The Impact of Human Allelic Variation on HIV-1 Disease

Cleo G. Anastassopoulou and Leondios G. Kostrikis*

Department of Hygiene and Epidemiology, Athens University Medical School, Athens, Greece

Abstract: Human allelic variants influence the susceptibility to HIV-1 infection and/or the subsequent rates of disease progression towards AIDS that average ten years, although they vary greatly among infected subjects. In this respect, studies involving multiply exposed persons who remain uninfected, long-term nonprogressors (who remain asymptomatic for fifteen years or more) or, in contrast, rapid progressors (who develop AIDS within two to three years post-infection) as well as seroincident cohorts of patients with defined seroconversion dates have contributed to our comprehension of the effects of different natural human polymorphisms on HIV-1 disease. The current article aims at providing an up-to-date review on these polymorphisms that may be broadly classified into three general categories: (1) those that control viral entry into susceptible cells (namely, chemokine and chemokine receptor polymorphisms), (2) mutational variants of genes involved in immune regulation, such as interleukin-10 (*IL-10*), interleukin-4 (*IL-4*), tumor necrosis factor-alpha (*TNF-alpha*), and mannose-binding lectin (*MBL*), and (3) polymorphisms in genes involved in the adaptive immune recognition by T cells, [human leukocyte antigen (*HLA*) type]. Particular emphasis has been placed on the state-of-the-art biotechnological methodologies, such as "spectral genotyping" that utilizes molecular beacons in conjunction with polymerase chain reaction in real-time (real-time-PCR), which were developed to assist with the characterization of some of these determinants. Elucidating the functional role of these factors via the application of such biotechnological assays is expected to further enhance our understanding of the pathogenesis of HIV-1 infection, and, eventually, to enrich our therapeutic arsenal with novel antiviral agents or strategic approaches.

Keywords: Polymorphisms, chemokines, real-time PCR, beacons, transmission, progression, allelic.

MAIN TEXT

Allelic Variation in Chemokines and Chemokines Receptors

The interaction of HIV-1 with specific cell surface molecules that trigger the fusogenic potential of its envelope glycoproteins, the trimeric gp120-gp41 complex, allows the virus to enter into its target cells by fusion at the plasma membrane [17, 55, 175, 177]. The CD4 antigen has been known to be the principal cell surface receptor for HIV-1 (and also for HIV-2 and SIV) since 1984 [46, 116, 159]. Nevertheless, it has also been known for almost as long that the presence of the CD4 molecule, although clearly necessary, is insufficient on its own to permit entry of HIV into susceptible cells. With rare exceptions, efficient HIV-1 or HIV-2 entry is not permitted by expression of human CD4 in non-human cells [142], most probably because non-human cells lack a factor essential for CD4-dependent fusion, as shown by complementation experiments involving chimeras between human and non-human cells [9, 29, 57, 85]. The identity of the different co-factors that were supposed to be utilized by HIV-1 strains of different phenotypes ["macrophage" (M)-tropic and "T-cell line" (T)-tropic] in order to fuse with $CD4^+$ cells, as determined by studies from Broder and Berger [28], remained elusive until early 1996 [70].

At that time, a member of the seven-transmembrane spanning family of chemokine receptors initially termed "fusin," was identified in a seminal paper from Berger's group to be the entry co-factor (co-receptor) for T-tropic HIV-1 strains [70]; however, once its natural ligand was discovered to be stromal derived factor-1 (SDF-1), the CXC-chemokine, the term "fusin" was altered to CXCR4 [22, 189]. Having identified CXCR4 as a co-receptor for T-tropic isolates, it was reasonable to assume that the still unknown co-factor for M-tropic viruses would be another chemokine receptor. Indeed, the knowledge that the beta-chemokines macrophage inflammatory proteins 1-alpha and 1-beta (MIP-1-alpha and MIP-1-beta, respectively) and RANTES (regulated on activation, normal T cell expressed and secreted) exhibited antiviral activity against M-tropic HIV-1 isolates *in vitro* [39], provided the basis for the discovery of CCR5 as the entry co-factor for these strains by five groups simultaneously [3, 37, 51, 56, 58]. Monocytotropic, non-syncytium-inducing variants that use CCR5 as co-receptor (M-tropic or R5 isolates) constitute, in fact, the most common phenotype of HIV-1 strains transmitted sexually, while they are usually replaced by variants with altered tropism that expand to utilize CXCR4 (T-tropic or X4 isolates) later into the course of infection [44, 236].

The CD4-dependent direct interaction of HIV-1 gp120 with CCR5 was demonstrated by follow-up studies; more specifically, the binding of M-tropic gp120 to CD4 exposes

*Address correspondence to this author at the Athens University Medical School, Department of Hygiene and Epidemiology, 75 Mikras Asias Street, GR-115 27 Athens (Goudi), Greece; Phone: +30-210-748-6382; Fax: +30-210-748-6382; E-mail: lkostrik@med.uoa.gr

1570-162X/03 $41.00+.00

or creates a binding site on gp120 for CCR5 [2, 91, 252, 264]. T-tropic gp120 has also been shown to bind to CD4 and CXCR4 to form a ternary complex [130]. A conformational change induced in the biochemically unstable, native envelope glycoprotein complex [204, 266] by the binding of the gp120 to the CD4 receptor and, then, to a co-receptor (typically CCR5 or CXCR4) has been proposed to trigger the fusion reaction with the following order of events: the hydrophobic portion of the transmembrane subunit, gp41, becomes inserted into the cell membrane, thereby initiating the coalescence of the viral and cell membranes that allows for the release of the viral core into the cytoplasm and the initiation of a new cycle of infection [Reviewed in [20, 36, 53, 54, 61, 128, 176, 266]].

Other chemokine receptors, notably CCR3 and to a lesser extent CCR2b and CX3CR1, also support HIV-1 entry into susceptible cells, although usually at lower efficiency than CCR5 and for a more limited set of isolates [37, 41, 42, 44, 56, 97, 224, 236]. Several other orphan seven-transmembrane receptors may also serve as co-receptors for HIV-1 and, probably more importantly, for SIV [52, 68, 132, 136, 202, 213, 224]. Their significance in HIV-1 transmission and pathogenesis *in vivo* remains to be determined. Undoubtedly, however, *CCR5* expression constitutes a very important determinant of these parameters *in vivo*, as outlined below.

Another attachment factor promoting infection of cells that express CD4 and chemokine receptors is DC-SIGN. The initial contact between dendritic cells and resting T cells, for instance, is thought to take place via DC-SIGN, a type II membrane protein with a C-type lectin ectodomain. In a recently published study, Mummidi *et al*. analyzed the structure of the gene and discovered an extensive repertoire of transcripts predicted to encode both for membrane-associated and soluble isoforms that exhibit inter-individual variation in expression levels, a discovery that may have important implications in the establishment of the complex interactions of the "immunological synapse" between antigen-presenting and T-cells and, thereby, in HIV-1 pathogenesis [184].

The role of chemokines receptors and chemokines as well as the consequences of their mutational patterns on HIV-1 disease have been examined in detail by several excellent reviews [19, 33, 74, 93, 108, 168, 191, 192, 198, 217]. The corresponding effects in pediatric HIV-1 disease have been reviewed elsewhere [155].

CCR5-Δ32

$CD4^+$ T-cells of certain individuals who had been multiply exposed to HIV-1 sexually and yet remained uninfected were known to be resistant to infection by M-tropic HIV-1 strains [200]. Furthermore, these cells were incapable of supporting fusion mediated by the envelope glycoproteins of M-tropic viruses [58]. These individuals were soon demonstrated to be homozygous for a 32-base-pair deletion, beginning in the region encoding for the third extracellular domain of CCR5 and resulting in a frame shift and premature stop codon in its fifth transmembrane domain [135]. Independent, simultaneous studies by two other groups drew identical conclusions [49, 228]. The CCR5 gene contains a single open reading frame (exon 4) of only 1,055 base pairs; despite the complementation by increased beta-chemokine expression [199], its expression, and, hence, infection by HIV-1 isolates that use the CCR5 co-receptor, is prevented by this deletion not only in $CD4^+$ T-cells [135, 228], but also in macrophages [43, 209] and dendritic cells [83]. The importance of homozygosity for the *CCR5-Δ32* allele in preventing HIV-1 transmission was more formally demonstrated by three studies involving the *CCR5* genotyping of large cohorts of HIV-1-infected and -uninfected individuals [49, 95, 269].

Interestingly, the *CCR5-Δ32* allele was found to be unique to Caucasian populations, while follow-up studies indicated that it is most prevalent in North-Western Europe and less so in Southern Europe [5, 15, 38, 138, 153, 188]. Homozygosity for the *CCR5-Δ32* allele is estimated to be around 1% in North American Caucasians, although frequencies up to 3% have been reported in some European countries [49, 95, 153, 269]. Heterozygotes were found at frequencies around 15% and up to 35%, respectively, in the same populations, although they were always in Hardy-Weinberg equilibrium. In unselected Caucasian populations, the overall *CCR5-Δ32* allele frequency is around 0.10, while native African, American Indian and East Asian ethnic groups seem to lack the variant allele [162].

Based on the geographic cline of the *CCR5-Δ32* allelic frequencies, it has been suggested that this defect in the CCR5 gene may have conferred a selective advantage to ancestral Caucasian populations through resistance to infectious pathogen(s) that also utilized CCR5, such as the bubonic plague-causing *Yersinia pestis* and the smallpox (variola) virus [129, 241]. By use of coalescence theory, the *CCR5-Δ32*-containing ancestral haplotype was estimated to have originated approximately 700 years ago [49, 241]. Apart from the high prevalence of sexually-transmitted diseases and the lack of prevention programs, the absence of this variant allele in Africa is thought to provide an explanation for the severity of HIV-1 disease especially in sub-Saharan regions, compared with populations of European descent where the allele is present [243]. The identification of several other allelic variants of CCR5-coding genes, the majority of which yield non-synonymous (amino acid-changing) substitutions in the protein products, reinforces the hypothesis that carriers of such mutational variants would be selected for by infectious diseases [5, 31, 32, 153, 207, 268].

No individual homozygous for the *CCR5-Δ32* allele was found to be infected with HIV-1 in those initial studies, indicating that the absence of *CCR5* expression was strongly protective either against HIV-1 transmission or the systemic establishment of infection [49, 95, 269]. The identification since then of eight infected *CCR5-Δ32* homozygotes, all of whom exhibited early $CD4^+$ T cell decline, suggested that the protective effect of this polymorphism is strong but not absolute [13, 21, 86, 127, 193, 232, 249]. Notably, these studies further revealed that *CCR5-Δ32*-mediated resistance is associated with the acquisition of X4 (or R5X4 [80, 185]) HIV-1 variants, the pathogenetic potential of which may

differ substantially from both late-stage X4 strains or from early X4 strains acquired by individuals harboring other *CCR5* genotypes [172].

On the other hand, heterozygosity for the *CCR5-Δ32* allele is not protective against HIV-1 transmission [49, 95, 269], presumably because the protein expressed from the wild-type allele is modestly not as efficient, but sufficient to permit infection *in vivo* as it is *in vitro* [265]. Nonetheless, progression to AIDS and death does takes place less rapidly in HIV-1-infected individuals who are heterozygous for the *CCR5-Δ32* allele, as manifested by reductions in viral load and in the rate of $CD4^+$ T-cell decline in these patients compared to those with wild-type *CCR5* alleles [95]. The conferred delay in time-to-death was estimated to average 2-4 years following seroconversion in different cohort studies, with indications that the greatest protective effect is exerted in the earlier years of infection [47, 49, 95, 171, 269]. Studies of smaller cohorts have yielded similar results, albeit of more limited statistical power. Heterozygosity for the *CCR5-Δ32* allele was not found to affect perinatal HIV-1 transmission, as shown by two initial studies on small pediatric cohorts [63, 220].

In heterozygotes for the *CCR5-Δ32* allele, the levels of CCR5 expression on CD4 T lymphocytes are lower -but nonetheless greater than 50% reduced as would be predicted by a simple gene dosage effect- compared to those of homozygotes for the wild type allele [177, 265]; formation of dimeric truncated/normal polypeptide complexes in the endoplasmic reticulum is believed to retard the transport of normal CCR5 to the cell surface [16]. The reduced expression levels of CCR5 and the difference in the production of beta-chemokines may also be related to the two- to five-fold reduction in viral load levels observed in heterozygotes for *CCR5-Δ32* compared to wild-type slow progressors [260].

In general, however, it can be claimed that heterozygosity for the *CCR5-Δ32* allele is associated with lower pre-AIDS viral loads and delayed disease progression, while homozygosity is linked with incomplete non-transmission [1, 66, 92, 109, 149, 162, 166, 170, 212, 242]. Viral phenotype, nevertheless, constitutes an important parameter that has to be taken into account when considering the effects of this polymorphism, since the maximum protective effect of *CCR5-Δ32* heterozygosity appears to be exerted in individuals harboring R5 HIV-1 strains [26, 170]. Similar effects to the *CCR5-Δ32* have been described for another much more infrequent mutation, *CCR5-m303* [207]. *CCR5-m303* in combination with *CCR5-Δ32* also appears to confer resistance to HIV-1 infection. It should also be noted that heterozygosity for the *CCR5-Δ32* allele has been associated with protection against the appearance of several AIDS-related conditions, such as non-Hodgkin's B cell lymphoma [50, 208], AIDS dementia complex [259], and reduced risk of toxoplasmosis [165].

CCR2-64I

The CCR2 gene lies within 14 kb of *CCR5* on chromosome 3 and their encoded proteins exhibit a 82% sequence homology [206, 239]. In a mode similar to the heterozygous *CCR5-Δ32* genotype, possession of one or both *CCR2-64I* alleles was reported to reduce the rate of progression to AIDS and death by about 2 years, with the greatest effect again exerted in the earlier years of infection; however, HIV-1 transmission was not affected by the state of *CCR2-64I* allele, whether homozygous or heterozygous [239]. In addition, no functional differences were identified between cells from *CCR2-64I* carriers compared to wild-type individuals by *in vitro* studies [131, 148]. The placement of the conservative amino acid change (valine-to-isoleucine) in a membrane-spanning region of CCR2 not associated with any known protein binding site [239] as well as the fact that CCR2 is rarely used as an HIV-1 co-receptor *in vitro* [17, 44, 55, 56, 177, 236], rendered these findings on *CCR2* unexpected. Additional studies did not identify an impact of *CCR2-64I* on disease progression, further confusing the issue [65, 98, 171].

Using the methodology of spectral genotyping, we found that the presence of the *CCR2-64I* allele was protective against disease progression in subjects from the Chicago Multicenter AIDS Cohort Study of homosexual men (MACS study) [122]; however, this effect was only visible in the subset of the cohort where the date of infection was well defined (seroincident or seroconvertor subjects) [122, 215], in agreement to the conclusions drawn by O'Brien and colleagues [238, 239]. The impact of the *CCR2-V64I* allele was masked in the subset of the cohort that was comprised only of individuals who survived HIV-1 infection long enough to join (seroprevalent subjects) because the *CCR2-V64I* allele selects against rapid progression, thus highlighting the importance of the type of cohorts chosen for host genetics analyses. Studies by other investigators also confirmed the association between the *CCR2-64I* allele and delayed disease progression [6, 88, 151, 167, 181, 215, 258].

A recently published meta-analysis of individual-patient data involving 19 prospective cohort and case-control studies from the United States, Europe, and Australia demonstrated that both the *CCR5-Δ32* and the *CCR2-64I* alleles are associated with decelerated progression to AIDS (Relative Hazard, RH among seroconverters, 0.74 and 0.76, respectively; $P = 0.01$ for both), a lower risk for death (RH among seroconverters, 0.64 and 0.74, respectively; $P < 0.05$ for both), and lower plasma RNA levels after seroconversion (difference, -0.18 $\log_{10}$ copies/mL and -0.14 $\log_{10}$ copies/mL; $P < 0.05$ for both) [99]. No clear protective effects on the risk for death following AIDS diagnosis for carriers of either allele were, nonetheless, found by this meta-analysis that did not show any differences to exist between seroconverters and seroprevalent patients. A first report implicating homozygosity for the *CCR2-64I* allele in natural resistance to heterosexual HIV-1 transmission has also been published recently, although larger studies are needed to confirm this finding [137].

Unlike *CCR5-Δ32*, the *CCR2-64I* allelic variant is relatively common, with frequencies ranging from 10% in Caucasians to 25% in Asians. In African-Americans and Hispanics frequencies of 15 and 17% have been reported, respectively. The presence of this variant has been

determined to contribute to the slow rate of disease progression shown by 21 to 46% of HIV-1-infected commercial sex workers in Nairobi, Kenya [6]. This increased frequency of the *CCR2-64I* allele in native Africans has been suggested to counteract the absence of *CCR5-Δ32* in this population group [191].

The mechanism by which the *CCR2-64I* allele, which does not prevent the co-receptor from being functional, might exert a protective effect on HIV-1 progression *in vivo* remains unknown, although it is possible that this effect is achieved by cross-regulation with other co-receptors [131]. However, a recent *in vitro* study showed that the *CCR2-64I* allele does not influence the expression of CCR5 [148]. The initially formed hypotheses that this mutation was tracking either the *CCR5-Δ32* variation, or another upstream regulatory allele of *CCR5* by linkage disequilibrium were proven to be incorrect [239]. The first hypothesis was rejected on the basis that *CCR2-64I*-bearing chromosomes were *CCR5*+, while *CCR5-Δ32* chromosomes were always *CCR2*+ [239]. The second hypothesis was rejected because the CCR5 promoter haplotype in question (*CCR5P1*, as described below) that is carried along on a chromosome with *CCR5-Δ32* and *CCR2-64I* is associated with accelerated, rather than decelerated, disease progression [151]. The finding that the CCR2-64I protein may dimerize with CXCR4, causing its retention in the endoplasmic reticulum and its reduced expression on the cell surface has not been confirmed [163]. The *CCR2-64I* mutation has been found to be in linkage disequilibrium with another polymorphism in the regulatory region of *CCR5*, *CCR5-59653-T*, a finding that is, nevertheless, of unknown significance [122, 151, 181].

Other CCR5 Polymorphisms

Although the CCR5 gene was cloned in 1996, only small sections of its 5′ -untranslated region (5′ -UTR) were initially identified [210, 227]. The details of the mechanism whereby non-coding factors might influence the expression of *CCR5* became clearer in late 1997 with the publication of two studies on the *CCR5* promoter [178, 182]. In this respect, the discovery by Mummidi *et al.* that *CCR5* had twin promoters, and that there were genetic polymorphisms in the 5′ -UTR, was of particular importance [182]. The CCR5 gene has four exons and two introns, with exons 2 and 3 being uninterrupted by an intron and with exon 4 and portions of exon 3 being common to all *CCR5* transcripts. Exon 4 contains the open reading frame, 11-nucleodies of the 5′ -UTR and the complete 3′ -UTR. The twin promoters of the gene function as follows: the first (P_U), upstream of exon 1, is a weak promoter in leukocytic cells, while the second downstream (P_D) is a strong, constitutive promoter that includes the intron-like region between exons 1 and 3 [182]. In exons 1 and 2 of *CCR5*, several single nucleotide polymorphisms were identified, while others were noted as existing but were not identified [182].

Polymorphisms in the *cis*-regulatory regions of mammalian genes have been known to have significant impact on protein expression. For instance, a single nucleotide change may be sufficient to create a one-log difference in the transcriptional activity of two otherwise identical promoters by alterations in the ability of transcriptional regulatory proteins to bind to the different alleles [111]. The best characterized such phenomenon has been the human beta-globin gene, where single mutations in the regulatory regions are associated with decreased beta-globin production, leading to beta-thalassemia [111]. At present, over 300 different beta-thalassemia alleles are known, including 12 transcriptional mutants, many of which impact on the clinical syndrome, albeit in a complex manner. The *TNF-2* allele of the TNF-alpha gene is an example of the notion that some regulatory region polymorphisms can increase protein expression [160]. In a similar mode, the *CCR5* promoter polymorphisms may have a significant impact on protein expression and disease progression. The evolution of the elements controlling the function of the CCR5 gene is thought to have contributed to the different pathogenesis of HIV-1 (immunosuppression) and SIV (natural resistance) in human and non-human primates, respectively [183].

Possible influences of the two *CCR5* promoters on transcriptional efficiency have been identified by Mummidi *et al.* [182]. In view of its twin promoter architecture, studies of the expression of the CCR5 gene in different cell types relevant to HIV-1 infection might be particularly interesting. The production of alternative mRNA transcripts from more than one promoters has been shown to be important for the temporal regulation of organ or tissue development or cell-type specific gene expression, for instance in response of different cells to the same or different external stimuli or in metabolic conditions [10]. By transcribing a single gene from multiple promoters, an organism gains in flexibility, since a single promoter region may not always be sufficient to accommodate all necessary pieces of information to permit the differential expression of the same gene in different cells in response to the same signals, or in the same cell in response to different signals [229]. The possibilities that different mRNA transcripts from different promoters may be translated with variable efficiency [10, 125, 147, 229], and such mRNAs can differ in stability, exemplified by the regulatory complexities of the c-*myc* proto-oncogene [18, 125], emphasize the importance of studying *CCR5* (and *CXCR4*) expression not only at the mRNA, but also at the protein level.

Two of the polymorphic sites in the 5′ -UTR of *CCR5* were C/T at nucleotide 59353 and G/A at nucleotide 59402 [182]. These sites are designated *353C* and *353T*, and *402G* and *402A*, respectively. A recently published study indicated that HIV-exposed but persistently seronegative, *CCR5-Δ32*-negative, female sex workers from northern Thailand tended to have higher frequencies of *CCR5-59402GG* compared with controls [240]. Several other polymorphisms within the promoter or regulatory region of *CCR5* that may impact on HIV-1 disease by modifying the CCR5 expression levels, possibly stemming from selective adaptive changes to older pathogens [14], have also been described [5, 31, 78, 158, 181, 207, 247].

For example, homozygotes for *59029-G* allele in the regulatory region may exhibit decelerated progression to AIDS compared to homozygotes for the *59029-A* allele

[158]. Other promoter haplotypes may be linked with accelerated disease progression. The *CCR5P1* allele, one of the four *CCR5P1-P4* variants that are commonly found among both Caucasians and African-Americans, was found to be in linkage disequilibrium with *CCR5-2459A* [4], and correlated in a recessive manner with rapid progression to AIDS in Caucasians [151]. A plausible explanation for the correlation of *CCR5P1* allele with rapid disease progression, the first such association to be described, may be an up-regulation of *CCR5* transcription in response to tissue-specific transcription factors, leading to an increase in available cell surface co-receptors.

Initial studies did not reveal an effect of the different *CCR5* haplotypes on HIV-1 transmission [122, 151]. A more recent study indicated that certain *CCR5* haplotype pairs are associated with altered susceptibility to perinatal HIV-1 infection and disease progression rates in children [145]. Yet another variant, the *CCR5-59356-T/T* mutant genotype, which is more prevalent in African-Americans than in Hispanics or Caucasians, has recently been associated with a significantly higher rate of perinatal HIV-1 infection, possibly contributing to the observed increased HIV-1 prevalence rates in Africa [121, 123].

CXCR4

CXCR4 is a highly conserved gene [179]. External influences on CXCR4 expression are not well understood. Interleukin-2 (IL-2) stimulation of quiescent $CD4^+$ T-cells has been found to modestly down-regulate cell surface CXCR4 expression, simultaneously with much stronger up-regulation of CCR5 [24, 35, 174]. The inverse relationship between CCR5 and CXCR4 expression makes biological sense. CXCR4, a widely expressed chemokine receptor responsible for routine, SDF-1-induced T-cell chemotaxis along the epithelial cell surfaces of blood vessels, mediates "baseline motility" of T-cells [206]. In contrast, the up-regulated CCR5 in response to inflammation and tissue damage directs T-cells to migrate to where they are specifically needed, in response to localized gradients of MIP-1-alpha, MIP-1-beta or RANTES on epithelial cell surfaces [206]. Once moving in a specific direction, a T-cell does not require the non-specific motile stimulus to be exerted via CXCR4 and down-regulates this protein. A rapid up-regulation of CXCR4 expression in response to TNF-alpha, at least in a promyelocytic line, has also been reported [216]. Cycloheximide could induce this effect of TNF-alpha, suggesting that the entailed mechanism might involve degradation of a labile transcriptional repressor rather than regulatory factors involving de novo protein synthesis [216]. Furthermore, the association of CXCR4 internalization with PMA-induced phosphorylation of its intracellular domains is suggestive of the existence of down-regulatory effects at the protein level [84].

CX3CR1 I249 M280

Another potential co-receptor for HIV is CX3CR1 [41, 42, 97, 164, 211, 224]. The ligand of this leukocyte chemotactic, but rarely used co-receptor that is particularly expressed in the brain, is fractalkine. The effects of the CX3CR1 allelic variants on HIV-1 disease have been examined in two reviews [33, 93]. Data from three cohorts of patients from France indicated that HIV-1-infected individuals homozygous for a structural variant of this allele, CX3CR1 I249 M280, exhibit accelerated progression to AIDS [69]. These variants were rather common since they were determined to occur at frequencies of 26 and 13% for the valine to isoleucine change at position 249 (V249I) and for the threonine to methionine substitution at position 280 (T280M), respectively. This latter substitution was also reported to be associated with increased risk of HIV-1 transmission. Nevertheless, the association of the CX3CR1 variant with accelerated disease progression was not confirmed by a subsequent study of three North American cohorts, MACS, the D.C. Gay cohort (DCG), or the Multicenter Hemophilia Cohort Study (MHCS), involving a total of 481 patients [157], or by the Genetics of the Resistance to Infection by the Immunodeficiency Virus (GRIV) study that involves a large case-control cohort of nonprogressors and rapid progressors, representing the extreme disease outcomes from a pool of 30,000 patients [89]. Therefore, further studies are deemed necessary to evaluate the impact of this polymorphism on HIV-1 disease.

SDF1-3′A

The chemokine Stromal-Derived Factor (SDF) that is produced by stromal, mesothelial and endothelial cells is considered to be the only known natural ligand of CXCR4, the co-receptor preferentially utilized by the later-stage-HIV-1 variants (X4 variants). Indeed, it has been demonstrated that infection with X4 variants is blocked by SDF-1 [22, 189].

Experimental studies using gene knockout mice demonstrated that CXCR4 co-receptor dramatizes a critical role in several crucial to survival biological processes, including hematopoiesis, cerebellar development, and vascularization of the gastrointestinal tract, and, therefore, the low degree of genetic variability exhibited by both CXCR4 and SDF-1 is justified. Hence, only two natural polymorphisms have been described for the CXCR4 gene [40, 150]. For the SDF-1 gene that is located on chromosome 10q11.1, a single Gly→Ala transition polymorphism at position 801 (with position 1 as the A of the start codon) in the 3′ untranslated region of SDF-1-*beta*, one of the two isoforms produced by alternative splicing of the mRNA [235], has been discovered [263]. The precise location of the variant is 37 base pairs from two DNA segments that are highly conserved (88% and 92% homologous between human and mouse SDF-1 homologs, respectively), and thus subjected to functional constraints from evolutionary divergence, possibly because they contain recognition signals for RNA- or DNA-binding regulatory factors [263].

Several epidemiological studies of the effect of this polymorphism on HIV-1 disease progression in adults have yielded conflicting results [Reviewed in [33, 93, 108, 168, 191, 192, 221, 237]]. An initial genetic analysis of 2,857 patients from five cohorts demonstrated a remarkable association of *SDF1-3′A* homozygosity with delayed

disease progression to full-blown AIDS [263]. Furthermore, the recessive protective effect against progression to AIDS by *SDF1-3′A* homozygosity was actually found to be several-fold stronger than that conferred by either *CCR5Δ32* or *CCR2V64I* heterozygosity alone. This functional epidemiological interaction, termed "epistasis" in genetics, may account for the enhanced protection observed for individuals that are simultaneously *SDF1-3′A* homozygous and *CCR5Δ32* or *CCR2V64I* heterozygous.

Disease progression was thought to be slowed in these patients firstly by *CCR5* and *CCR2* variants which could restrict the availability of CCR5 co-receptors that mediate the replication and spread of early stage R5 HIV strains, and, secondly, by the *SDF1-3′A* variant that might delay the emergence of X4 tropic strains. The precise mechanism by which the *SDF1-3′A* polymorphism may confer protection remains unknown. Nevertheless, it has been speculated that this variant allele may lead to the up-regulation of the synthesis of SDF-1 in local compartments, thus blocking the switch to X4 strains *in situ* and the ensuing AIDS accelerating process by competitive inhibition for CXCR4. Direct evidence for this hypothesis is lacking [8], partly due to the limited tissue distribution of SDF-1 *in vivo* (SDF-1-*beta* is expressed in lymphoid tissues but not in the peripheral blood), and partly due to its tendency to aggregate in serum [11, 23, 214].

The association of the *SDF1-3′A* polymorphism with delayed disease progression barely reached the limit of statistical significance (with a P value = 0.05) in the French GRIV cohort of slow progressors [88], while in other studies no such association was identified [60, 167]. On the contrary, subsequent studies on seroincident cohorts revealed an association between *SDF1-3′A* homozygosity and increased viral replication [12], or even accelerated progression to death [25, 181, 257]. Furthermore, a late protective effect of homozygosity was implied by a study that indicated prolonged survival after AIDS diagnosis [257].

The conflicting results of these studies might be accounted for by statistical power issues, especially since homozygotes for *SDF1-3′A* are rare (about 6%) because this effect is recessive. However, the outcome of a recently published meta-analysis of individual-patient data, identified neither an early, nor a late protective effect of this allele variant from AIDS (RH for seroconverters and seroprevalent patients, 0.99 and 1.03, respectively), death (RH, 0.97 and 1.00), or death after development of AIDS (RH, 0.81 and 0.97; $P > 0.5$ for all) [99].

Interestingly, a study of postnatal breast milk transmission in a cohort of mother-infant pairs in Nairobi, Kenya indicated an association between maternal *SDF1-3′A* heterozygosity and an increased risk of vertical HIV-1 transmission [104]. In perinatally infected children, no effect of the infant SDF1 genotype on either the mother-to-child transmission or on disease progression has been observed [104, 146] [Reviewed in [155]]. Another recent study confirmed the lack of association of the mutant allele with the risk of vertical transmission, although it also reported an association with accelerated HIV-1 disease progression in perinatally infected children [251]. Future analyses will elucidate the role of SDF1 genotype on HIV-1 disease particularly in children.

RANTES

The risk of acquiring HIV-1 and the rate of disease progression following infection with the virus may also be influenced by polymorphisms in the chemokine *RANTES* promoter, as shown by recent studies, providing thus a possible explanation for the apparently discrepant results on the role of this beta-chemokine [33, 93, 221].

RANTES may suppress the infection of cells with R5 HIV-1 strains by blocking its ligand, CCR5 [7, 200]. However, RANTES exerts pleiomorphic effects on T cell activation and HIV-1 replication *in vitro*, as shown by the suppression of HIV-1 in T cell cultures and the enhancement of viral replication at higher concentrations, especially in macrophage cultures. Secretion levels of RANTES and MIP-1-beta from PBLs of different individuals vary widely and are inversely correlated with the rate of disease progression [199, 267]. Moreover, higher levels of RANTES are secreted by $CD4^+$ lymphocytes from exposed but uninfected rather than HIV-1-infected subjects [199, 225].

In a Japanese cohort, the *–403A/-28G* allele of the *RANTES* promoter region was determined to be associated, in a dominant manner, with lower rates of $CD4^+$ cell depletion with respect to other alleles [134]. *In vitro* data indicated that $CD4^+$ lymphocytes from individuals with this variation secreted increased levels of RANTES compared to those who lacked this haplotype, thus accounting for the observed association with slower depletion of $CD4^+$ T cells and delayed disease progression. The contribution of this haplotype to HIV-1 epidemiology in other parts of the world was suggested to be minimal, since the *–403A/-28G* allele is uncommon in non-Far East Asians [79].

A subsequent study of this allelic variant in Caucasians demonstrated that *403A* does contribute to protection against disease progression following infection with the virus, although, simultaneously it also constitutes a risk factor of acquiring HIV infection by almost doubling the likelihood of becoming infected with the virus [156]. The explanation for this apparently contradictory observation provided by the authors of this study is that HIV entry may be facilitated by the increased RANTES concentration by promoting inflammation at mucosal surfaces, while virus spread is hindered following infection due to the competition between the virus and RANTES for CCR5.

A very recently published study that included genetic analysis data from five AIDS cohorts demonstrated that *403A* is associated with an increased frequency of HIV-1 infection, while it further identified two additional single nucleotide polymorphisms with similar effects: *In1.1C* in the first intron and *3′222C* in the 3′ -untranslated region [89]. The *In1.1C* allele, in particular, which down-regulates gene transcription (although this effect may be counteracted through linkage disequilibrium by the nonetheless weaker up-regulating effects of *–28G*), was strongly associated in a

dominant manner with accelerated HIV-1 disease progression in both European-American and African-American patients. Therefore, genotypes bearing the *In1.1C* allele may also contribute to the rapid disease progression rates observed in Africa.

Genotyping of Human Alleles by "Spectral Genotyping"

In 1997, O'Brien's group found that a single point substitution (namely, a G→A transition at DNA position 190 from the ATG start site), resulting in the conservative replacement of valine by isoleucine at amino acid position 64 of the first transmembrane domain of the CCR2 protein (V64I), had a significant impact on disease progression in HIV-1-infected individuals [239]. As reported above, rapid epidemiological studies on the *CCR5-Δ32* allelic variant were rendered possible by the fact that the truncated DNA species could be readily detected by gel electrophoresis after PCR amplification of the *CCR5*-coding region [49, 95, 135, 228, 269]. The *CCR2-64I* allele, on the other hand, does not differ in length from the wild-type allele; therefore, its detection would have to be performed either by the unwieldy bulk sequencing or by the more rapid single-strand conformation polymorphism (SSCP) analysis [239]. The evident need for a less complicated, *CCR2*-allele-specific assay with a rapid end-point prompted us to develop a novel biotechnological assay for the evaluation of its effects on HIV-1 disease, "spectral genotyping" [122, 124, 254], the principles of which are outlined in Fig. (**1**). Spectral genotyping utilizes the modern technologies of molecular beacons in combination with PCR in real-time.

Molecular beacons are single-stranded oligonucleotide probes of hairpin-shape that fluoresce upon hybridization to target sequences. They are composed of a target recognition sequence that is flanked by two complementary sequences, with a fluorophore covalently attached to one end of the oligonucleotide and a non-fluorescent quencher attached to the other [Fig. (**1A**)]. Within the intramolecularly hybridized probe, no fluorescence is emitted because the fluorophore is found in close proximity to the quencher. However, the conformational reorganization induced by the hybridization of the probe to potential target sequences removes the quencher from the vicinity of the fluorophore, resulting in the emission of a detectable fluorescence signal [Fig. (**1A**)].

Using different fluorophores attached to different target recognition sequences allows for the detection of multiple targets in a single procedure by molecular beacons. As an example, genotyping of diallelic variations is achieved by using two molecular beacons, each possessing a spectrally distinguishable fluorophore. For *CCR2* genotyping, in particular, the wild-type allele is detected by FAM fluorescence (green), whereas the *CCR2-64I* allele is detected by HEX fluorescence (red) [Fig. (**1B**)]. The differential thermal stabilities of matched and mismatched nucleic acid hybridizations constitute the underlying principle of the assay.

For each molecular beacon, the temperature that maximizes the discrimination between the binding of each beacon to its perfectly complementary target and the binding to the other target is first identified, having first determined the thermal stability profiles, separately for the molecular beacon alone and for the two hybrids between the beacon and each DNA target (wild-type and mutant) [Fig. (**1C**)]. This temperature (60°C in the case of CCR2 genotyping) is then used in each thermal cycle of real-time PCR to generate fluorescence data measurements. Additional information on the mechanics of this assay is provided in the legend of Fig. (**1**) and in reference[124], while one set of representative results is shown in [Fig. (**1D**)].

Spectral genotyping was used to determine the *CCR2* genotype of 954 samples from the Chicago MACS study [Fig. (**1E**)]. The threshold cycle of the FAM fluorophore has been plotted against the threshold cycle of the HEX fluorophore for each sample. Samples for which no fluorescence increase was detectable throughout the course of the reaction (threshold cycle greater than 60) were considered to be negative. *CCR2* wild-type homozygotes were positive only for FAM fluorescence, whereas *CCR2-64I* heterozygotes were positive for both FAM and HEX, and *CCR2-64I* homozygotes were positive only for HEX fluorescence. To determine the specificity of the spectral genotyping assay, the genotypes of 75 randomly selected samples were also determined by DNA sequencing; comparison of the results of the two assays demonstrated that they were in complete agreement (data not shown).

Spectral genotyping combines the speed and precision of PCR-based techniques required to distinguish between allelic variants that may vary even by a single nucleotide, such as the wild-type and V64I alleles of *CCR2* [239], with the simplicity and flexibility of a fluorimetric endpoint method that allows the rapid processing of multiple samples since it eliminates the need for post-PCR analysis [124, 254].

IMMUNE REGULATION

Interleukin-10 (IL-10)

Macrophage growth, T-cell replication and inflammatory cytokines secretion from T helper cells are inhibited by IL-10 [71, 72]. HIV-1 replication has also been demonstrated to be inhibited in macrophages by this powerful T_H2-type cytokine that is produced by lymphoid cells [120, 230]. Furthermore, several studies, in which the levels of IL-10 have been measured in different groups of AIDS patients, concluded that IL-10 may control the proliferation of the virus, at least in part, by limiting the number of activated macrophages available for HIV-1 replication [62, 180, 196, 248].

HIV-1-infected individuals with a particular *IL-10* promoter haplotype have recently been reported to progress to AIDS more rapidly [234], but with a late effect manifested primarily about 5 years post-HIV-1 seroconversion [263]. This polymorphism, which involves a C→A transversion at position –592 upstream of the translation start site, designated as *IL10-5′-592A* (*IL10-5′A*), has been associated with reduced transcription of the

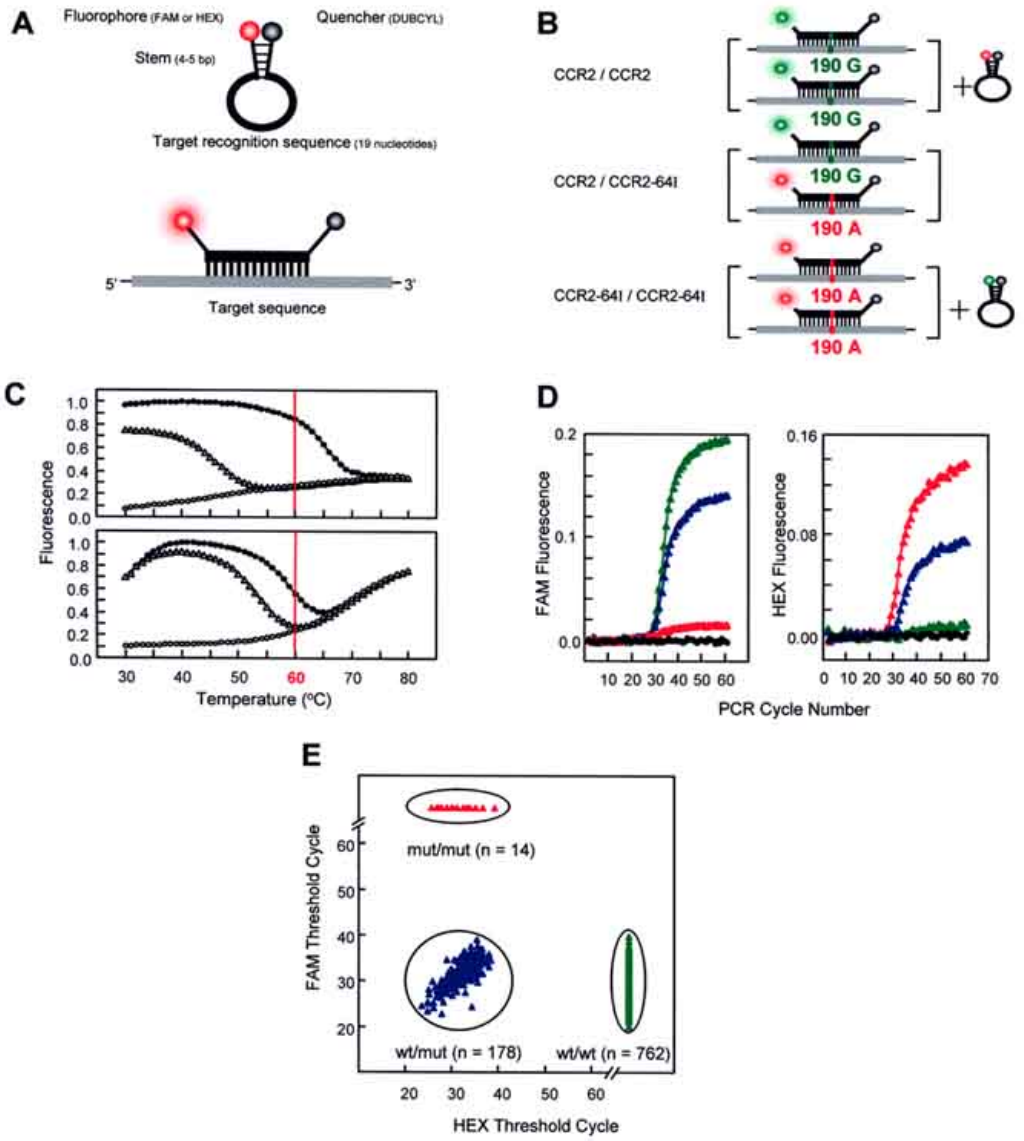

Fig. (1). Molecular beacons for CCR2 genotyping. **A.** Schematic representation of the structure of a molecular beacon before (upper) and after (lower) hybridization to target DNA. **B.** The principle of operation of spectral genotyping using binary molecular beacons. The wild-type beacon, which has fluorescein (FAM; green) as a fluorophore, has a target recognition sequence complementary to the wild-type CCR2 sequence (64V, nt 190-G); the mutant molecular beacon, with hexachloro-fluorescein (HEX; red) as the fluorophore, recognizes the sequence encoding 64I (nt 190-A). In wild-type homozygotes (CCR2/CCR2), the wild-type molecular beacon hybridizes to the target sequence and generates green fluorescence, whereas the mutant molecular beacon retains its stem-and-loop structure and produces no signal. In heterozygotes (CCR2/CCR2-64I), both molecular beacons hybridize to their targets, generating both green and red fluorescence. In mutant homozygotes (CCR2-64I/CCR2-64I), only the mutant beacon hybridizes, generating a red fluorescence, and the wild-type beacon remains dark. **C.** Comparison of the thermal stability of hairpin probes (open circles) for wild-type CCR2 (upper panel) and CCR2-64I (lower panel). For each beacon, the thermal stabilities differ between the perfectly complementary hybrids (closed circles) and the mismatched hybrids (open triangles). This influences the extent of fluorescence emission at different temperatures. The temperature selected (60°C) for hybridization in the PCR (indicated by the red line) allows optimal resolution of the different fluorescence signals. **D.** Changes in the fluorescence of FAM and HEX from four representative real-time PCR at the optimally discriminating temperatures. The changes in the FAM (green) component of the emission spectra from each reaction are shown in the left panel, and the HEX (red) component in the right panel. The color of each curve denotes the genotype of the template DNA present in each reaction: wild-type homozygote (green), heterozygote (blue), mutant CCR2-64I homozygote (red). The no-template control is indicated in black. **E.** A two-dimensional plot of the threshold cycles for FAM and HEX fluorescence obtained from 954 DNA samples using spectral genotyping. CCR2 wild-type homozygotes (wt/wt), positive for FAM only, are shown in green; heterozygotes (wt/mut), positive for both fluorophores, in blue; CCR2-64I homozygotes (mut/mut), positive for HEX only, in red. Spectral genotyping has been originally introduced by Kostrikis *et al.* (reference [124]).

gene two- to four-fold; the mutated allele specifies a DNA sequence that presumably fails to bind certain transcription factors that recognize the wild-type *IL10-5′A* allele [45, 218, 234]. In agreement to the published epidemiological reports, down-regulation in the production of IL-10 would release viral inhibition, thus facilitating HIV-1 replication and progression to AIDS.

The effect of the *IL10-5′A* allelic variant on HIV-1 disease has been examined in three reviews [33, 192, 221]. Similarly to the *CCR2-64I* and *CCR5-Δ32* polymorphisms, the effect of this mutation is also dominant, rendering heterozygotes and homozygotes for *IL10-5′A* indistinguishable. The frequencies of this allelic variant in different ethnic groups were as follows: Caucasians 23.6%, African-Americans 40%, Hispanics 33%, and Asians 60% (Reviewed in [33]). The results of these studies indicate that the role of IL-10 in HIV-1 disease merits further investigation.

Interleukin-4 (IL-4)

Produced primarily by activated $CD4^+$ T lymphocytes, mast cells, and basophils, interleukin-4 (IL-4) is a pleiotropic T_H2 cytokine with multiple immune response-modulating functions [112, 197]. IL-4 regulates differentially the two principal HIV-1 co-receptors: it down-regulates CCR5 expression, thus inhibiting the replication of R5 strains in T cells and macrophages, while it up-regulates the expression of CXCR4, thus enhancing the replication of X4 variants [256, 261, 262]. A C-to-T substitution at position –589 upstream of the open reading frame of *IL-4*, *IL-4-589T*, linked with increased transcription levels of the gene and augmented levels of serum IgE in asthmatic families, has been described [219]. Homozygosity for *IL-4-589T* was previously reported to be correlated with increased rates of acquisition of X4 variants and elevated serum IgE levels in HIV-1-infected Japanese subjects, and especially in individuals at advanced stages of the disease [186]. A lower frequency of this allelic variant was reported in HIV-1-infected individuals whose positive infection status had resulted from heterosexual contact compared to uninfected subjects. A very recently published analysis of the effect of the *IL-4-589T* allele on HIV-1 disease in 427 seroconverters of the French SEROCO cohort showed that *IL-4-589T* is indeed protective against disease progression to AIDS and death by reducing the replication of the virus and viral dynamics *in vivo* [187]. Further studies are needed to test the validity of these results.

Tumor Necrosis Factor-Alpha (TNF-Alpha)

HIV replication is stimulated by both TNF-alpha and TNF-beta (lymphotoxin); expression of the virus *in vitro* is mediated via the induction of nuclear factor NF-kB [59, 154]. Among patients with AIDS, increased levels of TNF-alpha have been reported [27]. Studies investigating the effect on disease progression of the four G→A transition polymorphisms in the promoter region of the TNF-alpha gene have yielded conflicting results (Reviewed in [33]). A weak association between homozygosity for *–308A* with long-term non-progression was identified by a study of homosexual men from CDC- and NIH-sponsored cohorts [119]; in contrast, none of these allelic variants were found to be significantly associated with progression to AIDS in the Dutch HIV-1 seropositive cohort [27]. Nevertheless, the small number of study subjects of both reports limits the power of any definite conclusions that may be drawn from these studies.

An additional study that examined polymorphisms of microsatellite genetic markers (regions of non-coding DNA sequences comprised by a variable number of tandemly repeated di-, tri- or tetra-nucleotides) within the TNF gene locus, found a strong association between the *TNF c2* microsatellite allele, which is located within the first intron of *TNF-beta* [255], with decelerated progression to AIDS [115]. However, this association might stem from linkage disequilibrium with other alleles within the major histocompatibility complex that possibly exert a more powerful effect on AIDS progression.

Mannose-Binding Lectin (MBL)

Acting in the first line of defense against a variety of pathogens before the establishment of adaptive immune protection by B and T cells, mannose-binding lectin (MBL) is a member of the collectin family of proteins, previously known as mannose-binding or mannan-binding protein [64, 94, 253]. Opsonization defects and impaired phagocytosis have been associated with low serum concentrations of this collectin [77, 244, 245]. The levels of circulating protein in the serum are determined in part by polymorphisms in the promoter region [144] and in the first exon of *MBL* [133, 143]. Specific amino acid variants associated with lower levels of circulating *MBL* in the serum include a G→D at codon 54 (allele *B*), a G→E at codon 57 (allele *C*), and a R→C at codon 52 (allele *D*) [143].

The genetic associations of *MBL* with HIV-1 disease have been examined in three reviews [33, 108, 217]. *MBL* variants have tentatively been associated with different rates of disease progression towards AIDS as well as non-specifically with certain secondary infections encountered during advanced immunodeficiency.

Early studies had shown that *in vitro* infection with HIV-1 could be inhibited by MBL [67]. In a more recent analysis of an HIV-1 Danish homosexual cohort, an association between any combination of the variant *MBL* alleles (*B*, *C*, and *D*) and increased susceptibility to HIV-1 infection or a significantly shorter survival time following AIDS diagnosis were identified [76]. A subsequent investigation in a Finnish HIV cohort corroborated these results, since homozygotes for the variant *MBL* alleles were enriched in this cohort of infected patients compared to healthy controls [195]. Similar analyses in Dutch patients failed to reveal an association with survival time after AIDS diagnosis, while the association of *MBL* allelic variants with slower disease progression was reduced to marginal levels [139]. Statistical power issues may again account for these discrepancies.

ADAPTIVE IMMUNE RECOGNITION BY T CELLS

Human Leukocyte Antigen (HLA) Type

The major histocompatibility complex (MHC), which is located in the short arm of chromosome 6, contains *HLA*, our most polymorphic set of genes that are pivotal to immune function [30, 205]. Genes in the HLA region are grouped into the following classes: Class I that encodes (among others) for HLA-A, B and C, class II that encodes (among others) for HLA-DR, DP, DQ and TAP (transporter proteins associated with antigen processing), and class III that contains (among others) tumor necrosis factor (TNF)-alpha and lymphotoxin (TNF-beta) genes. The principal role of class I HLA molecules is to present antigenic epitopes to T lymphocytes in order to induce specific immune responses that would eliminate any "foreign" material. Selective forces such as infectious disease morbidity and mortality are believed to contribute to the maintenance of the extraordinary polymorphism of the *HLA* genes [96, 194]. Substitutions of the *HLA* locus at the amino acid level are concentrated in the peptide-binding groove of these molecules, thus influencing the nature of peptidic epitopes that are presented to T cells.

The role of *HLA* alleles or haplotypes in HIV-1 disease has been examined in more than fifty published reports and reviews [i.e.[33, 48, 93, 106, 108, 113, 117, 168, 192, 217, 221]], while *HLA* type influences on pediatric HIV-1 infection have been reviewed elsewhere [155]. Fewer studies have dealt with *HLA* genes that exhibit associations with increased susceptibility or resistance to HIV-1 infection [90, 110, 140, 203, 223]. A recent investigation in a cohort of African sex workers demonstrated that increased susceptibility was strongly associated with *HLA-A23*, while reduced risk of acquiring HIV-1 infection was linked with a cluster of related class I alleles (*HLA-A2/A*6802*) and with *HLA-DR1* [141]. Many more reports have been published on the association of specific *HLA* allelic variants with varying disease progression rates [i.e.[101, 107, 126]].

Heterozygosity at all *HLA* class I loci confers protection against progression to AIDS, whereas homozygosity at the *HLA-A* or *HLA-B* or both loci restricts CTL responses, leading to rapid disease progression [114, 246]. In addition, haplotypes composed of *Cw*04-B*35* had consistently been associated with accelerated progression to AIDS [100, 102, 226, 231, 250]. By short tandem repeat (STR or microsatellite) genotyping across 10 Mega-base pairs encompassing the *HLA* and at 16 STRs located on other human genes, Carrington *et al*. were successful in attributing the association between rapid disease progression not to the general region of the human genome where this locus resides (on chromosome 6), but specifically to *B*35* and *Cw*04* alleles [34]. This large epidemiological study in 498 HIV-1 seroconverters from five separate cohorts correlated the long-term survival observed in 28 to 40% of HIV-1-infected Caucasian subjects with heterozygosity at all *HLA* class I loci, the absence of *B*35* and *Cw*04* alleles, or both [34]. On the contrary, *HLA* class I homozygosity at one or more loci was significantly associated with accelerated disease progression in both Caucasians and African-Americans; this effect was most pronounced in homozygotes at two or all three loci (*HLA-A, -B*, or –*C*), each one of which appeared to contribute independently to the association [34].

The *Cw*04-B*35* haplotype exhibits a co-dominant effect manifested by the more rapid progression to AIDS of homozygotes compared to heterozygotes and of heterozygotes compared to individuals lacking this haplotype. For B*35 subtypes other than the most common HLA-B*35 subtype, B*3501, and the Cw*04 molecules, no viral epitopes have been identified [105, 222, 233, 250]. As suggested by preliminary data, the rapid progression towards AIDS in subjects carrying the *Cw*04-B*35* haplotype is justified by the quality rather than the quantity of the total CTL response [[103] as cited by [33]]. A recently published study demonstrated that the effects of even a single amino acid change in the HLA-binding domains for HIV-1 antigens could have a substantial impact on the rate of disease progression; in particular, the influence of *HLA-B*35* in accelerating AIDS progression was attributable to HLA-B*35-Px alleles, some of which differ from HLA-B*35-PY alleles by a single amino acid residue [75].

Long-term nonprogression to AIDS has been associated with *HLA-B*57* [81, 107, 118] and *B*27* alleles [82, 107, 118, 161, 201] as well as with homozygosity for *HLA-Bw4*, more recently [73]. The role of *HLA-B* alleles with the Bw4 epitope that serve not only in the presentation of viral peptides for immune recognition, but also as ligands for natural killer cell inhibitory receptors, should be validated by additional studies [190]. Indeed, an initial investigation in over 1,000 HIV-1-infected subjects enrolled in five cohorts that was published earlier this year demonstrated an epistatic interaction to exist between the activating killer immunoglobulin-like receptor (KIR) allele *KIR3DS1* and *HLA-B Bw4-80I* that delays progression to AIDS [152]. According to Michael [169], in an editorial published together with this study, this research was particularly important because it implicated a critical interface, albeit through a yet speculative mechanism, between the innate [represented by the natural killer (NK) cells] and adaptive arms (represented by the CTLs) of the cellular immune response in controlling HIV replication, thus advancing the field of host genetic influences on HIV pathogenesis to a new level.

Furthermore, a study of a subgroup of HIV-1-infected long-term nonprogressors, with suppressed plasma viral replication to < 50 copies/mL and stable CD4 cell counts for at least two years in the absence of antiretroviral therapy, demonstrated an impressive association of *HLA-B*5701* class I allele with nonprogression, since 85% of the 13 nonprogressors versus a 9.5% of the 200 progressors carried this allele, respectively [173]. One of the largest conducted studies on the genetic influence of *HLA* alleles on HIV-1 disease confirmed the association of *B*27* and *B*57* with long-term nonprogression, although it also demonstrated that stronger associations exist between *B*14* and *C*8* and slow disease progression [87]. Unpublished data from 592 seroconverters indicated that the associations between *B*27* and *B*57* with delayed HIV-1 disease progression were reduced to insignificant levels after correction for multiple tests [33]. Most of the additional associations between *HLA*

haplotypes and the rate of HIV-1 disease progression have also been difficult to confirm in large cohorts of patients.

The mechanisms that govern the associations of *HLA* type with HIV-1 infection are not fully understood; however, *HLA* type is thought to affect the efficiency of the induced immune response to a large array of pathogens, including HIV-1. In this respect, more effective immune responses would be considered those that allow for the greatest repertoire of antigenic peptides to be presented to CTL; maximum *HLA* heterozygosity appears to have the potential to induce such effective antiviral immune responses to the constantly evolving spectrum of HIV-1 antigens ("hypothesis of overdominant selection" or "heterozygous advantage"). In contrast, unfavorable *HLA* genes or gene combinations could divert the immune system from eliciting efficient antiviral responses, although no evidence has been presented to support this hypothesis.

ACKNOWLEDGEMENTS

The Elizabeth Glazer Pediatric AIDS Foundation under 51086-25-PG provided grant support.

LIST OF ABBREVIATIONS

IL-10	=	Interleukin-10
IL-4	=	Interleukin-4
TNF-alpha	=	Tumor necrosis factor-alpha
MBL	=	Mannose-binding lectin
HLA	=	Human leukocyte antigen
Real-time-PCR	=	Polymerase chain reaction in real-time
SDF-1	=	Stromal derived factor-1
MIP-1-alpha and MIP-1-beta	=	Macrophage inflammatory proteins 1-alpha and 1-beta, respectively
RANTES	=	Regulated on activation, normal T cell expressed and secreted
MACS	=	Multicenter AIDS Cohort Study
RH	=	Relative hazard
5′ -UTR	=	5′ -untranslated region
IL-2	=	Interleukin-2
DCG	=	The D.C. Gay cohort
MHCS	=	The Multicenter Hemophilia Cohort Study
GRIV	=	The Genetics of the Resistance to Infection by the Immunodeficiency Virus, study
SSCP	=	Single-strand conformation polymorphism, analysis
MHC	=	Major histocompatibility complex
TAP	=	Transporter proteins associated with antigen processing
STR	=	Short tandem repeat
KIR	=	Killer immunoglobulin-like receptor
NK cells	=	Natural killer cells

REFERENCES

[1] Aarons E, Fernandez M, Rees A, McClure M, Weber J. (1997). AIDS. 11: 688-689.

[2] Alkhatib G, Ahuja SS, Light D, Mummidi S, Berger EA, Ahuja SK. (1997). Journal of Biological Chemistry. 272:19771-19776.

[3] Alkhatib G, Combadiere C, Broder CC, Feng Y, Kennedy PE, Murphy PM, Berger EA. (1996). Science. 272:1955-1958.

[4] An P, Martin MP, Nelson GW, Carrington M, Smith MW, Gong K, Vlahov D, O'Brien SJ, Winkler CA. (2000). AIDS. 14:2117-2122.

[5] Ansari-Lari MA, Liu XM, Metzker ML, Rut AR, Gibbs RA. (1997). Nature Genetics. 16:221-222.

[6] Anzala AO, Ball TB, Rostron T, O'Brien S J, Plummer FA, Rowland-jones SL. (1998). Lancet. 351:1632-1633.

[7] Arenzana-Seisdedos F, Virelizier JL, Rousset D, Clark-Lewis I, Loetscher P, Moser B, Baggiolini M. (1996). Nature. 383:400.

[8] Arya SK, Ginsberg CC, Davis-Warren A, D'Costa J. (1999). Journal of Human Virology. 2:133-138.

[9] Ashorn PA, Berger EA, Moss B. (1990). Journal of Virology. 64:2149-2156.

[10] Ayoubi TA, Van De Ven WJ. (1996). FASEB Journal. 10:453-460.

[11] Bajetto A, Bonavia R, Barbero S, Piccioli P, Costa A, Florio T, Schettini G. (1999). Journal of Neurochemistry. 73:2348-2357.

[12] Balotta C, Bagnarelli P, Corvasce S, Mazzucchelli R, Colombo MC, Papagno L, Santambrogio S, Ridolfo AL, Violin M, Berlusconi A, Velleca R, Facchi G, Moroni M, Clementi M, Galli M. (1999). The Journal of Infectious Diseases. 180:285-289.

[13] Balotta C, Bagnarelli P, Violin M, Ridolfo AL, Zhou D, Berlusconi A, Corvasce S, Corbellino M, Clementi M, Clerici M, Moroni M, Galli M. (1997). AIDS. 11:F67-71.

[14] Bamshad MJ, Mummidi S, Gonzalez E, Ahuja SS, Dunn DM, Watkins WS, Wooding S, Stone AC, Jorde LB, Weiss RB, Ahuja SK. (2002). Proceedings of National Academy of Sciences, U.S.A. 99:10539-10544.

[15] Barbouche RM, Hong L, Dellagi K, Kostrikis LG. (2001). Journal of Acquired Immune Deficiency Syndrome 26:298-299.

[16] Benkirane M, Jin DY, Chun RF, Koup RA, Jeang KT. (1997). Journal of Biological Chemistry. 272:30603-30606.

[17] Berger EA. (1997). AIDS. 11 Suppl A:S3-16.

[18] Berger EA, Doms RW, Fenyo EM, Korber BT, Littman DR, Moore JP, Sattentau QJ, Schuitemaker H, Sodroski J, Weiss RA. (1998). Nature. 391:240.

[19] Berger EA, Murphy PM, Farber JM. (1999). Annual Review of Immunology. 17:657-700.

[20] Binley J, Moore JP. (1997). Nature. 387:346-348.

[21] Biti R, Ffrench R, Young J, Bennetts B, Stewart G, Liang T. (1997). Nature Medicine. 3:252-253.

[22] Bleul CC, Farzan M, Choe H, Parolin C, Clark-Lewis I, Sodroski J, Springer TA. (1996). Nature. 382:829-833.

[23] Bleul CC, Fuhlbrigge RC, Casasnovas JM, Aiuti A, Springer TA. (1996). Journal of Experimental Medicine. 184:1101-1109.

[24] Bleul CC, Wu L, Hoxie JA, Springer TA, Mackay CR. (1997). Proceedings of National Academy of Sciences, U.S.A. 94:1925-1930.

[25] Brambilla A, Villa C, Rizzardi G, Veglia F, Ghezzi S, Lazzarin A, Cusini M, Muratori S, Santagostino E, Gringeri A, Louie LG, Sheppard HW, Poli G, Michael NL, Pantaleo G, Vicenzi E. (2000). The Journal of Infectious Diseases. 182:311-315.

[26] Bratt G, Sandstrom E, Albert J, Samson M, Wahren B. (1997). AIDS. 11:1415-1419.

[27] Brinkman BM, Keet IP, Miedema F, Verweij CL, Klein MR. (1997). The Journal of Infectious Diseases. 175:188-190.

[28] Broder CC, Berger EA. (1995). Proceedings of National Academy of Sciences, U.S.A. 92:9004-9008.

[29] Broder CC, Dimitrov DS, Blumenthal R, Berger EA. (1993). Virology. 193:483-491.

[30] Campbell RD, Trowsdale J. (1993). Immunology Today. 14:349-352.

[31] Carrington M, Dean M, Martin MP, O'Brien SJ. (1999). Human Molecular Genetics. 8:1939-1945.

[32] Carrington M, Kissner T, Gerrard B, Ivanov S, O'Brien SJ, Dean M. (1997). American Journal of Human Genetics. 61:1261-1267.

[33] Carrington M, Nelson G, O'Brien SJ. (2001). Immunological Letters. 79:131-140.

[34] Carrington M, Nelson GW, Martin MP, Kissner T, Vlahov D, Goedert JJ, Kaslow R, Buchbinder S, Hoots K, O'Brien SJ. (1999). Science. 283:1748-1752.

[35] Carroll RG, Riley JL, Levine BL, Feng Y, Kaushal S, Ritchey DW, Bernstein W, Weislow OS, Brown CR, Berger EA, June CH, St Louis DC. (1997). Science. 276:273-276.

[36] Chan DC, Kim PS. (1998). Cell. 93:681-684.

[37] Choe H, Farzan M, Sun Y, Sullivan N, Rollins B, Ponath PD, Wu L, Mackay CR, LaRosa G, Newman W, Gerard N, Gerard C, Sodroski J. (1996). Cell. 85:1135-1148.

[38] Christodoulou C, Poullikas M, Neumann AU, Kostrikis LG. (1997). AIDS Research and Human Retroviruses. 13:1373-1374.

[39] Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P. (1995). Science. 270:1811-1815.

[40] Cohen OJ, Paolucci S, Bende SM, Daucher M, Moriuchi H, Moriuchi M, Cicala C, Davey RT, Jr., Baird B, Fauci AS. (1998). Journal of Virology. 72:6215-6217.

[41] Combadiere C, Ahuja SK, Murphy PM. (1995). DNA Cell Biology. 14:673-680.

[42] Combadiere C, Salzwedel K, Smith ED, Tiffany HL, Berger EA, Murphy PM. (1998). Journal of Biological Chemistry. 273:23799-23804.

[43] Connor RI, Paxton WA, Sheridan KE, Koup RA. (1996). Journal of Virology. 70:8758-8764.

[44] Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. (1997). Journal of Experimental Medicine. 185:621-628.

[45] Crawley E, Woo P, Isenberg DA. (1999). Arthritis, Rheumatism. 42:2017-2018.

[46] Dalgleish AG, Beverley PC, Clapham PR, Crawford DH, Greaves MF, Weiss RA. (1984). Nature. 312:763-767.

[47] de Roda Husman AM, Koot M, Cornelissen M, Keet IP, Brouwer M, Broersen SM, Bakker M, Roos MT, Prins M, de Wolf F, Coutinho RA, Miedema F, Goudsmit J, Schuitemaker H. (1997). Annals of Internal Medicine. 127:882-890.

[48] Dean M, Carrington M, O'Brien SJ. (2002). Annual Review of Genomics and Human Genetics. 3:263-292.

[49] Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E, Donfield S, Vlahov D, Kaslow R, Saah A, Rinaldo C, Detels R, O'Brien SJ. (1996). Science. 273:1856-1862.

[50] Dean M, Jacobson LP, McFarlane G, Margolick JB, Jenkins FJ, Howard OM, Dong HF, Goedert JJ, Buchbinder S, Gomperts E, Vlahov D, Oppenheim JJ, O'Brien SJ, Carrington M. (1999). Cancer Research. 59:3561-3564.

[51] Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhart M, Di Marzio P, Marmon S, Sutton RE, Hill CM, Davis CB, Peiper SC, Schall TJ, Littman DR, Landau NR. (1996). Nature. 381:661-666.

[52] Deng HK, Unutmaz D, KewalRamani VN, Littman DR. (1997). Nature. 388:296-300.

[53] Doms RW. (2000). Virology. 276:229-237.

[54] Doms RW, Moore JP. (2000). Journal of Cell Biology. 151:F9-14.

[55] Doms RW, Peiper SC. (1997). Virology. 235:179-190.

[56] Doranz BJ, Rucker J, Yi Y, Smyth RJ, Samson M, Peiper SC, Parmentier M, Collman RG, Doms RW. (1996). Cell. 85:1149-1158.

[57] Dragic T, Charneau P, Clavel F, Alizon M. (1992). Journal of Virology. 66:4794-4802.

[58] Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA. (1996). Nature. 381:667-673.

[59] Duh EJ, Maury WJ, Folks TM, Fauci AS, Rabson AB. (1989). Proceedings of National Academy of Sciences, U.S.A. 86:5974-5978.

[60] Easterbrook PJ, Rostron T, Ives N, Troop M, Gazzard BG, Rowland-Jones SL. (1999). The Journal of Infectious Diseases. 180:1096-1105.

[61] Eckert DM, Kim PS. (2001). Annual Review of Biochemistry. 70:777-810.

[62] Edelman L, Deveau C, Raphael M, Monchatre E, Gabarre J, Deville-Chabrol A, Pialoux G, Emilie D, Joab I, Galanaud P. (1996). European Cytokine Netw. 7:785-791.

[63] Edelstein RE, Arcuino LA, Hughes JP, Melvin AJ, Mohan KM, King PD, McLellan CL, Murante BL, Kassman BP, Frenkel LM. (1997). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 16:243-246.

[64] Epstein J, Eichbaum Q, Sheriff S, Ezekowitz RA. (1996). Current Opinions in Immunology. 8:29-35.

[65] Eugen-Olsen J, Iversen AK, Benfield TL, Koppelhus U, Garred P. (1998). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 18:110-116.

[66] Eugen-Olsen J, Iversen AK, Garred P, Koppelhus U, Pedersen C, Benfield TL, Sorensen AM, Katzenstein T, Dickmeiss E, Gerstoft J, Skinhoj P, Svejgaard A, Nielsen JO, Hofmann B. (1997). AIDS. 11:305-310.

[67] Ezekowitz RA, Kuhlman M, Groopman JE, Byrn RA. (1989). Journal of Experimental Medicine. 169:185-196.

[68] Farzan M, Choe H, Martin K, Marcon L, Hofmann W, Karlsson G, Sun Y, Barrett P, Marchand N, Sullivan N, Gerard N, Gerard C, Sodroski J. (1997). Journal of Experimental Medicine. 186:405-411.

[69] Faure S, Meyer L, Costagliola D, Vaneensberghe C, Genin E, Autran B, Delfraissy JF, McDermott DH, Murphy PM, Debre P, Theodorou I, Combadiere C. (2000). Science. 287:2274-2277.

[70] Feng Y, Broder CC, Kennedy PE, Berger EA. (1996). Science. 272:872-877.

[71] Fiorentino DF, Bond MW, Mosmann TR. (1989). Journal of Experimental Medicine. 170:2081-2095.

[72] Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A. (1991). Journal of Immunology. 147:3815-3822.

[73] Flores-Villanueva PO, Yunis EJ, Delgado JC, Vittinghoff E, Buchbinder S, Leung JY, Uglialoro AM, Clavijo OP, Rosenberg ES, Kalams SA, Braun JD, Boswell SL, Walker BD, Goldfeld AE. (2001). Proceedings of National Academy of Sciences, U.S.A. 98:5140-5145.

[74] Gallo RC, Garzino-Demo A, DeVico AL. (1999). Journal of Clinical Immunology. 19:293-299.

[75] Gao X, Nelson GW, Karacki P, Martin MP, Phair J, Kaslow R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, O'Brien SJ, Carrington M. (2001). New England Journal of Medicine. 344:1668-1675.

[76] Garred P, Madsen HO, Balslev U, Hofmann B, Pedersen C, Gerstoft J, Svejgaard A. (1997). Lancet. 349:236-240.

[77] Garred P, Madsen HO, Hofmann B, Svejgaard A. (1995). Lancet. 346:941-943.

[78] Gonzalez E, Bamshad M, Sato N, Mummidi S, Dhanda R, Catano G, Cabrera S, McBride M, Cao XH, Merrill G, O'Connell P, Bowden DW, Freedman BI, Anderson SA, Walter EA, Evans JS, Stephan KT, Clark RA, Tyagi S, Ahuja SS, Dolan MJ, Ahuja SK. (1999). Proceedings of National Academy of Sciences, U.S.A. 96:12004-12009.

[79] Gonzalez E, Dhanda R, Bamshad M, Mummidi S, Geevarghese R, Catano G, Anderson SA, Walter EA, Stephan KT, Hammer MF, Mangano A, Sen L, Clark RA, Ahuja SS, Dolan MJ, Ahuja SK. (2001). Proceedings of National Academy of Sciences, U.S.A. 98:5199-5204.

[80] Gorry PR, Zhang C, Wu S, Kunstman K, Trachtenberg E, Phair J, Wolinsky S, Gabuzda D. (2002). Lancet. 359:1832-1834.

[81] Goulder PJ, Bunce M, Krausa P, McIntyre K, Crowley S, Morgan B, Edwards A, Giangrande P, Phillips RE, McMichael AJ. (1996). AIDS Research and Human Retroviruses. 12:1691-1698.

[82] Goulder PJ, Phillips RE, Colbert RA, McAdam S, Ogg G, Nowak MA, Giangrande P, Luzzi G, Morgan B, Edwards A, McMichael AJ, Rowland-Jones S. (1997). Nature Medicine. 3:212-217.

[83] Granelli-Piperno A, Moser B, Pope M, Chen D, Wei Y, Isdell F, O'Doherty U, Paxton W, Koup R, Mojsov S, Bhardwaj N, Clark-Lewis I, Baggiolini M, Steinman RM. (1996). Journal of Experimental Medicine. 184:2433-2438.

[84] Haribabu B, Richardson RM, Fisher I, Sozzani S, Peiper SC, Horuk R, Ali H, Snyderman R. (1997). Journal of Biological Chemistry. 272:28726-28731.

[85] Harrington RD, Geballe AP. (1993). Journal of Virology. 67:5939-5947.

[86] Heiken H, Becker S, Bastisch I, Schmidt RE. (1999). AIDS. 13:529-530.

[87] Hendel H, Caillat-Zucman S, Lebuanec H, Carrington M, O'Brien S, Andrieu JM, Schachter F, Zagury D, Rappaport

J, Winkler C, Nelson GW, Zagury JF. (1999). Journal of Immunology. 162:6942-6946.

[88] Hendel H, Henon N, Lebuanec H, Lachgar A, Poncelet H, Caillat-Zucman S, Winkler CA, Smith MW, Kenefic L, O'Brien S, Lu W, Andrieu JM, Zagury D, Schachter F, Rappaport J, Zagury JF. (1998). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 19:381-386.

[89] Hendel H, Winkler C, An P, Roemer-Binns E, Nelson G, Haumont P, O'Brien S, Khalilli K, Zagury D, Rappaport J, Zagury JF. (2001). Journal of Acquired Immune Deficiency Syndrome. 26:507-511.

[90] Hill AV. (1996). Nature Medicine. 2:395-396.

[91] Hill CM, Deng H, Unutmaz D, Kewalramani VN, Bastiani L, Gorny MK, Zolla-Pazner S, Littman DR. (1997). Journal of Virology. 71:6296-6304.

[92] Hoffman TL, MacGregor RR, Burger H, Mick R, Doms RW, Collman RG. (1997). The Journal of Infectious Diseases. 176:1093-1096.

[93] Hogan CM, Hammer SM. (2001). Annals of Internal Medicine. 134:978-996.

[94] Holmskov U, Malhotra R, Sim RB, Jensenius JC. (1994). Immunology Today. 15:67-74.

[95] Huang Y, Paxton WA, Wolinsky SM, Neumann AU, Zhang L, He T, Kang S, Ceradini D, Jin Z, Yazdanbakhsh K, Kunstman K, Erickson D, Dragon E, Landau NR, Phair J, Ho DD, Koup RA. (1996). Nature Medicine. 2:1240-1243.

[96] Hughes AL, Yeager M. (1998). Frontiers of Bioscience. 3:d509-516.

[97] Imai T, Hieshima K, Haskell C, Baba M, Nagira M, Nishimura M, Kakizaki M, Takagi S, Nomiyama H, Schall TJ, Yoshie O. (1997). Cell. 91:521-530.

[98] Ioannidis JP, O'Brien TR, Rosenberg PS, Contopoulos-Ioannidis DG, Goedert JJ. (1998). Nature Medicine. 4:536.

[99] Ioannidis JP, Rosenberg PS, Goedert JJ, Ashton LJ, Benfield TL, Buchbinder SP, Coutinho RA, Eugen-Olsen J, Gallart T, Katzenstein TL, Kostrikis LG, Kuipers H, Louie LG, Mallal SA, Margolick JB, Martinez OP, Meyer L, Michael NL, Operskalski E, Pantaleo G, Rizzardi GP, Schuitemaker H, Sheppard HW, Stewart GJ, Theodorou ID, Ullum H, Vicenzi E, Vlahov D, Wilkinson D, Workman C, Zagury JF, O'Brien TR. (2001). Annals of Internal Medicine. 135:782-795.

[100] Itescu S, Mathur-Wagh U, Skovron ML, Brancato LJ, Marmor M, Zeleniuch-Jacquotte A, Winchester R. (1992). Journal of Acquired Immune Deficiency Syndrome. 5:37-45.

[101] Itescu S, Rose S, Dwyer E, Winchester R. (1994). Proceedings of the National Academy of Sciences, U.S.A. 91:11472-11476.

[102] Jeannet M, Sztajzel R, Carpentier N, Hirschel B, Tiercy JM. (1989). Journal of Acquired Immune Deficiency Syndrome. 2:28-32.

[103] Jin X, Gao X, Ramanathan M Jr, Deschenes GR, Nelson GW, O'Brien SJ, Goedert JJ, Ho DD, O'Brien TR, Carrington M. (2002). Journal of Virology. 76:12603-12610.

[104] John GC, Rousseau C, Dong T, Rowland-Jones S, Nduati R, Mbori-Ngacha D, Rostron T, Kreiss JK, Richardson BA, Overbaugh J. (2000). Journal of Virology. 74:5736-5739.

[105] Johnson RP, Trocha A, Buchanan TM, Walker BD. (1993). Journal of Virology. 67:438-445.

[106] Just JJ. (1995). Human Immunology. 44:156-169.

[107] Kaslow RA, Carrington M, Apple R, Park L, Munoz A, Saah AJ, Goedert JJ, Winkler C, O'Brien SJ, Rinaldo C, Detels R, Blattner W, Phair J, Erlich H, Mann DL. (1996). Nature Medicine. 2:405-411.

[108] Kaslow RA, McNicholl JM. (1999). Proceedings of the Association of American Physicians. 111:299-307.

[109] Katzenstein TL, Eugen-Olsen J, Hofmann B, Benfield T, Pedersen C, Iversen AK, Sorensen AM, Garred P, Koppelhus U, Svejgaard A, Gerstoft J. (1997). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 16:10-14.

[110] Kaul R, Trabattoni D, Bwayo JJ, Arienti D, Zagliani A, Mwangi FM, Kariuki C, Ngugi EN, MacDonald KS, Ball TB, Clerici M, Plummer FA. (1999). AIDS. 13:23-29.

[111] Kazazian HH, Jr. (1990). Seminars in Hematology 27:209-228.

[112] Keegan AD, Nelms K, Wang LM, Pierce JH, Paul WE. (1994). Immunology Today. 15:423-432.

[113] Keet IP, Klein MR, Just JJ, Kaslow RA. (1996). AIDS. 10 Suppl A:S59-67.

[114] Keet IP, Tang J, Klein MR, LeBlanc S, Enger C, Rivers C, Apple RJ, Mann D, Goedert JJ, Miedema F, Kaslow RA. (1999). The Journal of Infectious Diseases. 180:299-309.

[115] Khoo SH, Pepper L, Snowden N, Hajeer AH, Vallely P, Wilkins EG, Mandal BK, Ollier WE. (1997). AIDS. 11:423-428.

[116] Klatzmann D, Champagne E, Chamaret S, Gruest J, Guetard D, Hercend T, Gluckman JC, Montagnier L. (1984). Nature. 312:767-768.

[117] Klein MR, Miedema F. (1995). Trends in Microbiology. 3:386-391.

[118] Klein MR, van der Burg SH, Hovenkamp E, Holwerda AM, Drijfhout JW, Melief CJ, Miedema F. (1998). Journal of General Virology. 79 (Pt 9):2191-2201.

[119] Knuchel MC, Spira TJ, Neumann AU, Xiao L, Rudolph DL, Phair J, Wolinsky SM, Koup RA, Cohen OJ, Folks TM, Lal RB. (1998). AIDS Research and Human Retroviruses. 14:305-309.

[120] Kollmann TR, Pettoello-Mantovani M, Katopodis NF, Hachamovitch M, Rubinstein A, Kim A, Goldstein H.

(1996). Proceedings of National Academy of Sciences, U.S.A. 93:3126-3131.

[121] Kostrikis LG. (2000). Teratology. 61:387-390.

[122] Kostrikis LG, Huang Y, Moore JP, Wolinsky SM, Zhang L, Guo Y, Deutsch L, Phair J, Neumann AU, Ho DD. (1998). Nature Medicine. 4:350-353.

[123] Kostrikis LG, Neumann AU, Thomson B, Korber BT, McHardy P, Karanicolas R, Deutsch L, Huang Y, Lew JF, McIntosh K, Pollack H, Borkowsky W, Spiegel HM, Palumbo P, Oleske J, Bardeguez A, Luzuriaga K, Sullivan J, Wolinsky SM, Koup RA, Ho DD, Moore JP. (1999). Journal of Virology. 73:10264-10271.

[124] Kostrikis LG, Tyagi S, Mhlanga MM, Ho DD, Kramer FR. (1998). Science. 279:1228-1229.

[125] Kozak M. (1991). Journal of Cell Biology. 115:887-903.

[126] Kroner BL, Goedert JJ, Blattner WA, Wilson SE, Carrington MN, Mann DL. (1995). AIDS. 9:275-280.

[127] Kuipers H, Workman C, Dyer W, Geczy A, Sullivan J, Oelrichs R. (1999). AIDS. 13:433-434.

[128] LaBranche CC, Galasso G, Moore JP, Bolognesi DP, Hirsch MS, Hammer SM. (2001). Antiviral Research. 50:95-115.

[129] Lalani AS, Masters J, Zeng W, Barrett J, Pannu R, Everett H, Arendt CW, McFadden G. (1999). Science. 286:1968-1971.

[130] Lapham CK, Ouyang J, Chandrasekhar B, Nguyen NY, Dimitrov DS, Golding H. (1996). Science. 274:602-605.

[131] Lee B, Doranz BJ, Rana S, Yi Y, Mellado M, Frade JM, Martinez AC, O'Brien SJ, Dean M, Collman RG, Doms RW. (1998). Journal of Virology. 72:7450-7458.

[132] Liao F, Alkhatib G, Peden KW, Sharma G, Berger EA, Farber JM. (1997). Journal of Experimental Medicine. 185:2015-2023.

[133] Lipscombe RJ, Lau YL, Levinsky RJ, Sumiya M, Summerfield JA, Turner MW. (1992). Immunological Letters. 32:253-257.

[134] Liu H, Chao D, Nakayama EE, Taguchi H, Goto M, Xin X, Takamatsu JK, Saito H, Ishikawa Y, Akaza T, Juji T, Takebe Y, Ohishi T, Fukutake K, Maruyama Y, Yashiki S, Sonoda S, Nakamura T, Nagai Y, Iwamoto A, Shioda T. (1999). Proceedings of National Academy of Sciences, U.S.A. 96:4581-4585.

[135] Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, MacDonald ME, Stuhlmann H, Koup RA, Landau NR. (1996). Cell. 86:367-377.

[136] Loetscher M, Amara A, Oberlin E, Brass N, Legler D, Loetscher P, D'Apuzzo M, Meese E, Rousset D, Virelizier JL, Baggiolini M, Arenzana-Seisdedos F, Moser B. (1997). Current Biology. 7:652-660.

[137] Louisirirotchanakul S, Liu H, Roongpisuthipong A, Nakayama EE, Takebe Y, Shioda T, Wasi C. (2002). Journal of Acquired Immune Deficiency Syndrome. 29:314-315.

[138] Lucotte G, Mercier G. (1998). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 19:174-177.

[139] Maas J, de Roda Husman AM, Brouwer M, Krol A, Coutinho R, Keet I, van Leeuwen R, Schuitemaker H. (1998). AIDS. 12:2275-2280.

[140] Macdonald KS, Embree J, Njenga S, Nagelkerke NJ, Ngatia I, Mohammed Z, Barber BH, Ndinya-achola J, Bwayo J, Plummer FA. (1998). The Journal of Infectious Diseases. 177:551-556.

[141] MacDonald KS, Fowke KR, Kimani J, Dunand VA, Nagelkerke NJ, Ball TB, Oyugi J, Njagi E, Gaur LK, Brunham RC, Wade J, Luscher MA, Krausa P, Rowland-Jones S, Ngugi E, Bwayo JJ, Plummer FA. (2000). The Journal of Infectious Diseases. 181:1581-1589.

[142] Maddon PJ, Dalgleish AG, McDougal JS, Clapham PR, Weiss RA, Axel R. (1986). Cell. 47:333-348.

[143] Madsen HO, Garred P, Kurtzhals JA, Lamm LU, Ryder LP, Thiel S, Svejgaard A. (1994). Immunogenetics. 40:37-44.

[144] Madsen HO, Garred P, Thiel S, Kurtzhals JA, Lamm LU, Ryder LP, Svejgaard A. (1995). Journal of Immunology. 155:3013-3020.

[145] Mangano A, Gonzalez E, Dhanda R, Catano G, Bamshad M, Bock A, Duggirala R, Williams K, Mummidi S, Clark RA, Ahuja SS, Dolan MJ, Bologna R, Sen L, Ahuja SK. (2001). The Journal of Infectious Diseases. 183:1574-1585.

[146] Mangano A, Kopka J, Batalla M, Bologna R, Sen L. (2000). Journal of Acquired Immune Deficiency Syndrome. 23:52-57.

[147] Marcu KB, Bossone SA, Patel AJ. (1992). Annual Review of Biochemistry. 61:809-860.

[148] Mariani R, Wong S, Mulder LC, Wilkinson DA, Reinhart AL, LaRosa G, Nibbs R, O'Brien TR, Michael NL, Connor RI, Macdonald M, Busch M, Koup RA, Landau NR. (1999). Journal of Virology. 73:2450-2459.

[149] Marmor M, Sheppard HW, Donnell D, Bozeman S, Celum C, Buchbinder S, Koblin B, Seage GR, 3rd. (2001). Journal of Acquired Immune Deficiency Syndrome. 27:472-481.

[150] Martin MP, Carrington M, Dean M, O'Brien SJ, Sheppard HW, Wegner SA, Michael NL. (1998). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 19:430.

[151] Martin MP, Dean M, Smith MW, Winkler C, Gerrard B, Michael NL, Lee B, Doms RW, Margolick J, Buchbinder S, Goedert JJ, O'Brien TR, Hilgartner MW, Vlahov D, O'Brien SJ, Carrington M. (1998). Science. 282:1907-1911.

[152] Martin MP, Gao X, Lee JH, Nelson GW, Detels R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, Trowsdale J, Wilson M, O'Brien SJ, Carrington M. (2002). Nature Genetics. 31:429-434.

[153] Martinson JJ, Chapman NH, Rees DC, Liu YT, Clegg JB. (1997). Nature Genetics. 16:100-103.

[154] Matsuyama T, Kobayashi N, Yamamoto N. (1991). AIDS. 5:1405-1417.

[155] Matt C, Roger M. (2001). Molecular Medicine. 7:583-589.

[156] McDermott DH, Beecroft MJ, Kleeberger CA, Al-Sharif FM, Ollier WE, Zimmerman PA, Boatin BA, Leitman SF, Detels R, Hajeer AH, Murphy PM. (2000). AIDS. 14:2671-2678.

[157] McDermott DH, Colla JS, Kleeberger CA, Plankey M, Rosenberg PS, Smith ED, Zimmerman PA, Combadiere C, Leitman SF, Kaslow RA, Goedert JJ, Berger EA, O'Brien TR, Murphy PM. (2000). Science. 290:2031.

[158] McDermott DH, Zimmerman PA, Guignard F, Kleeberger CA, Leitman SF, Murphy PM. (1998). Lancet. 352:866-870.

[159] McDougal JS, Kennedy MS, Sligh JM, Cort SP, Mawle A, Nicholson JK. (1986). Science. 231:382-385.

[160] McGuire W, Hill AV, Allsopp CE, Greenwood BM, Kwiatkowski D. (1994). Nature. 371:508-510.

[161] McNeil AJ, Yap PL, Gore SM, Brettle RP, McColl M, Wyld R, Davidson S, Weightman R, Richardson AM, Robertson JR. (1996). QJM:monthly journal of the Association of Physicians. 89:177-185.

[162] McNicholl JM, Smith DK, Qari SH, Hodge T. (1997). Emerging Infectious Diseases. 3:261-271.

[163] Mellado M, Rodriguez-Frade JM, Vila-Coro AJ, de Ana AM, Martinez AC. (1999). Nature. 400:723-724.

[164] Meucci O, Fatatis A, Simen AA, Miller RJ. (2000). Proceedings of the National Academy of Sciences U.S.A. 97:8075-8080.

[165] Meyer L, Magierowska M, Hubert JB, Mayaux MJ, Misrahi M, Le Chenadec J, Debre P, Rouzioux C, Delfraissy JF, Theodorou I. (1999). The Journal of Infectious Diseases. 180:920-924.

[166] Meyer L, Magierowska M, Hubert JB, Rouzioux C, Deveau C, Sanson F, Debre P, Delfraissy JF, Theodorou I. (1997). AIDS. 11:F73-78.

[167] Meyer L, Magierowska M, Hubert JB, Theodorou I, van Rij R, Prins M, de Roda Husman AM, Coutinho R, Schuitemaker H. (1999). AIDS. 13:624-626.

[168] Michael NL. (1999). Current Opinion in Immunology. 11:466-474.

[169] Michael NL. (2002). Nature Medicine. 8:783-785.

[170] Michael NL, Chang G, Louie LG, Mascola JR, Dondero D, Birx DL, Sheppard HW. (1997). Nature Medicine. 3:338-340.

[171] Michael NL, Louie LG, Rohrbaugh AL, Schultz KA, Dayhoff DE, Wang CE, Sheppard HW. (1997). Nature Medicine. 3:1160-1162.

[172] Michael NL, Nelson JA, KewalRamani VN, Chang G, O'Brien SJ, Mascola JR, Volsky B, Louder M, White GC, 2nd, Littman DR, Swanstrom R, O'Brien TR. (1998). Journal of Virology. 72:6040-6047.

[173] Migueles SA, Sabbaghian MS, Shupert WL, Bettinotti MP, Marincola FM, Martino L, Hallahan CW, Selig SM, Schwartz D, Sullivan J, Connors M. (2000). Proceedings of the National Academy of Sciences U.S.A. 97:2709-2714.

[174] Mo H, Monard S, Pollack H, Ip J, Rochford G, Wu L, Hoxie J, Borkowsky W, Ho DD, Moore JP. (1998). AIDS Research and Human Retroviruses. 14:607-617.

[175] (1993). In:Moore JP, Jameson BA, Weiss RA, Sattentau QJ, The HIV-cell fusion reaction. Boca Raton, USA, pp 233-289.

[176] Moore JP, Stevenson M. (2000). Nature Reviews Molecular Cell Biology. 1:40-49.

[177] Moore JP, Trkola A, Dragic T. (1997). Current Opinion in Immunology. 9:551-562.

[178] Moriuchi H, Moriuchi M, Fauci AS. (1997). Journal of Immunology. 159:5441-5449.

[179] Moriuchi M, Moriuchi H, Turner W, Fauci AS. (1997). Journal of Immunology. 159:4322-4329.

[180] Muller F, Aukrust P, Nordoy I, Froland SS. (1998). Blood. 92:3721-3729.

[181] Mummidi S, Ahuja SS, Gonzalez E, Anderson SA, Santiago EN, Stephan KT, Craig FE, O'Connell P, Tryon V, Clark RA, Dolan MJ, Ahuja SK. (1998). Nature Medicine. 4:786-793.

[182] Mummidi S, Ahuja SS, McDaniel BL, Ahuja SK. (1997). Journal of Biological Chemistry. 272:30662-30671.

[183] Mummidi S, Bamshad M, Ahuja SS, Gonzalez E, Feuillet PM, Begum K, Galvis MC, Kostecki V, Valente AJ, Murthy KK, Haro L, Dolan MJ, Allan JS, Ahuja SK. (2000). Journal of Biological Chemistry. 275:18946-18961.

[184] Mummidi S, Catano G, Lam L, Hoefle A, Telles V, Begum K, Jimenez F, Ahuja SS, Ahuja SK. (2001). Journal of Biological Chemistry. 276:33196-33212.

[185] Naif HM, Cunningham AL, Alali M, Li S, Nasr N, Buhler MM, Schols D, de Clercq E, Stewart G. (2002). Journal of Virology. 76:114-3124.

[186] Nakayama EE, Hoshino Y, Xin X, Liu H, Goto M, Watanabe N, Taguchi H, Hitani A, Kawana-Tachikawa A, Fukushima M, Yamada K, Sugiura W, Oka SI, Ajisawa A, Sato H, Takebe Y, Nakamura T, Nagai Y, Iwamoto A, Shioda T. (2000). Journal of Virology. 74:5452-5459.

[187] Nakayama EE, Meyer L, Iwamoto A, Persoz A, Nagai Y, Rouzioux C, Delfraissy JF, Debre P, McIlroy D, Theodorou I, Shioda T. (2002). The Journal of Infectious Diseases. 185:1183-1186.

[188] Nasioulas G, Dean M, Koumbarelis E, Paraskevis D, Gialeraki A, Karafoulidou A, Mandalaki T, Hatzakis A. (1998). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 17:181-182.

[189] Oberlin E, Amara A, Bachelerie F, Bessia C, Virelizier JL, Arenzana-Seisdedos F, Schwartz O, Heard JM, Clark-

Lewis I, Legler DF, Loetscher M, Baggiolini M, Moser B. (1996). Nature. 382:833-835.

[190] O'Brien SJ, Gao X, Carrington M. (2001). Trends in Molecular Medicine. 7:379-381.

[191] O'Brien SJ, Moore JP. (2000). Immunological Reviews. 177:99-111.

[192] O'Brien SJ, Nelson GW, Winkler CA, Smith MW. (2000). Annual Review of Genetics. 34:563-591.

[193] O'Brien TR, Winkler C, Dean M, Nelson JA, Carrington M, Michael NL, White GC, 2nd. (1997). Lancet. 349:1219.

[194] Parham P, Ohta T. (1996). Science. 272:67-74.

[195] Pastinen T, Liitsola K, Niini P, Salminen M, Syvanen AC. (1998). AIDS Research and Human Retroviruses. 14:695-698.

[196] Patarca R, Sandler D, Maher K, Hutto C, Martin NL, Klimas NG, Scott GB, Fletcher MA. (1996). AIDS Research and Human Retroviruses. 12:1063-1068.

[197] Paul WE. (1991). Blood. 77:1859-1870.

[198] Paxton WA, Kang S. (1998). Seminars in Immunology. 10:187-194.

[199] Paxton WA, Liu R, Kang S, Wu L, Gingeras TR, Landau NR, Mackay CR, Koup RA. (1998). Virology. 244:66-73.

[200] Paxton WA, Martin SR, Tse D, O'Brien TR, Skurnick J, VanDevanter NL, Padian N, Braun JF, Kotler DP, Wolinsky SM, Koup RA. (1996). Nature Medicine. 2:412-417.

[201] Phillips RE, Rowland-Jones S, Nixon DF, Gotch FM, Edwards JP, Ogunlesi AO, Elvin JG, Rothbard JA, Bangham CR, Rizza CR, McMichael AJ. (1991). Nature. 354:453-459.

[202] Pleskoff O, Treboute C, Brelot A, Heveker N, Seman M, Alizon M. (1997). Science. 276:1874-1878.

[203] Plummer FA, Ball TB, Kimani J, Fowke KR. (1999). Immunology Letters. 66:27-34.

[204] Poignard P, Saphire EO, Parren PW, Burton DR. (2001). Annual Review of Immunology. 19:253-274.

[205] Powis SH, Geraghty DE. (1995). Immunology Today. 16:466-468.

[206] Premack BA, Schall TJ. (1996). Nature Medicine. 2:1174-1178.

[207] Quillent C, Oberlin E, Braun J, Rousset D, Gonzalez-Canali G, Metais P, Montagnier L, Virelizier JL, Arenzana-Seisdedos F, Beretta A. (1998). Lancet. 351:14-18.

[208] Rabkin CS, Yang Q, Goedert JJ, Nguyen G, Mitsuya H, Sei S. (1999). Blood. 93:1838-1842.

[209] Rana S, Besson G, Cook DG, Rucker J, Smyth RJ, Yi Y, Turner JD, Guo HH, Du JG, Peiper SC, Lavi E, Samson M, Libert F, Liesnard C, Vassart G, Doms RW, Parmentier M, Collman RG. (1997). Journal of Virology. 71:3219-3227.

[210] Raport CJ, Gosling J, Schweickart VL, Gray PW, Charo IF. (1996). Journal of Biological Chemistry. 271:17161-17166.

[211] Raport CJ, Schweickart VL, Eddy RL, Jr., Shows TB, Gray PW. (1995). Gene. 163:295-299.

[212] Rappaport J, Cho YY, Hendel H, Schwartz EJ, Schachter F, Zagury JF. (1997). Lancet. 349:922-923.

[213] Reeves JD, McKnight A, Potempa S, Simmons G, Gray PW, Power CA, Wells T, Weiss RA, Talbot SJ. (1997). Virology. 231:130-134.

[214] Rempel SA, Dudas S, Ge S, Gutierrez JA. (2000). Clinical Cancer Research. 6:102-111.

[215] Rizzardi GP, Morawetz RA, Vicenzi E, Ghezzi S, Poli G, Lazzarin A, Pantaleo G. (1998). Nature Medicine. 4:252-253.

[216] Roberts BD, Butera ST. (1997). AIDS. 11:1886-1888.

[217] Roger M. (1998). FASEB Journal. 12:625-632.

[218] Rosenwasser LJ, Borish L. (1997). American Journal of Respiratory Critical Care Medicine. 156:S152-155.

[219] Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klinnert M, Borish L. (1995). Clinical and Experimental Allergy. 25 Suppl 2:74-78.

[220] Rousseau CM, Just JJ, Abrams EJ, Casabona J, Stein Z, King MC. (1997). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 16:239-242.

[221] Rowland-Jones S, Pinheiro S, Kaul R. (2001). Cell. 104:473-476.

[222] Rowland-Jones S, Sutton J, Ariyoshi K, Dong T, Gotch F, McAdam S, Whitby D, Sabally S, Gallimore A, Corrah T, Takiguchi M, Schultz T, McMichael A, Whittle H. (1995). Nature Medicine. 1:59-64.

[223] Rowland-Jones SL, Dong T, Fowke KR, Kimani J, Krausa P, Newell H, Blanchard T, Ariyoshi K, Oyugi J, Ngugi E, Bwayo J, MacDonald KS, McMichael AJ, Plummer FA. (1998). Journal of Clinical Investigation. 102:1758-1765.

[224] Rucker J, Edinger AL, Sharron M, Samson M, Lee B, Berson JF, Yi Y, Margulies B, Collman RG, Doranz BJ, Parmentier M, Doms RW. (1997). Journal of Virology. 71:8999-9007.

[225] Saha K, Bentsman G, Chess L, Volsky DJ. (1998). Journal of Virology. 72:876-881.

[226] Sahmoud T, Laurian Y, Gazengel C, Sultan Y, Gautreau C, Costagliola D. (1993). AIDS. 7:497-500.

[227] Samson M, Labbe O, Mollereau C, Vassart G, Parmentier M. (1996). Biochemistry. 35:3362-3367.

[228] Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy

G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M. (1996). Nature. 382:722-725.

[229] Schibler U, Sierra F. (1987). Annual Review of Genetics. 21:237-257.

[230] Schols D, De Clercq E. (1996). Journal of Virology. 70:4953-4960.

[231] Scorza Smeraldi R, Fabio G, Lazzarin A, Eisera NB, Moroni M, Zanussi C. (1986). Lancet. 2:1187-1189.

[232] Sheppard HW, Celum C, Michael NL, O'Brien S, Dean M, Carrington M, Dondero D, Buchbinder SP. (2002). Journal of Acquired Immune Deficiency Syndrome. 29:307-313.

[233] Shiga H, Shioda T, Tomiyama H, Takamiya Y, Oka S, Kimura S, Yamaguchi Y, Gojoubori T, Rammensee HG, Miwa K, Takiguchi M. (1996). AIDS. 10:1075-1083.

[234] Shin HD, Winkler C, Stephens JC, Bream J, Young H, Goedert JJ, O'Brien TR, Vlahov D, Buchbinder S, Giorgi J, Rinaldo C, Donfield S, Willoughby A, O'Brien SJ, Smith MW. (2000). Proceedings of the National Academy of Sciences, U.S.A. 97:14467-14472.

[235] Shirozu M, Nakano T, Inazawa J, Tashiro K, Tada H, Shinohara T, Honjo T. (1995). Genomics. 28:495-500.

[236] Simmons G, Wilkinson D, Reeves JD, Dittmar MT, Beddows S, Weber J, Carnegie G, Desselberger U, Gray PW, Weiss RA, Clapham PR. (1996). Journal of Virology. 70:8355-8360.

[237] Simonsen JN, Fowke KR, MacDonald KS, Plummer FA. (1998). Current Opinion in Microbiology. 1:423-429.

[238] Smith MW, Carrington M, Winkler C, Lomb D, Dean M, Huttley G, O'Brien SJ. (1997). Nature Medicine. 3:1052-1053.

[239] Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, Goedert JJ, O'Brien TR, Jacobson LP, Kaslow R, Buchbinder S, Vittinghoff E, Vlahov D, Hoots K, Hilgartner MW, O'Brien SJ. (1997). Science. 277:959-965.

[240] Sriwanthana B, Hodge T, Mastro TD, Dezzutti CS, Bond K, Stephens HA, Kostrikis LG, Limpakarnjanarat K, Young NL, Qari SH, Lal RB, Chandanayingyong D, McNicholl JM. (2001). AIDS Research and Human Retroviruses. 17:719-734.

[241] Stephens JC, Reich DE, Goldstein DB, Shin HD, Smith MW, Carrington M, Winkler C, Huttley GA, Allikmets R, Schriml L, Gerrard B, Malasky M, Ramos MD, Morlot S, Tzetis M, Oddoux C, di Giovine FS, Nasioulas G, Chandler D, Aseev M, Hanson M, Kalaydjieva L, Glavac D, Gasparini P, Kanavakis E, Claustres M, Kambouris M, Ostrer H, Duff G, Baranov V, Sibul H, Metspalu A, Goldman D, Martin N, Duffy D, Schmidtke J, Estivill X, O'Brien SJ, Dean M. (1998). American Journal of Human Genetics. 62:1507-1515.

[242] Stewart GJ, Ashton LJ, Biti RA, Ffrench RA, Bennetts BH, Newcombe NR, Benson EM, Carr A, Cooper DA, Kaldor JM. (1997). AIDS. 11:1833-1838.

[243] Sullivan AD, Wigginton J, Kirschner D. (2001). Proceedings of the National Academy of Sciences, U.S.A. 98:10214-10219.

[244] Summerfield JA, Ryder S, Sumiya M, Thursz M, Gorchein A, Monteil MA, Turner MW. (1995). Lancet. 345:886-889.

[245] Super M, Thiel S, Lu J, Levinsky RJ, Turner MW. (1989). Lancet 2:1236-1239.

[246] Tang J, Costello C, Keet IP, Rivers C, Leblanc S, Karita E, Allen S, Kaslow RA. (1999). AIDS Research and Human Retroviruses. 15:317-324.

[247] Tang J, Shelton B, Makhatadze NJ, Zhang Y, Schaen M, Louie LG, Goedert JJ, Seaberg EC, Margolick JB, Mellors J, Kaslow RA. (2002). Journal of Virology. 76:662-672.

[248] Than S, Hu R, Oyaizu N, Romano J, Wang X, Sheikh S, Pahwa S. (1997). The Journal of Infectious Diseases. 175:47-56.

[249] Theodorou I, Meyer L, Magierowska M, Katlama C, Rouzioux C. (1997). Lancet. 349:1219-1220.

[250] Tomiyama H, Miwa K, Shiga H, Moore YI, Oka S, Iwamoto A, Kaneko Y, Takiguchi M. (1997). Journal of Immunology. 158:5026-5034.

[251] Tresoldi E, Romiti ML, Boniotto M, Crovella S, Salvatori F, Palomba E, Pastore A, Cancrini C, de Martino M, Plebani A, Castelli G, Rossi P, Tovo PA, Amoroso A, Scarlatti G. (2002). The Journal of Infectious Diseases. 185:696-700.

[252] Trkola A, Dragic T, Arthos J, Binley JM, Olson WC, Allaway GP, Cheng-Mayer C, Robinson J, Maddon PJ, Moore JP. (1996). Nature. 384:184-187.

[253] Turner MW. (1996). Immunology Today. 17:532-540.

[254] Tyagi S, Kramer FR. (1996). Nature Biotechnology. 14:303-308.

[255] Udalova IA, Nedospasov SA, Webb GC, Chaplin DD, Turetskaya RL. (1993). Genomics. 16:180-186.

[256] Valentin A, Lu W, Rosati M, Schneider R, Albert J, Karlsson A, Pavlakis GN. (1998). Proceedings of the National Academy of Sciences, U.S.A. 95:8886-8891.

[257] van Rij RP, Broersen S, Goudsmit J, Coutinho RA, Schuitemaker H. (1998). AIDS. 12:F85-90.

[258] van Rij RP, de Roda Husman AM, Brouwer M, Goudsmit J, Coutinho RA, Schuitemaker H. (1998). The Journal of Infectious Diseases. 178:1806-1811.

[259] van Rij RP, Portegies P, Hallaby T, Lange JM, Visser J, Husman AM, van 't Wout AB, Schuitemaker H. (1999). The Journal of Infectious Diseases. 180:854-857.

[260] Walli R, Reinhart B, Luckow B, Lederer E, Loch O, Malo A, Wank R, Schlondorff D, Goebel FD. (1998). Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 18:229-233.

[261] Wang J, Harada A, Matsushita S, Matsumi S, Zhang Y, Shioda T, Nagai Y, Matsushima K. (1998). Journal of Leukocyte Biology. 64:642-649.

[262] Wang J, Roderiquez G, Oravecz T, Norcross MA. (1998). Journal of Virology. 72:7642-7647.

[263] Winkler C, Modi W, Smith MW, Nelson GW, Wu X, Carrington M, Dean M, Honjo T, Tashiro K, Yabe D, Buchbinder S, Vittinghoff E, Goedert JJ, O'Brien TR, Jacobson LP, Detels R, Donfield S, Willoughby A, Gomperts E, Vlahov D, Phair J, O'Brien SJ. (1998). Science. 279:389-393.

[264] Wu L, Gerard NP, Wyatt R, Choe H, Parolin C, Ruffing N, Borsetti A, Cardoso AA, Desjardin E, Newman W, Gerard C, Sodroski J. (1996). Nature. 384:179-183.

[265] Wu L, Paxton WA, Kassam N, Ruffing N, Rottman JB, Sullivan N, Choe H, Sodroski J, Newman W, Koup RA, Mackay CR. (1997). Journal of Experimental Medicine. 185:1681-1691.

[266] Wyatt R, Sodroski J. (1998). Science. 280:1884-1888.

[267] Xiao L, Rudolph DL, Owen SM, Spira TJ, Lal RB. (1998). AIDS. 12:F137-143.

[268] Zhang L, Carruthers CD, He T, Huang Y, Cao Y, Wang G, Hahn B, Ho DD. (1997). AIDS Research and Human Retroviruses. 13:1357-1366.

[269] Zimmerman PA, Buckler-White A, Alkhatib G, Spalding T, Kubofcik J, Combadiere C, Weissman D, Cohen O, Rubbert A, Lam G, Vaccarezza M, Kennedy PE, Kumaraswami V, Giorgi JV, Detels R, Hunter J, Chopek M, Berger EA, Fauci AS, Nutman TB, Murphy PM. (1997). Molecular Medicine. 3:23-36.