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KIR-HLA intercourse in HIV disease

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Abstract

Human leukocyte antigen (HLA) class I loci are essential to an effective immune response against a wide variety of pathogenic microorganisms, and they represent the prototypes for genetic polymorphism that are sustained through balancing selection. The functional significance of HLA class I variation is better exemplified by studies involving HIV type 1 (HIV-1) than any other infectious organism. HLA class I molecules are essential to the acquired immune response, but they are also important in innate immunity as ligands for the killer cell immunoglobulin-like receptors (KIR), which modulate natural killer cell activity. Here we concentrate on the interaction between the *HLA-B* and *KIR3DL1/KIR3DS1* genes, describe the effects of these loci on HIV disease, and discuss questions that remain unresolved.

Genetic variation affects HIV infection outcome

The influence of host genetic variation as a significant determinant for outcome to HIV infection is becoming increasingly well-accepted among the HIV scientific community. An extensive body of literature in this regard has focused on the gene encoding the major co-receptor for HIV, CCR5 [1–6], and the loci encoding its ligands [7,8]. The primary role (although not necessarily the only role) of these polymorphisms in altering HIV infection or disease progression has to do with viral entry into host cells. Most other genetic variants associated with HIV outcome identified to date occur within or near genes encoding molecules involved in the acquired or innate immune response. To some extent, this inclination could reflect a selection bias by researchers in this field because immune response genes are the logical first-line candidates in defense against any infectious disease and all but one study so far [9] have used candidate gene approaches to study effects of genetic variation on HIV disease. Still, it is not surprising that the genes most fundamental to the immune response and also most polymorphic in the human genome, human leukocyte antigen (HLA) class I, are front and center in terms of the effects of their polymorphism on HIV (Table 1). Their centrality in determining the inter-individual levels of protection against HIV has become further ingrained with the discovery of HLA class I as ligands for the killer cell immunoglobulin-like receptors (KIR), a polymorphic set of molecules that modulate natural killer (NK) cell activity [10].

NK cells are components of the innate immune system, representing the first line of defense against virally infected cells and tumor cells [11–14]. NK cells are actively inhibited by targets expressing self major histocompatibility complex (MHC) class I [15], but they reject

cells that are missing class I [16,17]. Thus, downregulation of class I on tumor cells or virally infected cells, a mechanism that allows these cells to escape cytotoxic T lymphocyte recognition [18], theoretically confers vulnerability to NK cell-mediated extermination (i.e. ‘missing self’) [19], a concept that was recently validated in murine cytomegalovirus (MCMV) infection [20]. Furthermore, the activating receptor NKG2D, which recognizes autologous molecules upregulated by cellular stress (reviewed in [10]), has been implicated in NK cell killing of transformed cells [21], supporting the general concept of recognition of ‘induced self’ by NK cell receptors [22]. In addition, a subset of activating receptors allows NK cells to recognize ‘non-self,’ either MHC class I-like structures encoded by a virus [23,24] or MHC class I itself present on allogeneic cells [25–29]. Finally, activating NK receptors could also be able to detect a combination of MHC class I and virus, because the activating receptor Ly49P specifically recognizes MCMV-infected cells if they express the mouse MHC class I allele H-2D^k (i.e. ‘altered self’) [30]. Recognition of ‘missing self,’ ‘induced self,’ ‘non-self’ and ‘altered self’ might contribute to the HIV-specific NK cell response.

Among the human NK receptor families, only the *KIR* genes are highly polymorphic and therefore could explain to some extent the differential responses to viral infections and reproductive success across individuals. In rodents, the *KLR* gene family, termed *Ly49*, has been expanded and shares many functional and molecular genetic characteristics in common with *KIR* in humans [31]. Thus, the *Ly49* family in mouse serves as an excellent model for shaping hypotheses regarding the biology of *KIR* in humans, and in particular, responsiveness to viral infection. In this review, we focus on recent genetic and functional data implicating variation at the *HLA* class I and *KIR* loci, in particular the *HLA-B* and *KIR3DL1* and *KIR3DS1* loci, as determinants in HIV disease outcomes.

Marriage of KIR and their HLA class I ligands

The *KIR* gene cluster maps to chromosome 19q13.4 and is not linked to the *HLA* class I loci on chromosome 6p21.3. Haplotypes of the *KIR* locus vary in the number and type of genes present, and all *KIR* genes show allelic polymorphism. Much of the variability in gene copy number has to do with the presence or absence of activating *KIR*. *HLA-A*, *HLA-B*, and *HLA-C*, which encode ligands for KIR, are exceptionally polymorphic as well, but each of these genes is present on every chromosome 6. The ligands for most KIR are unknown, but among those for which a ligand has been defined, the specificity is dependent on only a single or very few amino acids, such that a given KIR might recognize a large number of different HLA allotypes.

Among the various *KIR* genes, *KIR3DL1* and *KIR3DS1* (*KIR3DL1/S1*), which are alleles of the same locus, have been a major target of both evolutionary and disease association studies (particularly for HIV and AIDS) [32]. *KIR3DL1/S1* is the only *KIR* gene encoding both inhibitory (KIR3DL1) and activating (KIR3DS1) receptors. Inhibitory KIR3DL1 allotypes bind HLA-B molecules with the Bw4 motif [33,34], an epitope present in the α -1 helix of the peptide binding groove of HLA-B that was first defined serologically [35]. About 40% of all HLA-B allotypes contain the Bw4 motif; all others contain the Bw6 motif, which is not a ligand for KIR3DL1. Position 80 of the Bw4 epitope is dimorphic and appears to affect its interaction with KIR3DL1 subtypes. In general, Bw4 allotypes with isoleucine at position 80 (Bw4–80I) appear to be better ligands for most of the KIR3DL1 allotypes tested [33,36,37]. However, direct [38] and indirect [39] data suggest that Bw4 allotypes with threonine at position 80 (Bw4–80T), particularly HLA-B*2705, are better ligands for other KIR3DL1 subtypes. This is worth careful consideration, because B*27 is a well-documented, protective allotype against AIDS progression, and most B*27 alleles contain the Bw4–80T motif [40–42]. Because expression of HIV *nef* (negative factor)

induces downregulation of some HLA class I molecules, including HLA-B, this could be sensed via inhibitory KIRs, including KIR3DL1. In addition, the stronger the interaction between KIR3DL1 and HLA-B, the more deeply HLA-B will be missed by NK cells in this recognition of ‘missing self.’

More contentious is the putative receptor-ligand relationship between the activating KIR3DS1 and Bw4 allotypes, especially those with Bw4–80I. The initial hurdle was to show that KIR3DS1 is actually expressed on the cell surface, which was well established in 2007 by four groups [43–46]. Each of these groups also showed that KIR3DS1 confers activating signals to NK cells. The second hurdle has been to define the ligand for KIR3DS1, a more elusive task. Although KIR3DS1 shares >95% similarity with KIR3DL1 in its extracellular domain, assays measuring potential KIR3DS1 interactions with cell surface Bw4 or Bw4 tetramers folded with various viral peptides have not indicated binding of KIR3DS1 to Bw4 [43,44]. However, recent experiments (discussed below) indicate that KIR3DS1 can recognize ‘altered self’ in the context of HLA-B Bw4–80I [47], similar to the MCMV studies [30].

Layering of complexity: variegated expression of KIR

The ligand-receptor relationship between KIR and HLA is unusual compared to most other such pairings in the genome in that for any functionally relevant KIR-HLA pair, it is possible for one or the other or neither of these to be present in the genome of a given individual, both of which are functionally null. This situation results from the extreme polymorphism of both *KIR* and *HLA* loci, in addition to their physically unlinked status. On top of this, a given KIR is expressed on only some NK cell clones within an individual and different KIR can diverge in the frequency at which they are expressed within the NK cell population [48] as well as in the intensity with which they are expressed (Figure 1). Whether a *KIR* gene is expressed on a given NK cell clone is determined during NK cell maturation, and once acquired, the pattern of expression remains stable [48]. The frequency of KIR expression on NK cells is likely to be an important determinant in the strength of an NK cell response against viral infection, particularly because the number of NK cells expressing a given MHC-specific NK cell receptor has been shown to affect the degree of graft rejection [49]. Further study of the variability in frequency of expression across distinct *KIR* genes and alleles is timely and essential to understanding the relative importance of this variation in different diseases.

The rules governing acquisition of KIR by developing NK cells are largely unclear, but appear hard-wired in the genome [50], with a small but significant effect of the presence of HLA-encoded KIR ligands [51] (Figure 2). HLA class I does affect the functionality of NK cells: NK cells expressing inhibitory KIR specific for self HLA class I are more responsive upon stimulation through activating receptors than NK cells that do not express inhibitory KIR specific for self HLA class I [52–55] (Figure 2). In humans, this was shown experimentally by measuring interferon- γ (IFN- γ) production and CD107a mobilization (a surrogate marker for cytotoxic activity) by NK cells in response to targets expressing ligands for activating (but not inhibitory) NK receptors [52,54]. In these assays, KIR3DL1⁺ NK cells from Bw4/Bw4 individuals responded more vigorously than KIR3DL1[−] NK cells from Bw4/Bw4 individuals and KIR3DL1⁺ NK cells from Bw6/Bw6 individuals [55]. Thus it is plausible that the combination of *KIR* and *HLA* genes of an individual will determine the proportion of functionally mature NK cells and thereby the ability to recognize ‘missing self,’ ‘induced self,’ ‘non-self’ and ‘altered self.’

KIR3DS1: in the thick of HIV resistance

Activating *KIR* have been associated with several diseases [32] and the *KIR3DS1* gene has engendered particular attention in HIV disease pathogenesis (Table 2). Although most genetic association studies agree that *KIR3DS1*, an allele that has a phenotypic frequency of ~39% in European Americans and 12% in African Americans, is probably protective against HIV, different conclusions regarding the requirement for the putative ligand Bw4–80I have emerged.

KIR3DS1 in combination with *HLA-B Bw4–80I* was associated with slow progression to AIDS in a group of ~1000 HIV seroconverters, and neither *Bw4–80I* without *KIR3DS1* nor *KIR3DS1* without *Bw4–80I* had any effect on disease progression [56]. There was a weak protective effect of this compound genotype on viral load, and a rather strong protective effect against opportunistic infections in 1184 individuals, which included the seroconverters used in the previous study and 109 additional seroprevalent individuals [57].

Smaller studies arrived at somewhat different conclusions. In a study of a group of 191 individuals [58], the opposite effect was observed: *KIR3DS1* considered by itself and the compound genotype of *KIR3DS1* + *Bw4–80I* was associated with rapid progression to AIDS, and this was statistically significant for *KIR3DS1* + *Bw4–80I*. However, *KIR3DS1* + *Bw4–80I* appeared to be protective in terms of CD4 decline relative to having *KIR3DS1* alone, although this effect was not significant. Because only 34 individuals were positive for both *KIR3DS1* and *Bw4–80I*, it is difficult to know whether the opposite effect of this compound genotype on CD4 decline and progression to AIDS could be at least partially due to power issues. Rather than a *KIR3DS1* effect, this study [58] revealed a detrimental effect of *KIR2DL2* and *KIR2DS2* on CD4 T cell decline and progression to AIDS.

A study of 255 individuals indicated that *KIR3DS1* independently associates with higher CD4 T cell counts, but does not have an effect on viral load levels [59]. On the other hand, *Bw4–80I* independently associated with lower viral loads, but had no effect on CD4 counts. The group with *KIR3DS1* + *Bw4–80I* had lower viral loads and higher CD4 T cell counts, but not significantly in either case. The authors concluded that both *KIR3DS1* and *Bw4–80I* are protective, but not in a synergistic manner.

As the genetic association studies did not reach entirely concordant results, it is of interest to consider functional studies on the interaction between *KIR3DS1*, *HLA-B* and HIV. Mouse data point to the possibility that activating NK receptors can detect a combination of MHC class I and a virus (i.e. ‘altered self’) [30]. Given the remarkable degree of convergent evolution between mouse *Ly49* and human *KIR* in terms of function, it is not unreasonable to consider specific allotypes of *HLA* class I as ligands for activating *KIR* upon viral infection or some other cellular lesion.

The protective effect of *KIR3DS1* + *Bw4–80I* was substantiated with functional data measuring inhibition of HIV replication in an autologous effector-target cell assay amongst a group of 36 individuals with various *KIR-HLA* genotypes [47], the first study to address the functional significance of a *KIR-HLA* genetic association. In this study, *KIR3DS1* positive NK cells inhibited HIV replication in Bw4–80I positive T cells to a significantly greater extent relative to the three other putatively ‘null’ situations: *KIR3DS1* positive NK cells in response to Bw4–80I negative T cells, *KIR3DS1* negative NK cells in response to Bw4–80I positive T cells, or *KIR3DS1* negative NK cells in response to Bw4–80I negative T cells. Based on the functional and genetic data, a model was proposed in which *KIR3DS1* on NK cells interacts with Bw4–80I on HIV infected target cells, conferring a measurable level of control over the virus.

More recently, NK cells from HIV infected patients were tested for IFN- γ production and CD107a upregulation, both markers of activation, after stimulation with HLA class I negative targets [60]. The strongest effects were observed in assays measuring IFN- γ production, where NK cells from *KIR3DS1* positive individuals showed greater production of IFN- γ compared to those without *KIR3DS1*. This was also the case for the *KIR3DS1* + *Bw4-80I* positive group compared to those who did not have this compound genotype, and for those with *KIR3DS1* + *Bw4-80I* compared to those who have *KIR3DS1*, but are missing *Bw4-80I* [60]. Statistics measuring strength of the effect of these genotypes were not provided in this study, but the strength of the response to class I deficient targets appeared greatest for the comparison of those with the compound genotype *KIR3DS1* + *Bw4-80I* versus those without this genotype. Interestingly, *KIR3DS1* + *Bw4-80I* positive individuals showed a rather strong IFN- γ response compared to those who have *KIR3DS1*, but are missing *Bw4-80I*. However, statistical power was limited in this comparison because the number of individuals in both groups were small (11 versus 9, respectively) and the difference was not significant. The authors concluded that *KIR3DS1* associates with high NK cell functions in a manner that is independent of *Bw4-80I*, but an increase in sample numbers in the *KIR3DS1* + *Bw4-80I* positive versus *KIR3DS1* positive *Bw4-80I* negative comparison groups would help solidify or refute this conclusion. Together, these findings suggest that *KIR3DS1* positive NK cells are intrinsically more active, an effect that might depend on HLA-B.

Biological science is rarely straightforward and even small differences in the way two different studies are performed (in terms of either experimental or analytical methodology) can affect the outcome, and therefore the conclusions of a study. However, one possibility is that *KIR3DS1* binds certain *Bw4* alleles, perhaps after modulation by HIV infection.

Inhibition translates into activation: *KIR3DL1* subtypes in HIV disease

The inhibitory *KIR3DL1* locus is among the most polymorphic of the *KIR* loci based on current data (<http://www.ebi.ac.uk/ipd/kir/>). *KIR3DL1* allotypes differ in the level of their expression on cell surfaces [61,62] and these differences have functional repercussions [36,51]. It was proposed that the more inhibitory allotypes would associate with faster disease progression, because virtually all studies of *KIR* in HIV disease conclude that activating genotypes and phenotypes correlate with protection. To determine whether expression levels of *KIR3DL1* might affect outcomes to HIV infection, alleles were grouped according to Gardiner *et al.* [61] into high (*KIR3DL1**h), low (*KIR3DL1**l), or no expression groupings [39]. HLA-B *Bw4* molecules are known ligands for *KIR3DL1* [34] and data indicate that the best ligands for the *KIR3DL1* subtypes tested are the HLA-B *Bw4-80I* allotypes [33,36] (although not all *KIR3DL1* or *Bw4* subtypes have been tested), so those with *Bw4-80I* or *Bw4-80T* were grouped separately. Because *KIR3DS1* + *Bw4-80I* was protective in these same cohorts, all individuals with this compound genotype were excluded from the analysis. To compare various *KIR3DL1* + *Bw4* groupings, individuals with *Bw6/Bw6* (the alternative to *Bw4* based on the dimorphic serological motif at position 77–83 of the HLA-B molecule) were used as the consistent reference group in all analyses because these individuals have no ligand for any *KIR3DL1* subtype. Both disease progression analyses (n = 915) and viral load analyses (n = 901) were performed. Analysis of individual *KIR3DL1* alleles revealed that only the unexpressed *KIR3DL1**004 allotype in the presence of *Bw4* had a protective effect. This raises the possibility that *KIR3DL1**004 is indeed functional, perhaps by interaction with *Bw4* intracellularly (as is the case for the interaction of *KIR2DL4* and HLA-G [63]), or alternatively by altering the function of other receptors. Surprisingly, individuals possessing the highly expressed, highly inhibitory allotypes, *KIR3DL1**h, along with *Bw4-80I* ligands had the lowest mean viral loads and progressed at a slower rate to AIDS relative to other *KIR3DL1* + *HLA-B* genotypes [39].

The *B*57* allele, which has the *Bw4-80I* motif, in combination with the *KIR3DL1*h* allotype showed stronger protection both in terms of AIDS progression and viral load than any other genetic variant identified to date (odds ratio = 0.1 for viral load and relative hazard ratio = 0.26 for progression to AIDS). *B*27*, the second most protective allele in the cohorts, contains the *Bw4-80T* motif, and interestingly, this allele showed greater protection in the presence of *KIR3DL1*1*, suggesting that *B*27* (and perhaps other *Bw4-80T* allotypes) might have greater affinity for one or more of the *KIR3DL1*1* allotypes (Figure 3). Binding assays will be necessary to confirm or refute this possibility. Thus, level of expression and affinity of *KIR3DL1* for the various *Bw4* ligands could both contribute to functionality of these receptors on effector cells (Figure 2).

So why would highly expressed, highly inhibitory *KIR3DL1* subtypes confer, in general, relative protection against HIV? Well-substantiated models of NK cell repertoire development propose that NK cells must acquire sufficient inhibitory signals to quench autoreactivity through recognition of self class I ligands [48,64,65]. The larger the contribution of a given receptor-ligand pairing to NK cell inhibition under homeostatic conditions (as exemplified by the range expected to occur across high- and low-expressing *KIR3DL1* subtypes [52,55]), the more potent a ‘missing self’ response will be when the interaction between that inhibitory receptor and its ligand is lost. The interaction could be lost upon viral infection if class I is downregulated, as is the case in HIV infection. In addition, as proposed above, the activation potential of the NK cell pool (i.e. its responsiveness to ‘missing self,’ ‘induced self,’ ‘non-self’ and ‘altered self’) is expected to correlate with the expression frequency and level of the *KIR3DL1* allele and its affinity for the available HLA class I ligands.

The Cadillac of protection: preventing infection

The effect of genetic variation on HIV infection is poorly understood compared with its effect on outcomes to infection, such as disease progression or viral load levels. Apart from homozygosity for a deletion variant in the *CCR5* co-receptor for HIV, *CCR5Δ32*, there are no polymorphisms that consistently show strong protection against HIV infection. Similar to the situation observed for AIDS progression, it is likely that there are many genetic variants that, when considered individually, have quite small effects on risk of HIV infection. Such variants collectively, however, could have substantial additive or epistatic effects.

The innate immune response probably weighs in when it comes to protection from HIV infection, at least in some cases. Indeed, NK cell activity in a group of 37 exposed uninfected (EU) intravenous drug users (IVDU) was significantly greater than that from 10 infected patients and 28 unexposed individuals [66]. The differences were striking for both NK cytolytic activity and cytokine production. Notably, NK cells from the HIV-infected patients showed similar measurements of NK cell activity before and after HIV infection, indicating that their relatively low levels of responses were intrinsic and not a result of HIV infection. Furthermore, low responsiveness was the norm, because the HIV-infected individuals and the unexposed individuals showed similar levels of response (with slightly better responses amongst the unexposed group). The data support the idea that strong NK cell responses could, under some circumstances, protect from HIV infection.

KIR3DS1 homozygosity was recently reported to be protective against HIV infection in a study involving 80 HIV-negative IVDU compared with individuals with primary HIV infection (odds ratio = 2.87) [67]. This protection was not dependent on *Bw4-80I*, suggesting once again that the ligand for *KIR3DS1* is not *Bw4-80I*. As the authors discuss, it is also possible that *KIR3DS1* is simply marking the true protective variant, which might confer recessive protection. In general, this study contrasts with the previous observation

that two copies of *KIR3DS1* in the absence of *Bw4-80I* associates rather strongly with rapid disease progression [56]. A more recent study from this group showed that the combination of *KIR3DL1*h* and *HLA-B*57* was associated with a reduced risk of infection [68], which is in agreement with the effect of this compound genotype on disease progression [39]. Thus, genetic protection from infection and that from disease progression are not necessarily one and the same, and as for all genetic disease associations, functional data to address the basis of protection or susceptibility are warranted.

The presence or absence of specific *KIR* genes has been a primary focus in studies attempting to measure the potential influence of differential KIR activity in human disease [32] and functional studies are emerging to explain some of the genetic results [47,60,69]. A follow-up study of EU, HIV⁺, and unexposed Vietnamese individuals focusing on specific receptors has made clear that genetic presence or absence data provide only part of the *KIR* picture as a whole [70]. This study shows that the frequency of specific *KIR* transcript detection in peripheral blood mononuclear cells and the levels of those *KIR* transcripts in the NK cell population can differ significantly between HIV⁺ and EU individuals. These differences are not completely dependent on the presence of the given *KIR* gene in the genome of that individual. In general, NK cells from EUs as compared to those from HIV⁺ patients were characterized by patterns of *KIR* expression that are expected to result in NK cell activation. Of particular interest in the context of this review, there was a high *KIR3DS1* to *KIR3DL1* transcript ratio in the EUs. These differences between EUs and HIV⁺ groups in mRNA levels of certain *KIR* emphasize the need to consider not only the presence or absence of each *KIR* gene, but also expression levels, and allelic differences when studying effects of these loci on human disease.

Concluding remarks

Genetic association studies all indicate a role for KIR-HLA interactions in the control of HIV infection, but disagree on the exact nature of these associations. Generally, they demonstrate an association of *KIR3DL1/S1* and *HLA-B*, either alone or in combination, with viral load, CD4 decline and/or progression to AIDS. More recent functional studies with NK cells expressing KIR3DS1 at least partially support a protective role for KIR3DS1 in HIV control, but fail to resolve the discrepancies among the genetic studies. The current challenge is to understand the molecular nature of the interactions among KIR, HLA and HIV. Such molecular studies could in turn help understand the divergent results obtained in the genetic association studies.

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Figure 1.

Effects of *KIR* diversity on NK cell repertoire and function. Most *KIR* display presence or absence polymorphism (**top**). *KIR* alleles also differ in level and frequency of expression (high, low, or no), in which a nonexpressed allele (no) is likely to be equivalent to the absence of the corresponding *KIR* gene. Both types of polymorphism affect the contribution of the *KIR* in question to the overall NK repertoire, represented here by four NK cells for each situation. Some *KIR* allotypes are expressed at high levels on a large proportion of NK cells (left NK repertoire); others are expressed at lower levels by a small proportion of NK cells (center NK repertoire), and nonexpressed or absent alleles probably do not influence

the NK repertoire (right NK repertoire). In addition, the affinity of a given KIR for its HLA class I ligands influences the strength of the signals received via the KIR. Note that this figure depicts the effect of a single *KIR* gene, and that the overall *KIR* repertoire on NK cells is an overlay of multiple *KIR* genes, each expressed largely independently of the others.

Figure 2.

Effects of inhibitory KIR-HLA interactions on NK cell responsiveness. Each KIR repertoire is represented by four NK cells, with individual NK cells expressing no, low or high levels of an inhibitory KIR on the cell surface. NK cells expressing a given inhibitory KIR in the presence of its HLA class I ligand (**top left**), are predicted to be more responsive to activating stimuli (indicated in dark green) than in the absence of its ligand (**bottom left**). In addition, the presence of HLA ligand increases the proportion of cells expressing the corresponding inhibitory KIR, but decreases the expression levels of this KIR on the NK cell surface. In the case of inhibitory KIR allotypes that are expressed at lower levels or frequencies (**center**), the effects of absence (bottom center panel) and presence of HLA ligand (top center panel) will be less pronounced. Note that this figure depicts the effect of a single *KIR* gene, and that the overall *KIR* repertoire on NK cells is an overlay of multiple *KIR* genes, each expressed largely independently of the others.

Figure 3. Combinations of *KIR3DL1/S1* and *Bw4* protect against HIV-1 disease progression. Genotypes are ordered by degree of protection. Hazard ratios shown (colored dots) are relative to the *Bw6/Bw6* control group. Lines through the dots represent 95% confidence intervals. Red dots, *B*57* with *3DL1* genotypes; green dots, *B*27* with *3DL1* genotypes; blue dots, *Bw4-80I* with *3DL1/S1* genotypes; orange dots, *Bw4-80T* with *3DL1* genotypes; yellow dots, *Bw4* with or without *3DL1*004*; black dot, *3DS1* without *Bw4-80I*.

Table 1*HLA* and *KIR* variants that influence HIV-1 infection and disease progression

Gene	Genotype	Effect	Refs
<i>HLA</i>	<i>HLA-A, HLA-B, HLA-C</i> homozygosity	Accelerate disease progression	[71,72]
	<i>B*35Px</i>	Accelerate disease progression	[73]
	<i>B*57, B*27, Bw4</i>	Slower disease progression	[40,56,74–76]
	<i>A1-B8-DR3</i>	Accelerate disease progression	[77]
	<i>G*0105N</i>	Protection against infection	[78,79]
	<i>G*010108</i>	Increased risk of infection	[79]
	<i>E*0103</i>	Protection against infection	[78]
	<i>HLA-C-35</i> (35 kb upstream of <i>HLA-C</i>)	Lower viral load	[9]
<i>KIR</i>	<i>2DS2 2DL2</i>	Faster rate of CD4 T cell decline	[58]
	<i>3DS1</i>	Slower rate of CD4 T cell decline	[59]
	<i>3DS1</i> homozygosity	Protect against infection	[67]
<i>KIR+</i>	<i>3DS1 + Bw4-80I</i>	Slower disease progression	[56]
<i>HLA</i>		Slower progression to opportunistic infections	[57]
	<i>3DL1 + B*57s</i>	Slower disease progression	[80]
	<i>3DL1*h + Bw4-80I</i>	Slower disease progression, lower viral load	[39]
	Absence of cognate <i>HLA</i> ligand for inhibitory <i>KIR</i>	Protect against infection	[81]

Table 2Multiple effects of *KIR3DL1/S1* on HIV-1 infection and disease progression

Type of study	N ^a	Results	Refs
<i>KIR3DS1 + HLA-B Bw4-80I</i>			
Genetic	~1000	Slower disease progression	[56]
Genetic	1184	Slower progression to opportunistic infections but not malignancy	[57]
Genetic	391	Lower viral load	[57]
Cellular	36	Inhibition of HIV-1 replication	[47]
Genetic	191	Slower rate of CD4 ⁺ T cell decline but faster disease progression	[58]
<i>KIR3DS1</i>			
Genetic	255	Slower rate of CD4 ⁺ T cell decline	[59]
Functional	60	Increased IFN- γ production	[60]
Genetic	384	Homozygosity–protection against infection	[67]
<i>KIR3DS1 expression</i>			
Functional	70	Higher levels of expression in HIV-1-exposed uninfected individuals	[70]

^a Abbreviations: N, the number of individuals included in the study; IFN- γ , interferon- γ .