A Review of the Role of the Human Leukocyte Antigen (HLA) System as a Host Immunogenetic Factor Influencing HIV Transmission and Progression to AIDS

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INTRODUCTION

The Major Histocompatibility Complex (MHC, the HLA region in humans) has long been shown to be an important host genetic risk factor in infectious disease as well as a variety of autoimmune diseases and cancers, with associations with susceptibility or resistance in well over 50 different diseases (Ryder *etl al*. 1979; Tiwari and Terasaki 1985; Singh *et al*. 1997; Thorsby 1997; Hill 1998; Lechler and Warrens 2000). Several of these diseases have a viral etiology. The role of the MHC in immunologic susceptibility to viral infection was originally discovered by Zinkernagel and Doherty, who determined that virus-specific cytotoxic T cells recognize both a viral antigen and a polymorphic MHC molecule (MHC restriction) (Zinkernagel and Doherty 1974). HLA class I restriction with cytotoxic T-cell lymphocytes (CTL) plays a major role in the immune response to and destruction of virally infected cells. The HLA system has since been found associated with susceptibility or resistance to many different viruses, and over the past ten years, a variety of studies have reported an HLA association with human immunodeficiency virus (HIV) transmission and disease progression to Acquired Immune Deficiency Syndrome (AIDS).

HIV infection in susceptible hosts begins a slow progressive degeneration of the immune system, characterized by a decline of CD4+ T cells that, in the absence of medication as a rule eventually results in immunodeficiency, opportunistic infections, and death. After the primary infection, host cellular and humoral immune responses generally act to keep the virus under control, but over time the virus eventually overcomes these immune responses. There are, however, HIV-positive persons who have not required treatment and continue to survive and do well despite the HIV-1 infection. Generally termed long term non-progressors (LTNP), these individuals are very important in HIV-1 host immunogenetic analyses. In addition, individuals in high risk groups who have been exposed to HIV-1 infection, but have not yet become infected or whose HIV-1 viral RNA levels are not yet detectable, would be important to recruit as controls in association studies. There are many host immunogenetic factors that may modulate the clinical variations of HIV-1 disease, and the HLA system in particular has been implicated as a critical influence on the clinical course of HIV infection.

Outcome heterogeneity in HIV infection and progression to AIDS makes it difficult to quantify the severity in progression of this disease. To date at least four different outcome endpoints have been used in disease association analyses, including time from seroconversion to AIDS, survival/death, the rate of decline of the prognostic CD4+ T cell count ($<200/mm^3$), and the CDC 1987 and 1993 case definitions (CDC 1987: www.cdc.gov/mmwr/vol36_su1.htm, and CDC 1993: www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm). HIV risk groups studied include homosexual men, hemophiliacs, intravenous drug users (IVDUs), and heterosexual partners of infected subjects, prostitutes, and perinatally exposed infants. Each of these groups has their own co-factors such as use of drugs and routes of infection which make it difficult to compare studies. Seroprevalent cohorts may have biased disease progression rates, whereas consecutively enrolled seroconverter cohorts will not have biased rates. Analysis of HLA association with specific AIDS-defining or AIDS-related clinical outcomes, including for example Karposi's sarcoma (KS) (Papasteriades *et al*. 1984), tuberculosis (TB) (Singh *et al*. 1983; Mehra 1990) and cytomegalovirus (CMV) (Iannetti *et al*. 1988), many of which have their own HLA associations independent of HIV infection, can confound the role of HLA polymorphism using this broader definition of AIDS.

Over sixty papers on HLA association with HIV transmission and progression to AIDS have been published to date, covering a variety of different populations and risk groups. Many of the studies of HLA associations with HIV infection and AIDS progression have rather limited patient and control sample numbers, some studies use overlapping populations which make comparisons between studies difficult, and most rely on serologic typing of HLA for both the class I and II loci. Moreover, these association studies use a variety of outcome measures in their analyses, compounding the difficulties in making compar-

isons between studies. Despite the inconsistencies in the results of HLA-HIV association research, some relatively clear and consistent associations with respect to HIV infection and progression to AIDS have emerged. An aspect of HLA disease association analysis that has improved in the past five years is the development of the higher resolution PCR-based molecular typing methods for both HLA class II and class I loci; these methods have largely replaced the less accurate and less discriminating serologic typing methods. Finally, more recent studies on HLA associations with HIV and AIDS tend to include larger cohort sample sizes, a critical element because the extensive allelic diversity of the HLA loci makes it difficult to obtain statistical significance for association with any individual allele or haplotype. In this review we focus on HLA associations that, for the most part, examine general outcome parameters including AIDS-free versus AIDS positive status, case definitions as defined by the Centers for Disease Control (CDC), time to AIDS, survival, and decline in CD4+ T cells over time. HLA associations with specific clinical AIDS-related outcomes are not reviewed here. Our focus was also primarily on studies since 1995, as HLA-HIV association manuscripts before 1995 are reviewed by Just (Just 1995). Because of the extreme polymorphism of HLA we focused our review on larger studies with greater power, however to present studies covering a wider variety of risk groups, we also included a selection of smaller studies on perinatal, transfusion and IV drug users. In addition, because there are so few transmission association analyses, we have included smaller studies here as well. These smaller cohort studies are presented for information only, and must be considered preliminary, as they need to be confirmed by studies using larger cohorts.

The HLA Complex and Heterogeneity

The HLA loci reside in a ~3500 kb segment of the human MHC on chromosome 6p21.31 (Figure 1) and are the most polymorphic of any mammalian gene system, with some loci having more than 400 alleles. The HLA loci encode cell surface molecules that are composed of two antigen classes. Class I antigens are present on the surface of all nucleated cells, where they bind and present peptides derived from the cytosol (viral and self peptides) to circulating CD8+ T cells. The class I cell surface heterodimer has one MHC encoded highly polymorphic alpha chain, with the polymorphic residues clustering within the peptide binding cleft, encoded by exons 2 and 3 of the gene, complexed with the monomorphic molecule, beta-2 microglobulin. Class II molecules are MHC encoded alpha-beta chain heterodimers found on the surface of B cells, macrophages and other antigen presenting cells, where they bind and present primarily exogenously derived peptides (bacteria and chemical toxins) to circulating CD4+ T cells. With the exception of the HLA-DQA1 locus, the beta chain loci are much more polymorphic than the alpha chain loci and the highly polymorphic regions are localized to exon 2 and encode the peptide binding cleft. For both the class I and the class II molecules, the polymorphic amino acid residues in the binding groove interact with the specific residues of the peptide or of the TCR. The extent of HLA polymorphism observed in pop-

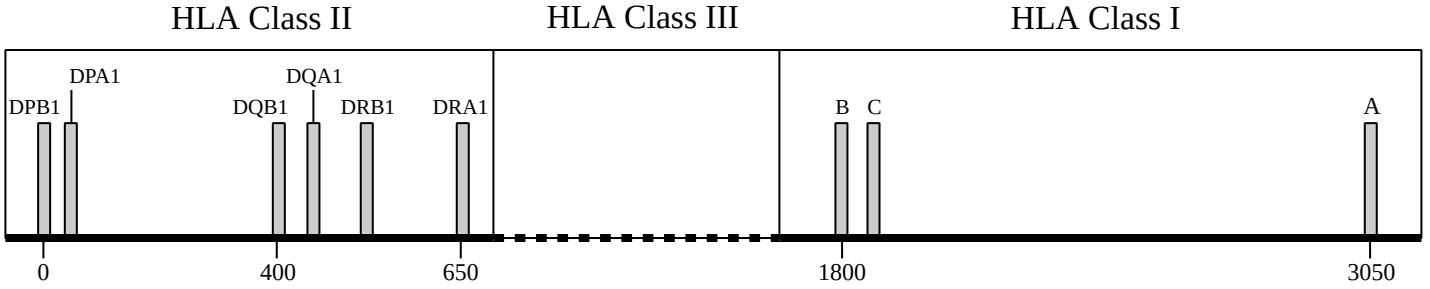

Figure 1. The highly polymorphic HLA genes in the MHC are the class I A, B, C and class II DRB1, DQB1, DQA1 and DPB1 loci. Much of the polymorphism in the HLA class I and II exons cannot be detected by serologic HLA typing methods. Molecular typing methods based on PCR can accurately distinguish the many allelic sequence variants identified at these loci. A small proportion of the nucleotide sequence polymorphisms are "silent," whereas the vast majority of polymorphisms result in amino acid changes, primarily in the peptide binding groove; these polymorphic residues contact either the peptide, the TCR, or both. As of 2001, class I HLA-A has 229 alleles (24 serogroups), HLA-B has 446 alleles (48 serogroups), HLA-C has 111 alleles (8 serogroups), and class II DRB1 has 298 alleles (17 serogroups), DQB1 has 48 alleles (7 serogroups), and there are 22 DQA1 and 96 DPB1 alleles (not detectable by serological methods) (http://www3.ebi.ac.uk/Services/imgt/hla/cgi-bin/statistics.cgi).

ulations is maintained by balancing selection and specifically pathogen-driven selection (Klitz *et al*. 1986; Lawlor *et al*. 1990; Hill *et al*. 1991; Hill *et al*. 1992; Hill 1998), with potential heterozygote advantage (Black and Hedrick 1997). The nature and localization of the polymorphism allows for differential binding and presentation of peptide, consequently the extensive allelic diversity is likely to be functionally significant in terms of disease susceptibility and progression. Different populations tend to exhibit frequency distributions of alleles and extended haplotypes particular to that group. These population differences can potentially confound HLA disease association studies that differ with respect to ethnic groups in cases and controls, making analysis of individual allele or haplotype associations between studies more difficult. Concordant results between studies of different ethnic groups serves to support the HLA association for both groups, whereas discordant results between studies may mean that the associated allele is a simply a marker for a nearby disease-related locus, that the different ethnic groups have different HLA disease susceptibility alleles, that there was measurement error in determining HLA or outcomes, and/or that there were spurious findings due to multiple comparisons.

Mechanisms of Host MHC Response to HIV

The MHC class I and class II gene products are critical in the regulation of immunity against viral infections, and consequently play an important role in the control of the course of HIV infection and disease. Controlling CD4+ depletion by virus-specific cytotoxic T-cell lymphocytes (CTL) is an important immunogenetic response toward protecting individuals both from infection and progression to AIDS once HIV infected (Gotch *et al*. 1996; Rowland-Jones *et al*. 1997). Allelic variants of the HLA molecule can bind and display various antigenic peptides with differing affinities, thereby influencing the efficiency of immune protection by both the specificity and affinity of peptide binding and recognition by T cells (Gotch *et al*. 1996). Other loci in the MHC can also play important roles in the HLA-TCR restriction system, influencing HLA assembly and antigen presentation, giving rise to individual variation in the immune response. In addition, the HIV-1 virus mutates rapidly, effectively generating extreme diversity with remarkable between and even within individual variability. There are now two major HIV-1 groups (M and O), with the major group M diversifying into several regional clades (A through I, with B being the most prevalent in the West), subspecies, and there are also dramatic intra-individual variations, giving rise to the concept of “quasi-species”. This extreme viral diversity within an individual during the course of infection may allow the virus to evade HLA-TCR restriction at two levels, including peptide binding in the HLA molecule and TCR recognition (Callahan *et al*. 1990).

HLA ASSOCIATION WITH HIV-1 TRANSMISSION

Many of the earlier studies of HLA alleles associated with HIV-1 transmission included very small and diverse study populations with differing routes of exposure. Some studies contained prevalent HIV infected cases which could reflect progression of HIV-1 disease rather than susceptibility to infection, and most had little to no molecular confirmation of HLA alleles, resulting in no consistent HLA class I or II associations with HIV-1 infection (Just 1995). However, there is considerable evidence developing from a small number of individuals who have been exposed to HIV (some repeatedly exposed) but do not seroconvert or show any signs of HIV infection. These observations suggest that, in some cases, natural immunity may protect exposed individuals from HIV infection and that HLA-restricted CTLs may be responsible for the protective immunity (Shearer and Clerici 1996). Individuals who have been exposed but do not have HIV include prostitutes and others that engage in unprotected sex with HIV+ partners, infants born of HIV+ mothers, those exposed to contaminated blood products through transfusions, health care workers, and intravenous drug users (IVDU) with a history of needle sharing. Some of these individuals have been shown to exhibit HIV-specific HLA-restricted CTL responses, in the absence of HIV-specific antibodies. In fact, a strong T cell response, including but not limited to HLA class I –restricted CTL responses, has long been invoked as a major factor in protective immunity against HIV infection and AIDS progression (Clerici and Shearer 1994). Table 1 illustrates the significant HLA allele and haplotype associations with HIV transmission.

HLA Association with Protection from HIV-1 Infection

HLA B35, the most common Gambian HLA class I allele has been associated with resistance to infection in a cohort of HIV-exposed but uninfected Gambian sex-workers, who demonstrated B35-restricted CTL response to both HIV-2 and HIV-1 cross-reactive peptide epitopes (Rowland-Jones *et al*. 1995). In the Gambia, while most recent infections are with HIV-1, HIV-2 was initially the predominant strain and may have therefore primed the immune response with cross-reactive peptides in the sex-workers. HIV-2 appears to be less pathogenic and has a lower transmissibility and virus load than HIV-1 infection (DeCock *et al*. 1993). The explanation for finding HIV-specific, B35-restricted CTL in these apparently uninfected women is that they have been repeatedly HIV-exposed but have been immunized by exposure to HIV (Rowland-Jones

Table 1. HLA Association with HIV-1 Transmission

TRANSMISSION: NEGATIVE (PROTECTIVE) ASSOCIATION

HLA Allele or Haplotype	Risk Group	Cases and Controls	Population	Reference
HLA Class I Associations:				
A2	perinatal	125 HIV+ mothers, and 39 HIV+, 121 HIV- infants	African (Nairobi, Kenya)	Mac Donald *et al*., 1998
A2-A*6802 supertype (*0202/05/14 and *6802)	prostitutes	122 HIV+ seroconversions, 110 HIV-	African (Nairobi, Kenya)	Mac Donald *et al*., 2000; Rowland-Jones *et al*., 1998
A11	prostitutes	14 HIV- HEPS SW, 9 HIV+ SW controls, 9 HIV- controls	Northern Thailand	Sriwanthana, *et al*., 2001
B18	prostitutes	17 HIV- SW (HEPS), 19 HIV+ SW controls, 22 HIV- controls	Northern Thailand	Beyrer *et al*., 1999
B*44, B*55	mixed	56 HIV+, 56 HIV-	Amerindian & Hispanic (Argentina)	de Sorrentino *et al*., 2000
B8	transfusion	20 HIV + , unspecified number HIV- controls	Caucasian (Australian)	Geczy *et al*., 2000
B35 + HIV-2 prior infection	prostitutes	20 HIV + , unspecified number HIV- controls	African (Gambia)	Rowland-Jones *et al*., 1995
B*5801 + HIV-2 prior infection	mixed	18 HIV + , unspecified number HIV- controls	African (Gambia)	Bertoletti *et al*., 1998
HLA Class II Associations:				
DRB1*0102 >prot *0101	prostitutes	122 HIV+ seroconversions, 110 HIV-	African (Nairobi, Kenya)	Mac Donald *et al*., 2000
DRB1*13(*1301-3), *1501	perinatal	45 HIV+, 63 seroreverting infants	mixed	Winchester *et al*., 1995
DQB1*03032	mixed	52 HIV+ , 47 HIV-	Caucasian & African American	Roe *et al*., 2000
DQB1*0603	mixed	52 HIV+, 241 HIV-	Caucasian & African American	Achord *et al*., 1996

Table 1. cont.

TRANSMISSION: POSITIVE (SUSCEPTIBLE) ASSOCIATION				
HLA Allele or Haplotype	Risk Group	Cases and Controls	Population	Reference
HLA Class I Associations:				
HLA class I concordance between mother and child	perinatal	HIV+ mothers and their 39 HIV+, 121 HIV- infants	African (Nairobi, Kenya)	Mac Donald *et al*., 1998
HLA class I concordance between mother and child	perinatal	HIV+ mothers and their infants	Ariel multicenter cohort	Polycarpou *et al*., submitted
A*2301	prostitutes	HIV+ seroconversions, 110 HIV-	African (Nairobi, Kenya)	Mac Donald *et al*, 2000
A32, A25	transfusion	HIV + , unspecified number HIV- controls	Caucasian (Australian)	Geczy *et al*., 2000
A*24, B39, B18	mixed	HIV+, 56 HIV-	Amerindian & Hispanic (Argentina)	de Sorrentino *et al*., 2000
HLA Class II Associations:				
DRB1*03011	perinatal	HIV+, 63 seroreverting infants	mixed	Winchester *et al*., 1995
DQB*0603 (Cauc.), DQB1*0602 (African Amer.)	mixed	HIV+ , 47 HIV-	Caucasian & African American	Roe *et al*., 2000
DQB1*0604	perinatal	HIV+, 52 seroreverting infants	African American	Just, Abrams *et al*., 1995
DQB1*0605 (African Amer.), DQB1*0602 (Cauc.)	mixed	HIV+, 241 HIV-	Caucasian & African American	Achord *et al*., 1996

Notes:
1) An asterix (*) denotes HLA allelic designation determined by molecular means. No asterix denotes serologic resolution and typing.
2) SW = sex worker
3) HEPS= highly exposed, persistently seronegative

et al. 1995). CTL from HIV-2 infected patients with cross-reactivity to HIV-1 were also detected in a study that examined CTL response to HIV-1 Gag protein (Bertolett*iet al*. 1998). In this study, patients with B*5801 and HIV-2 exhibited enhanced response to HIV-1 epitopes that could play a role in cross-protection.

In a group of African sex-workers from Nairobi, the Pumwani Sex Worker cohort, a strong protective effect against HIV seroconversion is seen with HLA class II DRB1*01, and in particular DRB1*0102, suggesting that DRB1-restricted CD4+ cells may play a role in protecting against HIV challenge (MacDonald *et al*. 2000). Class I protective associations in this group include the HLA-A2-A*6802 supertype, consisting of A*0202, *0205, *0214 and *6802, with no apparent added effect of homozygosity for multiple A2/6802 supertype alleles. (Rowland-Jones *et al*. 1998; MacDonald *et al*. 2000). The A2/6802 supertype is especially important epidemiologically as ∼40% of the world population possess alleles within this supertype, which share highly conserved HIV-1 epitopes, and are targets of protective cellular immune responses. A2 and HLA class I discordance between mother and child were also found to be protective in a cohort of Nairobi HIV+ mothers and their newborn children (MacDonald *et al*. 1998).

These African female sex workers have higher documented exposure to HIV than any other group in the world and are routinely exposed to several different strains of HIV-1 (A, D, and C), and the CTL responses in these women exhibit cross-clade reactivity (Rowland-Jones *et al*. 1998; Rowland-Jones *et al*. 1999). Once primed, the CTL responses could be boosted by repeated exposure in the prostitutes, whereas they are known to be transient after single exposure, as shown in data from health care workers (Pinto *et al*. 1995) and perinatal exposure (Rowland-Jones *et al*. 1993). The combined epidemiologic HLA data provide further evidence that the resistance to HIV-1 infection in this cohort is a natural protective cellular immunity to HIV-1 (Fowke *et al*. 1996; Goh *et al*. 1999; MacDonald *et al*. 2000). A recent report on late seroconversion in HIV-resistant Nairobi prostitutes, however, demonstrated that, in the absence of detectable virus escape mutations, seroconversion can still rarely occur and may relate to reduced antigenic exposure due to reduction in sex work over the preceding year (Kaul *et al*. 2001). It may be that viral phenotype, dosage and/or route of exposure are critical, in addition to host genetics, in determining whether the new exposure results in boosting of protective immunity or the establishment of productive infection in these HIV-1 seronegative subjects with pre-existing HIV-1-specific CD8+ responses (Kaul *et al*. 2001).

Another study of neonates and HLA class II associations with protection from HIV-1 infection includes a study of 63 seroreverting infants, identifies the protective alleles DRB1*1501 and DRB1*13 (*1301–3), which is also associated with long-term nonprogression of HIV to AIDS (Winchester *et al*. 1995).

HLA types that are marginally associated with susceptibility or protection to HIV-1 infection need further analysis for confirmation. For example, HLA class I A*2401, A11 or B18, are found marginally associated with a reduction in the risk of HIV-1 seroconversion in African Pumwani and Northern Thailand Sex Worker cohorts (Beyrer *et al*. 1999; MacDonald *et al*. 2000; Sriwanthana *et al*. 2001); however A24 and B18 are increased in a group of patients of Hispanic and Amerindian ethnicities from Argentina, suggesting that they are associated with susceptibility to infection in that population (de Sorrentino *et al*. 2000). And, the frequency of HLA B8 is decreased in a small study population of 20 transfusion patients with acquired HIV-1 from Australia (Geczy *et al*. 2000), suggesting that it is protective against infection in this group. However, as discussed in more detail below, B8 is often found increased in patients with rapid HIV-1 progression, which may reflect different roles for HLA in the biology of HIV transmission versus progression to disease. Again, these studies need further confirmation with larger sample sizes to confirm the HLA associations.

The above findings of HLA associations with HIV protection in different populations underscore the importance of protective immunity against HIV and HLA-restricted CTL induction in HIV vaccine design. However, the HLA effect is neither completely necessary nor sufficient for resistance to infection. In addition to host genetic factors, other environmental factors could play a substantial role in determining HIV-1 infection status, including the pathogenecity of the virus, and the timing of the infection and exposure to drugs (recreational or therapeutic) could modify the initial immune response to the virus, potential confounding cofactors that need to be considered in any analysis of HLA association with HIV transmission.

HLA Association with Susceptibility to HIV-1 Infection

Susceptibility to infection in mother-to-child transmission of HIV-1 was studied in a group of Nairobi patients and controls, in which HLA class I concordance represents a risk factor for HIV-1 transmission (MacDonald *et al*. 1998). In this study, each extra HLA concordant allele that a child has in common with its mother more than doubled the estimated risk of transmission, in a dose-effect relationship. A more recent study with 203 maternal-infant pairs (Polycarpou et al. submitted) also reported that HLA class I but not class

II concordance between mother and child increased the risk of transmission (OR = 4.16; p = 0.028).

Individually, HLA A*2301, is associated with a substantially increased risk of HIV-1 seroconversion in an African cohort of prostitutes from Nairobi (MacDonald *et al*. 2000). The serologically related A*2401 is increased in a group of patients of Hispanic and Amerindian ethnicities from Argentina, and with B18 and B39, are increased suggesting that they are associated with susceptibility to infection (de Sorrentino *et al*. 2000). Finally, HLA-A32 and A25 are found decreased in a small study of transfusion acquired HIV+ patients from Australia, suggesting that they contribute susceptibility to HIV-1 infection (Geczy *et al*. 2000)

The HLA class II loci most frequently associated with susceptibility to HIV-1 infection in a number of smaller population studies include DQB1*0604, which is consistently associated with increased risk of HIV infection among African American children born to HIV-1 infected mothers (Just *et al*. 1995), and DQB1*0201, *0602, *0605 and *0603 with greater risk of susceptibility to HIV infection in Caucasians and African Americans (Roe *et al*. 2000). HLA class II DRB1*03011 is associated with susceptibility to infection in seroreverting infants (Winchester et al. 1995). Further research involving larger sample sizes will be necessary to confirm the associations noted in many of the studies noted here.

HLA ASSOCIATION WITH SUSCEPTIBILITY FOR RAPID HIV-1 DISEASE PROGRESSION TO AIDS

Table 2A illustrates the HLA alleles and haplotypes found associated with rapid HIV-1 disease progression to AIDS, including some association data on the TAP loci.

Class I Homozygosity

In principle, homozygosity at HLA loci might decrease the number of viral epitopes which could serve as a target for CTLs. HLA class I homozygosity, and especially two locus homozygosity, appears to be associated with AIDS progression, as reported in studies using different cohorts, including Caucasian American and European homosexuals, African heterosexual women, and mixed risk groups and population cohorts (Carrington *et al*. 1999; Hendel *et al*. 1999; Keet *et al*. 1999; Tang *et al*. 1999). The maintenance of HLA genetic variation appears to be a selective advantage against pathogenic agents, and HLA heterozygosity may therefore play a major role in combating infectious disease. An increase in infectious disease when there is an overall population decrease in MHC heterozygosity is found in many species (Watkins *et al*. 1988; Black and Hedrick 1997; Evans *et al*. 1997), and lends credence to the hypothesis of maintenance of the extensive observed MHC polymorphism by mechanisms of balancing selection and overdominance (heterozygote advantage).

In the Carrington report, Kaplan-Meier survival curves for seroconverters from three cohorts indicated that having two homozygous class I loci decreases the mean survival time significantly, and that homozygosity at two or more loci enhances the rate of progression to AIDS, compared with heterozygous individuals at each respective locus (Carrington *et al*. 1999). Data from other studies suggest that each locus appears to contribute separately to the protective effect associated with heterozygosity, with an additive effect of homozygosity on progression. Of note, although homozygosity at class I loci is disadvantageous following natural infection, homozygosity at class I was not significantly disadvantageous when analyzed for vaccine response (Kaslow *et al*. 2001).

Bw4 Homozygosity

HLA-B alleles can be divided into two groups, those expressing the "public specificity" (a serological epitope found on many different alleles) Bw4 (IARL amino acid) and those expressing Bw6 (RNLRG amino acids) motifs, at amino acid positions 77–83 in exon 2 of the B locus. Evidence for protection from HIV-1 viremia and AIDS associated with Bw4 homozygosity was recently presented by Flores-Villanueva and colleagues (Flores-Villanueva *et al*. 2001) in a study of HIV-1 seroconverters, including long-term non-progressors with control of viremia ("controllers", HIV-1 RNA $<$1000 copies/ml plasma). The Bw4 (IALR amino acid) motif also functions as a ligand for a natural killer cell (NK) immunoglobin receptor (KIR). One interpretation of the Bw4 association is the assumption that NK cells play a major role in controlling viral replication and that the presence of two copies of the Bw4 epitope affects the activation of NK cells. An alternative explanation is simply that the protective alleles HLA-B*57 and B*27 carry the Bw4 epitope and association with Bw4 need not reflect the putative effect on NK cell activation and function (O'Brien *et al*. 2001). Of course, effects of B locus allelic diversity on T cell activation or of NK activation for controlling viremia need not be mutually exclusive.

B*35

B*35 is the most consistently associated HLA allele correlated with accelerated HIV disease. A strong association of B*35 (B35 from serologic data) with rapid progression to AIDS has been observed in many studies on a wide

Table 2A. Rapid Progression (RP): Positive (Susceptible) Association

HLA Allele	HLA Haplotype	Risk Group	Cases HIV+	Population	Reference
HLA Class I Associations:					
A23; B37, B49, B35; Cw*04	B35-Cw*04	homosexual	241	2 cohorts; Cauc. (American)	Kaslow *et al.* 1996; Saah *et al.*, 1998
A*2301		pediatric	36 LTNP, 14 RP	mixed	Chen *et al.*, 1997
A29, B22 [split 54,55,56] B35 (trend), C16 (trend)		mixed	75 RP, 200 SP, no Rx	Cauc. (European)	Hendel *et al*, 1999
Class I Homozygosity with natural infection		vaccine volunteers	291 HIV-	mixed	Kaslow *et al.*, 2001
Class I Homozygosity		mixed	140 males; 202 females	Cauc. (Dutch) males; Rwandan females	Tang *et al.*,1999
Class I Bw4 Homozygosity; B*08, B*35, B*44		mixed	39, no Rx, incl. 20 LTNP	mixed	Flores-Villanueva *et al.*, 2001
A24; Class I A, B Homozygosity		homosexual	382 seroconverters	5 cohorts; mixed	Keet *et al.*, 1999
B*35; Cw*04; Class I Homozygosity	B35-Cw*04	mixed	498	Cauc. (American)	Carrington *et al.*, 1999
B*35Px (x = 3502-04; includes also B53)		mixed	850	mixed cohorts; Cauc. (American), African Am., mixed	Gao *et al.*, 2001
B35		mixed	33, incl. 20 LTNP; 853 HIV- (class I typing)	mixed	Paganelli *et al.*, 1998
B35		homosexual	106 HIV+, 866 HIV-	Cauc. (Dutch)	Klein *et al.*, 1994
B35		hemophiliac	144	Cauc. (French)	Sahmound *et al.*, 1993
B8		transfusion	20	Cauc. (Australian)	Geczy *et al.*, 2000
	A1-B8-DR3	IV drug users	260	mixed	Brettle *et al.*, 1996
B21, B35	A1-B8-DR3	mixed	180	Cauc. (European)	Kaplan *et al.* 1990
	A1-B8-DR3	IV drug users	262	Cauc. (Scottish)	McNeil *et al.*, 1996
	A1-Cw7-B8-DR3-DQ2 A11-Cw4-B35-DR1-DQ1	mixed	variable	mixed	Summarized from Just, 1995, Review

Table 2A. cont.

HLA Allele	HLA Haplotype	Risk Group	Cases HIV+	Population	Reference
HLA Class II Associations:					
	DRB1*12-DQB1*0301	homosexual	381 seroconverters	5 cohorts; mixed	Keet *et al*., 1999
DR11		mixed	75 RP, 200 SP, no Rx	Cauc. (European)	Hendel *et al*, 1999
DR1 and DR11		mixed	33, incl. 20 LTNP; 153 HIV- (class II typing)	mixed	Paganelli *et al*., 1998
	DRB1*0301-DQA*0501-DQB*0201	perinatal	81	Cauc. (Spanish)	Just *et al*., 1996
	DRB1*0301-DQA*0501-DQB*0201	perinatal	37	African American	Just, Abrams *et al*., 1995
DPB1*0101 (consensus: -asp-glu-ala-val at amino acid position 84-87)		perinatal	54 HIV+ and 52 HIV-	African American	Just *et al*., 1992
HLA and TAP Associations:					
	A28(68) or A32 +TAP2.3; A23 or Cw*04 minus TAP2.3; B8 or B40(60) + TAP2.1; and DRB1*12-DQB1*0301	3 cohorts	375	Cauc. (American)	Keet *et al*., 1999
	A28 + TAP2.3; A24 + TAP2.1 or 2.3; A29 + TAP2.1, A23 minus TAP2.3; B8 + TAP2.1, B60 + TAP2.1 or 2.3; DRB1*0401-DQA1*03-DQB1*0301, DRB1*12-DQA1*0501-DQB1*0301, DR*13-DQA1*0102-DQB1*0604, or DRB1*14-DQA1*0101-DQB1*0503 + TAP1.2	homosexual	241	Cauc. (American)	Kaslow *et al*. 1996; Saah *et al*., 1998

Notes:
1) An asterix (*) denotes HLA allelic designation determined by molecular means. No asterix denotes serologic resolution and typing.
2) RP = rapid progressor
3) SP = slow progressor
4) LTNP = long term nonprogressor
5) Cauc = Caucasian
6) AA or African Am.= African American
7) ALT = French LTNP cohort
8) IMMUNOCO = French standard progressors cohort
9) Rx = chemotherapy

variety of risk groups, comprised of Caucasians for the most part, and analyzed using various outcomes analyses (Kaplan *et al*. 1990; Sahmoud *et al*. 1993; Klein *et al*. 1994; Kaslow *et al*. 1996; Paganelli *et al*. 1998; Carrington *et al*. 1999; Hendel *et al*. 1999; Flores-Villanueva *et al*. 2001) (for earlier studies see (Just 1995)). The B*35 effect is co-dominant and a homozygous state increases the susceptibility (Carrington *et al*. 1999; Gao *et al*. 2001).

More recently, the influence of a B*35 subtype in accelerated progression was reported, implicating B*35Px as a susceptibility allele in both Caucasians and African Americans (Gao et al. 2001). B*35Px includes B*3502/3/4 and B*5301, which have the amino acid proline in the peptide binding groove pocket number 2, and anything but tyrosine in pocket 9. The B*35Px susceptibility alleles all encode products with no more than 3 amino acid differences among the entire HLA molecule and, based on this hypothesis, differ from B*3501,in terms of disease association (see below). The B53 allele is included in this group because of the close phylogenetic relationship with B35, and B*5301, which is more prevalent than B*35 in African Americans. B*5301, showed significant predisposition to rapid progression in African Americans (Carrington *et al*. 1999; Gao *et al*. 2001). Grouping HLA alleles by functional categories based on potential peptide binding regions may prove to be useful in HLA disease association analyses (Hughes *et al*. 1996). One difficulty, however, with this approach is that the relationship of the number of predicted peptides binding to a given HLA molecule to a specific and protective immune response is not well-established. Nonetheless, this approach provides an opportunity to generate hypotheses relating the structure of the HLA molecule encoded by an asociated allele with an immune response that may account for the observed association. The Cw*04 association that was found associated with rapid progression was due to strong linkage disequilibrium with B*35 in those studies that analyzed these two markers (Kaslow *et al*. 1996; Carrington *et al*. 1999; Gao *et al*. 2001). In another serological study involving African sex workers, B35 was shown to be broadly cross-reactive, restricting CLT with both HIV-1 and HIV-2 sequences; the B35 alleles, however, were not resolved in this African group. (Rowland-Jones *et al*. 1995; Rowland-Jones *et al*. 1999); This study suggests that the B35-restricted CTL could have been primed first by HIV-2 exposure and subsequently boosted by exposure to HIV-1, and may thus represent protective immunity to HIV generated in response to repeated exposure of conserved epitopes (Rowland-Jones *et al*. 1999). In another study, evidence for an effective presentation of HIV-1 molecules by B*3501 demonstrated B*3501 was capable of recognizing large numbers of HIV epitopes, but this study also showed that natural mutations in B*3501-restricted HIV-1 CTL epitopes reduced both peptide binding and TCR recognition (Tomiyama *et al*. 1997). Based on this study, characterization of the B35 alleles in the African sex worker cohort to determine if they are B*3501, the most common B35 allele in Africans, would lend further support to the HIV-2 priming hypothesis in the study by Rowland-Jones and colleagues.

A1-B8-DR3: Alleles and Haplotype

The B8 and DR3 genes and the A1-B8-DR3 haplotype are associated with fast progression of HIV disease as reported by many research groups looking at different populations, including IV drug users (Brettle *et al*. 1996; McNeil *et al*. 1996), transfusion patients (Geczy *et al*. 2000), infants born to HIV-1 positive mothers (Just *et al*. 1995), and several earlier studies as summarized by Just (1995). The A1-B8-DR3 haplotype is part of an extended haplotype 8.1: HLA-A1, Cw7, B8, DR3, DR52a, DQ2, which includes DPB1*0101 and which has been associated with a wide variety of autoimmune diseases in Caucasian populations (Tiwari and Terasaki 1985; Modica *et al*. 1993; Caruso *et al*. 1996; Thorsby 1997; Lechler and Warrens 2000). In some studies, this haplotype has been associated with a dysfunctional immune response with increased antibody production, decreased Th-1 helper type cytokine, and DR3 associated deficiency of T cells with IgG Fc receptors in otherwise healthy subjects (Candore et al. 1998). As HIV-specific CTL are believed to play a key role in controlling the virus throughout HIV infection (Clerici and Shearer 1994; Kinter and Fauci 1996; Shearer and Clerici 1996), the resulting deficiency of effective T cells in individuals with A1, B8, DR3 alleles or haplotype could be a distinct biologic disadvantage in combating this disease.

A23 and A24

A23 (A*23 allele) and A24 (A*24 allele) are subtypes of the A9 serotype. A23 is associated with rapid disease progression in a large cohort of Caucasian homosexuals (Kaslow *et al*. 1996), as well as in a small pediatric cohort, in which A*2301 was the susceptible allele (Chen *et al*. 1997). A24 is a susceptible serotype of significance in a study of homosexual men from five cohorts of mixed ethnicity (Keet *et al*. 1999).

DR5 (DRB1*11 and *12) and DR6 (DRB1*13 and *14)

The serotype DR5 has been found consistently associated with rapid progression to AIDS in several earlier studies on HLA association with HIV-1 disease progression (reviewed in Just 1995). The DR5 serotype, however, can be split into DR11 (DRB1*11 alleles) and DR12 (DRB1*12 alleles). Using a

novel HLA profiling statistic, the haplotype DRB1*12-DQB1*0301 was found associated with more rapid progression to AIDS in a study analyzing a large number of seroconverters from 5 different cohorts (Keet *et al*. 1999). DR11 was also found to be associated with rapid progression to AIDS in a European cohort (Hendel *et al*. 1999), and in a small, mixed ethnic cohort with LTNP (Paganelli *et al*. 1998). The DR11 effect was reversed when DR4 (protective) was also present in the European cohort, and the negative DR11 effect became stronger when patients with the DR4 alleles were removed from the analysis (Hendel et al. 1999). Although the DR11 serogroup is associated with susceptibility, a protective effect was found with the allele DRB1*1102, which was significantly increased in a small study on HIV-1 positive African American and Caucasians with diffusely infiltrative CD8 lymphocytes syndrome (DILS) and slow progression to disease (Itescu *et al*. 1994), although much larger sample sizes will be needed to confirm DRB1*11 allelic associations. DR6 (DRB1*13 and DRB1*14 subtypes) alleles are associated with TAP alleles in more rapid progression of HIV disease (Kaslow *et al*. 1996) (discussed below).

HLA ASSOCIATION WITH SLOW HIV-1 DISEASE PROGRESSION TO AIDS (PROTECTION)

Several HLA class I alleles have been associated with relatively slower disease progression to AIDS, and confirmed in subsequent studies, including A*32, A25, A26, A*68, A23 and HLA-B*27 and B*57. Table 2B illustrates significant HLA alleles and haplotypes found associated with relatively slow HIV-1 disease progression to AIDS.

HLA-A protective alleles: A25, A26, A68, A23, and A32

A reproducibly strong protective effect is seen for A25, which is associated with slow progression in several studies (Hendel *et al*. 1999; Geczy *et al*. 2000). Associations with A25 and A26 with TAP2.3 alleles are correlated in two other studies that utilize novel HLA profiling statistics to quantitate HLA involvement with HIV disease progression (Kaslow *et al*. 1996; Keet *et al*. 1999), described further under TAP associations, below. HLA-A68 and A23 are also associated with TAP genes (A28(68), or A32 + TAP2.3, A23 or Cw*04 minus TAP2.3) (Kaslow *et al*. 1996; Saah *et al*. 1998) and accelerated disease.

A*32 has been shown to be associated with slow disease progression in two related mixed population cohort studies (Kaslow *et al*. 1996; Keet *et al*. 1999). A recent study on HLA association with CTL response to novel HIV-1 vaccines showed favorable prognosis with A*32(Kaslow *et al*. 2001). In addition, a small transfusion study in a group of HIV-1 infected, LT-NP Australian Caucasians also showed a trend toward protection with A32 (Geczy *et al*. 2000).

HLA-B*57 and B*27

Both B27 and B57, which are rare alleles in most populations, are consistently associated with slower progression to AIDS in HIV-1 infected subjects. The B27 association has been found in many different risk groups including IV drug users (McNeil *et al*. 1996), cohorts of homosexuals with mixed ethnicity (Kaslow *et al*. 1996; Keet *et al*. 1999; Gao *et al*. 2001), and other mixed risk groups (Hendel *et al*. 1999; Gao *et al*. 2001). A case-control study analyzing two French HIV-1 Cohorts looked at the combination of both HLA and chemokine receptor genotypes in a multivariate logistic regression model and concluded that individuals heterozygous for CCR5-delta32 and homozygous for SDF1 wild type have increased odds of being a LTNP, with a 47-fold odds increase when a HLA-B27 allele is present with HLA-DR6 absent (Magierowska *et al*. 1999). The mechanism behind the protective association with B27 is believed to involve recognition of conserved HIV-1 epitopes in p24 gag, leading to an immunodominant response (Kelleher *et al*. 2001) while accruing mutation abrogates B27 presentation. Finally, a recent study on HLA association with CTL response to novel HIV-1 vaccines demonstrated favorable response with B*57 and B*27 alleles, noting that higher proportions of HIV-1 negative vaccinees with B*27 or B*57 reacted at least once to both ENV and GAG protein in a lytic bulk CD8+ cytotoxic T-lymphocyte assay (Kaslow *et al*. 2001).

The B57 association with protection from HIV disease progression is one of the strongest HLA associations with slow disease progression in HIV-1 infected patients, and is confirmed by many studies (Kaslow *et al*. 1996; Saah *et al*. 1998; Costello *et al*. 1999; Hendel *et al*. 1999; Keet *et al*. 1999; Flores-Villanueva *et al*. 2001; Gao *et al*. 2001). In addition to these larger studies, researchers studying HIV-1 positive LTNP patients from Amsterdam found HLA-B57-restricted CTL responses targeted at multiple proteins of HIV-1, with CTL specific for Gag and RT being the most pronounced and associated with longer time to AIDS (Klein *et al*. 1998). In another very small cohort of LTNPs from Australia, B*5701 is highly associated with restriction of HIV replication (Migueles *et al*. 2000). Finally, B*5703 is consistently associated with slower disease in a study of Rwandan women (Costello *et al*. 1999).

Table 2B. Slow or Non-Progression: Negative (Protective) Association

HLA Allele	Haplotype	Risk Group	Cases	Popuation	Reference
HLA Class I Associations:					
A3, B14, B17, B27		mixed	70 ALT (153 IM-MUNOCO controls)	Cauc (French)	Magierowska *et al*., 1999
A32		mixed	20 LTNP	mixed	Paganelli *et al*., 1998
A32 (trend), A25 (trend)		transfusion	20	Cauc (Australian)	Geczy *et al*., 2000
A*32, B*27, B*57		vaccine volunteers	291 HIV-	mixed	Kaslow *et al*., 2001
B27 (trend)		IV drug users	262	Cauc. (Scottish)	McNeil *et al*., 1996
B27, B57		homosexual	375 seroconverters	5 cohorts; mixed	Keet *et al*., 1999
B*27, B*57		mixed	850	mixed cohorts; Cauc. (American), African Am.	Gao *et al*., 2001
B*5703		women		Rwandan women	Costello *et al*., 1999
B*57, B*44		mixed	39, no RX, incl. 20 LTNP	mixed	Flores-Villanueva *et al*., 2001
B14 [64,65], B27 (trend), B57 (trend), Cw8, Cw14 (trend)		mixed	75 RP, 200 SP no Rx	Cauc. (European)	Hendel *et al*, 1999
B27, B51, B57		homosexual	241	Cauc. (American)	Kaslow *et al*. 1996; Saah *et al*., 1998
B35		prostitutes	20	African Am.	Rowland-Jones *et al*., 1999
B35, B*5801		HIV-2 +	18 (no Rx, no symptoms)	African (Gambian)	Bertoletti *et al*., 1998

Table 2B. cont.

HLA Allele	HLA Haplotype	Risk Group	Cases HIV+	Population	Reference
HLA Class II Associations:					
	DRB1*13-DQB1*0603	homosexual	375 seroconverters	5 cohorts; mixed	Keet *et al*., 1999
DR6 [13, 14], DR7		mixed	70 ALT (153 IMMUNOCO controls)	Cauc (French)	Magierowska *et al*., 1999
DR1		mixed	20 LTNP	mixed	Paganelli *et al*., 1998
DR1, DR4		mixed	180	Cauc. (European)	Kaplan *et al*., 1990
DR11 + DR4 (slow progression)		mixed	75 RP, 200 SP no Rx	Cauc. (European)	Hendel *et al*, 1999
DR13, DRB1*1301, *1302, *1303, *1310		pediatric	36 LTNP 14 RP	mixed	Chen *et al*., 1997
DRB1*13; DRB1*1501		perinatal	46 HIV+, 63 seroreverting infants	African American and Hispanics	Winchester *et al*., 1995
DRB1*1102; DRB1*1301		mixed	145	mixed	Itescu *et al*., 1994
DQA1*0102		perinatal	106	African American	Just *et al*., 1992
DPB1*0101		perinatal	37 HIV+	African American	Just, Abrams *et al*., 1995
HLA and TAP Associations:					
	A25, A26, A32 or B18 and TAP2.3	homosexual	241	Cauc. (American)	Kaslow *et al*., 1996; Saah *et al*., 1998
	A25, A26, A29-33 (A19 split) + TAP2.3	homosexual	375 seroconverters	5 cohorts; mixed	Keet 99

Notes:
1) An asterix (*) denotes HLA allelic designation determined by molecular means. No asterix denotes serologic resolution and typing.
2) RP = rapid progressor
3) SP = slow progressor
4) LTNP = long term nonprogressor
5) Cauc = Caucasian
6) AA or African Am.= African American
7) ALT = French LTNP cohort
8) IMMUNOCO = French standard progressors cohort
9) Rx = chemotherapy

DR6 (DRB1*13 and *14)

DR6 (DRB1*13 and DRB1*14 subtypes) alleles have primarily been associated with accelerated disease (reviewed in (Just 1995), associated with TAP genes in (Kaslow *et al*. 1996)), but show correlation with slower progression in other studies. For example, DR6 is associated with slow progression in a European study that includes mixed risk groups (Magierowska *et al*. 1999). In addition, DRB1*13 is associated with slower progression to disease in two perinatal studies with mixed ethnic groups (Winchester *et al*. 1995; Chen *et al*. 1997); protective DRB13 alleles included DRB1*1301, 1302 and 1303 in these studies.

OTHER CLASS I AND II ASSOCIATIONS

In addition to the more consistently found associations described above, Table 2 also illustrates other HLA associations with progression to AIDS that were very significant in the different high risk groups but have yet to be confirmed by further studies. For example, class II associations include DQA1*0102, a protective allele, and DPB1*0101 and DPB1 alleles with the consensus sequence (–asp-glu-ala-val) at amino acid positions 84–87 in exon 2, which were found to be protective and susceptibility alleles, respectively, in a large cohort of African American infants born to mothers infected with HIV-1 (Just *et al*. 1992; Just *et al*. 1995).

HLA class I alleles associated with rapid disease progression that need further confirmation in new and larger studies include B37, B49 (Kaslow *et al*. 1996), B22 (including serotypes B54, B55, B56), A29 and C16 (Hendel *et al*. 1999), and B44 (Flores-Villanueva *et al*. 2001). The A29 negative association is interesting because A29 has been shown to restrict CTL-HIV clones, but was poor in recognizing autologous sequence variants (Wilson *et al*. 1997). Class I alleles associated with slower disease progression to AIDS that need further confirmation include A3, B14, B17 (Magierowska *et al*. 1999), B51 and B58 (Kaslow *et al*. 1996), with the B58 subtype, B*5801, found in a group of patients from Gambia with HIV-2 positive status (Bertoletti *et al*. 1998).

HLA & TAP HAPLOTYPES

A comprehensive novel statistical profiling analysis was used by Kaslow and colleagues to generate HLA profiles predictive of HIV disease progression (Kaslow *et al*. 1996; Saah *et al*. 1998; Keet *et al*. 1999). In these studies, HLA class I and II alleles and haplotypes are associated with TAP alleles as high risk combinations, where the TAP variants modified the time-to-AIDS in the presence of certain HLA variants that were unrelated to AIDS-free time in the presence of others (Table 1). Haplotypes DRB1*0401-DQA1*03-DQB1*0301, DRB1*12-DQA1*0501-DQB1*0301, DR*13-DQA1*0102-DQB1*0604, or DRB1*14-DQA1*0101-DQB1*0503 are associated with TAP1.2 and rapid progression. In addition, HLA- A24 + TAP2.1 or TAP2.3, and A28(68), or A32 + TAP2.3, A23 or Cw*04 minus TAP2.3, and HLA- B8 + TAP2.1, B40(60) + TAP2.1 or 2.3 are all associated with rapid progression. Kaslow and his colleagues also found several HLA class I and TAP haplotypes that were associated with slower progression of AIDS, including HLA-A25, 26, 68 or A29–33 + TAP 2.3, B18 and TAP2.3 (Kaslow *et al*. 1996; Keet *et al*. 1999). The possibility that the TAP alleles are markers for other tightly linked loci cannot be excluded, and further studies are warranted to evaluate these reported associations.

CONCLUSION

The very large body of reported data on HLA associations with HIV and disease progression includes some observations that have been consistently reproduced in different studies (*e.g*. the protective effects of B*27 and B*57, and the alleles specific to B*35 susceptibility), while some findings have not been confirmed. Differences in the methods and the resolution of HLA typing as well as differences in the clinical endpoints and in the populations studied may be responsible for some of these discrepancies. Some reported observations, especially in the smaller studies, may simply reflect type 1 error given the extent of multiple comparisons. Further analysis of large population-based studies of HLA association with HIV transmission, and disease progression to AIDS, are still needed to confirm and augment studies to date. There is a pressing need to create larger databases, including cohorts from different ethnicities, such as African, African-American and Asian populations, to test associations in different populations. Data from those studies will be invaluable to current HIV vaccination strategies involving induction of HIV-1 specific HLA class I-restricted CTL responses. Immunodominant viral epitopes that are well conserved between HIV clades could be used to overcome the hypervariability of the HIV in developing peptide-based vaccines, but the role and breadth of the host HLA class I haplotype response is also relevant, with the need for HLA-specific vaccines for groups carrying alleles less responsive to HIV. More rigorous molecular typing, excellent longitudinal data, appropriate statistical analysis, plausible biological associations, and replication in other populations

by independent groups are all attributes which will contribute to the confidence of the more established as well as the novel HLA associations with HIV transmission and AIDS progression.

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