoxic T lymphocytes (CTLs) during primary infection demonstrated by rapid selection of CTL escape virus. *Nature Med* 1997;3:205-11.
- Trachtenberg E, Korber B, Sollars C, et al. Advantage of rare HLA super-type in HIV disease progression. *Nat Med* 2003;9:928-35.

31. Kelleher A, Long C, Holmes E, et al. Clustered mutations in HIV-1 gag are consistently required for escape from HLA-B27-restricted cytotoxic T lymphocyte responses. *J Exp Med* 2001; 193:375-85.
32. Nowak M, May R, Philips R, et al. Antigenic oscillations and shifting immunodominance in HIV-1 infections. *Nature* 1995;375:606-11.
33. Nelson G, Kaslow R, Mann D. Frequency of HLA allele-specific peptide motifs in HIV-1 proteins correlates with the allele's association with relative rates of disease progression after HIV-1 infection. *Proc Natl Acad Sci USA* 1997;94:9802-7.
34. Douglas L, Mayers M. Drug-resistant HIV-1. *JAMA* 1998;279:2000-2.
35. Pantaleo G, Demarest J, Schacker T, et al. The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia. *Proc Natl Acad Sci USA* 1997;94:254-8.
36. Rosenberg E, Billingsley J, Angela M, et al. Vigorous HIV-1-specific CD4+ T-cell responses associated with control of viremia. *Science* 1997;278:1447-50.
37. Carrington M, Nelson G, Martin M, et al. HLA and HIV-1: heterozygotic advantage and B*35-Cw*04 disadvantage. *Science* 1999; 283:1748-52.
38. Smith P, Sarner L, Murphy M, et al. Ethnicity and discordance in plasma HIV-1 RNA viral load and CD4+ lymphocyte count in a cohort of HIV-1-infected individuals. *J Clin Virol* 2003;26:101-7.
39. Flores-Villanueva P, Yunis J, Delgado J, et al. Control of HIV-1 viremia and protection from AIDS are associated with HLA-Bw4 homozygosity. *Proc Natl Acad Sci USA* 2001;98:5140-5.
40. Huber C, Pons O, Hendel H, et al. Genomic studies in AIDS: problems and answers. Development of a statistical model integrating both longitudinal cohort studies and transversal observations of extreme cases. *Biomed Pharm* 2003;57:28-33.
41. Nixon D, Townsend A, Elvin J, Rizza C, Gallwey J, McMichael A. HIV-1 gag-specific cytotoxic T lymphocytes defined with recombinant vaccinia virus and synthetic peptides. *Nature* 1988;336:484-7.
42. Goulder P, Phillips R, Colbert R, et al. Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat Med* 1997;3:212-7.
43. Nietfeld W, Bauer M, Revrier M, et al. Sequence constraints and recognition by CTL of an HLA-B27-restricted HIV-1 gag epitope. *J Immunol* 1995;154:2189-97.
44. Madden D, Gorga J, Strominger J, Wiley D. The three-dimensional structure of HLA-B27 at 2.1 Å resolution suggests a general mechanism for tight binding to MHC. *Cell* 1992;70:1035-48.
45. Goulder P, Brander C, Tang Y, et al. Evolution and transmission of stable CTL escape mutations in HIV infection. *Nature* 2001;412:334-7.
46. McMichael A, Klenerman P. HLA leaves its footprints on HIV. *Science* 2002;296:1410-1.
47. Carrington M, Nelson G, O'Brien S. Considering genetic profiles in functional studies of immune responsiveness to HIV-1. *Immunol Letters* 2001;79:131-40.
48. Ioannidis J, Rosenberg P, Goedert J, et al. Effects of CCR5-Δ32, CCR2-64I, and SDF-1 3'A alleles on HIV-1 disease progression: an international meta-analysis of individual-patient data. *Ann Intern Med* 2001;135:782-95.