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3.1 Transmission

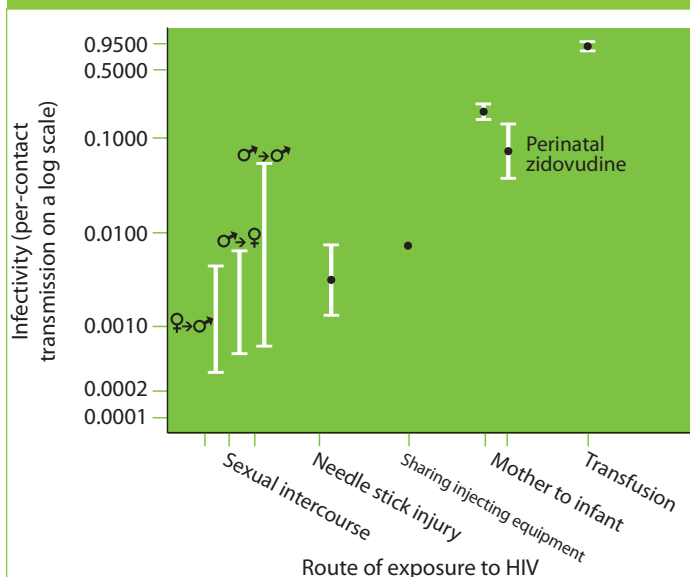
HIV is transmitted following contact with infected bodily fluids. The typical routes of transmission are unprotected sex, blood-to-blood contact (including needle-stick injuries, sharing injecting equipment and contaminated blood products) and vertical transmission (from mother to child before, during and after birth). Less common routes include tattooing, organ and tissue transplantation, artificial insemination and semi-invasive medical procedures. The most common mode of HIV transmission is sexual transmission at the genital mucosa accounting for 75-85% of cases worldwide. The probability of HIV transmission per episode of exposure varies (Figure 3.1). The risk of transmission per exposure may be influenced by factors such as co-existent genital ulcer disease, genetic factors and stage of HIV disease of the index case. It is estimated that transmission from a person with HIV infection acutely accounts for more than 34-50% of cases of newly-acquired HIV.^{1,2}

3.1.1 Sexual transmission of HIV Biological features

There are four basic steps in the sexual transmission of HIV: HIV contact with mucosal epithelium; HIV uptake by dendritic cells (DC); HIV transport to secondary lymphoid organs; and HIV infection of CD4 cells in secondary lymphoid organs. Following mucosal contact, HIV breaches the mucosal barrier, most likely following microtrauma, and is captured by DC in the lamina propria. DCs are antigen-presenting cells that initiate adaptive immune responses by presenting antigens to and activating CD4 cells. After capturing micro-organisms that enter mucosal tissues, DC migrate to secondary lymphoid organs, where they present microbial antigens to resting lymphocytes.

Attachment of HIV to DC occurs via binding of HIV envelope proteins to a family of molecules called C-type lectin receptors, which include DC-specific ICAM-3-grabbing non-integrin (DC-SIGN), mannose receptors and langerin. Each of these molecules can bind gp120, and they are expressed on different subtypes of DC.^{3,4} Among their many roles, DC act as vehicles to transport HIV to secondary lymphoid organs where they hand-over HIV to susceptible lymphocytes. Furthermore, DC present HIV antigens to activated CD4 cells. This potentiates both the infection of and replication in CD4 cells.⁵ DC express CD4 and CCR5 receptors,⁶ but not CXCR4.⁷ This may contribute to other factors leading to the preferential sexual transmission of R5 viral isolates.⁸ Early simian immunodeficiency virus (SIV) infection is also associated with massive depletion of CCR5 expressing activated CD4 cells from the gastrointestinal tract.^{9,10}

Figure 3.1 Infectivity and route of exposure



Note: This figure indicates the per-contact probability of HIV transmission. The infectivity ranges for sexual contact are derived from a comprehensive review of the literature, with the lower and upper limits derived from modelling per-contact transmission in different study populations. Each infectivity estimate for the other routes of infection originates from one representative study.

♀→♂ = female-to-male transmission;

♂→♀ = male-to-female transmission;

♂→♂ = male-to-male transmission;

Mother to infant = transmission with and without perinatal zidovudine treatment.

Source: Royce RA, Sena A, Cates W Jr, Cohen MS. Current concepts: sexual transmission of HIV. N Engl J Med 1997;336:1072-8. All rights reserved. Used with permission.

Host determinants of HIV transmission

Multiple studies of heterosexual transmission in developing countries have demonstrated that plasma viral load is a critical determinant of HIV transmission.¹¹⁻¹³ The risk of HIV transmission doubles for each ten-fold increase in plasma HIV viral load. The relationship between increased risk of HIV transmission per coital act and increased plasma HIV viral load is greatest in subjects under the age of 35 years.¹⁴ These studies support previous observations that people with primary and late-stage HIV infection are more likely to transmit HIV when viral load is high.¹⁵ Plasma HIV viral load usually correlates with HIV viral load in genital secretions.¹⁶ Like plasma HIV viral load, genital HIV viral load is high during the acute primary illness and during late stages of HIV infection. Other host factors that influence HIV transmission are listed in Table 3.1.

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Table 3.1 Biological factors affecting sexual transmission of HIV

Factors increasing transmission risk	Index	Recipient
Plasma viral load	√	N/A
Sexually transmissible infections	√	√
Foreskin ¹⁵	√	Increased risk for recipient
Menstruation ¹⁷	√	√
Bleeding during intercourse ¹⁵	√	√
Genital tract trauma	√	√
Intrauterine device ¹⁷	–	√
Medroxyprogesterone ¹⁸	–	√
Bacterial vaginosis ¹⁹	–	√
Factors decreasing transmission risk		
CCR5 Δ32 homozygosity	–	√
Barrier contraception	√	√
N/A = not applicable		
Reference: Adapted from Royce RA, Sena A, Cates W, Jr., Cohen MS. Sexual transmission of HIV. <i>N Engl J Med</i> 1997;336:1072-8.		

Role of sexually transmissible infections

Transmission and acquisition of HIV may be increased in patients with concurrent sexually transmissible infections (STI). Ulcerative STI are associated with increased transmission of HIV.¹⁴ Both symptomatic and asymptomatic STI increase genital HIV viral load and the numbers of cells within the genital tract expressing CCR5.²⁰⁻²² Mathematical models suggest that intercurrent STI may increase the likelihood of HIV transmission ten-fold.²³ Treatment of STI has been associated with declines in genital HIV viral load to baseline levels.²¹ These observations may explain the dramatic reductions in HIV transmission observed following the treatment of STI and provision of clinical support.²⁴

There is epidemiological evidence and biological plausibility to support an association between prevalent herpes simplex virus type 2 (HSV2) and HIV acquisition in both men and women.²⁵ HSV2 was found to have the strongest association with HIV acquisition in high-risk women in Tanzania compared with other STI.²⁶ The relative risk of HIV acquisition was higher for incident than for prevalent HSV2 in this study. Valacyclovir has been demonstrated to decrease plasma, vaginal and rectal HIV viral load in individuals with both HIV and HSV2.^{27,28} However, two large randomised trials failed to show a reduction in HIV acquisition in people who received acyclovir to prevent HSV2 recurrences.²⁹ Randomised trials of treatment of bacterial STI also did not show a reduction in HIV transmission.³⁰ There is no convincing evidence to date that treatment of STI results in prevention of HIV at the population level.³¹ Further studies are awaited to determine if the treatment of STI will have any real impact on HIV transmission.

The role of circumcision

Male circumcision has a profound effect on the risk of acquisition of HIV in heterosexual couples. Several large randomised prospective studies performed in Africa have shown a 70% reduction in risk of HIV acquisition following

circumcision.^{32,33} The role of circumcision in prevention of HIV in men who have sex with men remains to be determined.

3.1.2 HIV superinfection

Infection with two different HIV isolates is possible. HIV superinfection occurs when a second viral strain infects a person in whom HIV primary infection and seroconversion have already occurred. In contrast, HIV co-infection refers to the situation where two viral strains are present at the time of initial infection.³⁴ Dual HIV infection collectively refers to both HIV superinfection and co-infection.³⁵ Dual infection is a prerequisite for recombination events, which occur between isolates from different HIV subtypes resulting in circulating recombinant forms of HIV (Section 1.3).

Cases of superinfection have been reported in a variety of situations including intersubtype;³⁶ intrasubtype;³⁴ wild-type with drug resistant;³⁷ drug-resistant with wild-type;³⁸ and R5 only with dual tropic.³⁹ Recombination of superinfecting viruses has been documented in people with chronic infection. This has involved intersubtype recombination⁴⁰ and intrasubtype recombination involving multiclass drug resistant viruses.⁴¹ The exact incidence of superinfection is at present unknown. Cohort based studies have reported that superinfection occurred in 0-5% of patients.^{36,42-45}

The consequences of superinfection are unknown. Case reports have associated superinfection with accelerated clinical and surrogate marker progression.^{38,39} Superinfection with a drug resistant strain has been associated with impaired virological responses to antiretroviral treatment.³⁷ However, not all cases of superinfection have been associated with poorer outcomes as this process has been documented in two patients with long-term non-progressive HIV disease.⁴⁶ Studies have been unable to distinguish between co-infection and superinfection; however, they have consistently associated dual infection with higher viral load set points.^{47,48} Animal studies have found that animals protected from superinfection live longer than their superinfected counterparts.⁴³ On balance, evidence suggests that superinfection may have deleterious effects on HIV disease progression. It is not clear if superinfection itself leads to accelerated disease progression or if unidentified host factors contribute to the accelerated disease progression independent of superinfection.

It is unknown if all patients are at risk of HIV superinfection. Most reports of superinfection occur in patients with early HIV infection.⁴⁸ Animal studies suggest a window period followed initial infection during which superinfection is more common.⁴³ Mathematical models suggest that superinfection during the window of primary infection explains the rate of recombinant events observed within given populations.⁴⁹ However, superinfection has been documented to occur up to 12 years after initial infection.^{40,41,46,50} To date, no case of superinfection has occurred in people taking antiretroviral therapy.^{42,36} However, methods used in these studies may underestimate the true prevalence of superinfection. Case reports of superinfection with multiclass resistant HIV potentially suggest that even patients on antiretroviral therapy may be at risk of superinfection.⁴¹ Currently all patients with HIV should be considered to be at risk of superinfection. Therefore it is recommended that individuals with HIV infection take measures to prevent superinfection.

3.1.3 Mother-to-child transmission

Mother-to-child transmission can occur antepartum, intrapartum and postpartum via breast-feeding. Most cases of mother-to-child transmission occur during labour. As with sexual transmission, R5 viruses are more likely to be transmitted from mother to child.⁵¹ The mechanisms underlying these observations are not completely defined. The overall risk of vertical transmission of HIV is 25-30%. As for sexual transmission, maternal HIV viral load is the predominant risk factor for vertical transmission.⁵² However, HIV transmission can occur despite low maternal HIV viral load.⁵³ Mothers with plasma HIV viral load less than 1000 copies/mL have transmitted HIV to their infants. The prime determinant of transmission, in this context, is absence of maternal antiretroviral therapy. Transmission of HIV from mother to baby occurs in 10% of mothers not receiving antiretroviral therapy with low HIV viral load compared with less than 1% of mothers on antiretroviral therapy.⁵⁴ There is an increased risk of transmission either perinatally or postnatally when women contract HIV during pregnancy.

Other factors associated with an increased risk of perinatal HIV transmission include low maternal CD4 cell count, prolonged rupture of membranes, pre-term labour, chorioamnionitis, cigarette smoking or illicit drug use during pregnancy, and obstetric procedures such as amniocentesis and amniocentesis. Caesarean section before the onset of labour significantly reduces the risk of HIV transmission,⁵⁵ although the additional benefit of Caesarean sections in women receiving effective antiretroviral therapy remains unclear.

Breast-feeding approximately doubles the risk of mother-to-child transmission of HIV and accounts for approximately one third of cases of mother-to-child transmission.^{56,57} High levels of HIV in breast milk cells correlate with increased risk of transmission. Avoidance of breast-feeding has been suggested to reduce the risk of HIV transmission.⁵⁸ However, in resource-poor settings, breast milk substitutes may be difficult to obtain and benefits may be off-set by increased respiratory and gastrointestinal infections in non-breast-fed infants. Exclusive breast-feeding carries a lower risk of HIV transmission than mixed feeding in South Africa.⁵⁹ Other factors which increase the risk of postnatal HIV transmission include maternal nipple lesions, mastitis, low maternal CD4 cell count, infant oral thrush and breast-feeding for longer than 15 months.⁶⁰

Chemokine genetic polymorphisms influence the rate of mother-to-child transmission of HIV. Maternal heterozygosity for genotype SDF-1-3'A is associated with almost double the risk of transmission of HIV, independent of maternal plasma HIV viral load.⁶¹ Infant chemokine genetic polymorphisms have not been demonstrated to influence HIV acquisition rates.

3.1.4 HIV transmission by other bodily fluids

The risk of HIV transmission by oral sex and kissing is low. While infectious HIV is detected in the saliva, it is present in substantially reduced quantities compared with blood or genital secretions. Furthermore, the saliva contains endogenous antiviral factors including HIV-specific antibodies and a number of soluble factors such as secretory leukocyte protease inhibitor.³ Saliva may alter gp120 structure and lyse HIV-infected cells secondary to the inherent hypotonicity of the saliva. While

oral sex has been identified as the only reported risk factor in some patients,⁶² the likelihood that oral sex is an important transmission route of HIV is low. The low risk of HIV transmission via oro-genital sex is supported by a large cohort study in which no case of HIV transmission was identified in more than 210 person-years follow up in a cohort of HIV-discordant couples who engaged in protected anal or vaginal sex but unprotected oral sex without other risk factors for HIV.⁷ However, oral transmission of simian immunodeficiency virus (SIV) has been reported in a macaque model.⁶³ There is no evidence that HIV transmission can occur as a result of exposure to tears, sweat, faeces or urine.

3.2 Disease progression

3.2.1 Phases of HIV disease

HIV disease is characterised by three phases: acute primary illness, asymptomatic chronic illness and symptomatic chronic illness. The rate of progression from one phase to another is highly variable.

Following transmission, HIV initially replicates in regional lymph nodes. This results in a rapid rise in plasma viral load to levels in excess of one million copies/mL. This phase is accompanied by dissemination of HIV to lymphoid organs, gut and genital tract.⁶⁴ Following the peak in viraemia, plasma viral load decreases co-incident with the development of host cellular immune responses.⁶⁵ The peak in plasma viral load and development of cellular immune responses is associated with a symptomatic illness in 60-90% of patients.^{66,67}

The following features of the acute primary illness of HIV are associated with poorer prognosis:

- symptomatic primary illness⁶⁸
- longer duration of acute primary illness^{66,69}
- neurological symptoms⁷⁰
- presence of oral candidiasis⁷¹
- greater number of signs and symptoms⁷¹
- greater severity of symptoms.

The following laboratory markers have been associated with poorer prognosis during acute primary illness of HIV:

- baseline CD4 count⁷²
- baseline HIV DNA level⁷²
- slow decay of HIV viral load.⁷³

While the peak HIV viral load during acute primary illness is not predictive of HIV disease progression, it is associated with severity of symptoms, which has been linked to a poorer prognosis.⁷⁴ The acute primary illness generally resolves spontaneously within 14 days.⁷⁵

On resolution of the acute primary illness, the patient enters a prolonged, clinically asymptomatic period. Nevertheless, virological and immunological progression occurs during this period. Progressive, sub-clinical, immune deterioration results in the development of symptomatic HIV disease. Symptomatic HIV disease is divided into two phases that are not necessarily contiguous: symptomatic HIV infection (non-AIDS) and AIDS. Patients may present with an AIDS-defining illness without preceding HIV-related symptoms. Symptomatic non-AIDS events are markers of clinical immunodeficiency and predict progression to AIDS.⁷⁶

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3.2.2 Rates of disease progression

The rate of disease progression is highly variable among individuals, ranging from six months to more than 20 years. In the absence of treatment the median time to develop AIDS is 10-11 years.^{77,78} The median survival following AIDS in the absence of combination antiretroviral therapy (cART) is dependent on the CD4 cell count at AIDS diagnosis: 3.7 years if the CD4 cell count is less than 200 cells/ μ L and 1.3 years if the CD4 cell count is less than 70 cells/ μ L.⁷⁹ However, rates of disease progression to AIDS vary from rapid progression within six months of seroconversion,⁸⁰ to no significant progression. Individuals with no disease progression were previously referred to as long-term non-progressors. By definition, these patients had CD4 cell counts above 500 cells/ μ L and were asymptomatic despite more than ten years of infection without specific anti-HIV therapy. Between 1-5% of people with HIV infection fall into this category.⁸¹ However, with longer follow-up and the use of improved prognostic models, these people do eventually experience HIV disease progression.

The term elite controllers refers to people who maintain undetectable HIV viral loads in the absence of antiretroviral therapy (Section 2.3). Approximately 0.6% of people with HIV infection are considered elite controllers.⁸² Such people have been shown to have stronger HIV specific immune responses compared with people who do not control viral replication. Genetic factors known to be associated with slow progression of HIV disease were detected in less than 25% of these people;⁸³ 10% of such people had CD4 cell counts below 350 cells/ml and 3% had AIDS.⁸⁴ Elite controllers had increased levels of lipopolysaccharide associated with increased levels of immune activation when compared with HIV-negative controls.⁸⁴

3.2.3 Surrogate markers of disease progression

Laboratory findings, such as falling CD4 cell numbers, rising plasma HIV viral load and increasing CD38 expression by CD8 cells, are non-clinical, surrogate markers of disease progression. These markers correspond to fundamental aspects of HIV disease pathogenesis, namely immunodeficiency, viral replication and increased immune activation, respectively.

CD4 cell count

The CD4 cell count was the earliest surrogate marker used in HIV management.^{85,86} Absolute CD4 cell count, CD4 cell percentage and CD4 cell rate of decline have all been demonstrated to predict progression to AIDS.^{87,88} The risk of development of certain opportunistic infections can be stratified according to CD4 cell count. For instance, the relative risk of development of *Pneumocystis jirovecii* pneumonia in patients with CD4 cell counts less than 200 cells/ μ L (14%) is 4.9.⁷⁶

CD4 cell count declines gradually during HIV disease progression. The rate of decline accelerates over time, averaging 80-110 cells/ μ L per year.⁸⁹ Pre-seroconversion host factors such as the amount of T-cell receptor excision circles in CD4 cells predicts subsequent CD4 decline.⁹⁰ CD4 cell count is predictive of AIDS progression across all viral load strata, although its predictive value increases with duration of HIV infection.^{77,91} The CD4 cell count in blood, however, does not reflect total body CD4 cells which predominantly reside in lymphoid tissue. The massive depletion of CD4 cells from the

gastrointestinal tract early in HIV infection leads to a dramatic loss in the total CD4 pool which remains depleted throughout the natural history of untreated infection.⁹²

Plasma viral load

Plasma viral load is predictive of disease progression at all stages of infection and across all CD4 cell strata. Early studies suggested that, following an initial peak, during the acute illness of HIV, plasma viral load declined to a set point and remained stable during the asymptomatic phases of HIV, and then increased a few years prior to the development of AIDS.^{93,94} However, this pattern is not supported by other studies.^{89,95}

More recent reports demonstrate that plasma viral load gradually rises over time and that a setpoint is not reached.⁸⁹ In the initial three years following seroconversion, viral load changes are apparent only in people who develop AIDS within that period. After this time, viral load changes are detectable; both the viral load rate-of-increase and the absolute value predict an increased progression rate to AIDS.⁸⁹ HIV proviral DNA levels in peripheral blood mononuclear cells also predict progression to AIDS independently of both viral load and CD4 count.⁹⁶

CD38 expression on CD8 cells

CD38 is a cell-surface glycoprotein that is detected on lymphocytes and natural killer cells. Its expression is increased on activated lymphocytes. Upregulation of CD38 expression by CD8 cells during primary HIV illness⁹⁷ and other stages of HIV disease⁹⁸ is predictive of subsequent decline in CD4 cell count.

Furthermore, elevated expression of CD38 by CD8 cells late in HIV disease is a strong predictor of disease progression.⁹⁹ These observations underscore the importance of immune activation in the pathogenesis of HIV disease.

Other markers of immune activation have also been demonstrated to have prognostic significance in HIV disease progression. Soluble tumour necrosis factor (TNF) receptor is a stronger predictor of progression to AIDS than viral load.¹⁰⁰ Not all markers of CD8 activation indicate a poor prognosis. Increased expression of human leukocyte antigen DR-1 (HLA-DR) in the absence of CD38 is a good prognostic marker.⁹⁷

Interactions between surrogate markers of disease progression

CD38 expression by CD8 cells is the strongest single predictive marker of disease progression in all stages of HIV disease,⁹⁹ but models which incorporate CD38 activation, CD4 cell count and viral load predict disease progression most accurately.⁹¹ The strength of the predictive associations of the three separate markers changes over time.

In early HIV disease, the best predictive models include only CD38 and viral load, with CD4 cell count adding little further predictive power. In contrast, in the absence of CD38 measurement, CD4 cell count adds to the predictive power of viral load.⁷⁷ In late stage HIV infection, the best predictive models include all three surrogate markers.

These findings are consistent with previous reports stating that early viral load predicts subsequent CD4 cell count decline⁷⁷ and that CD4 cell count is a stronger predictor of disease progression in late HIV disease when viral load and CD4 cell count are used as single markers.¹⁰¹ However, in patients with a viral load less than 3000 copies/mL (when measured by branched chain DNA assay), CD4 cell count is a stronger predictor of disease progression than either viral load or CD38.⁹¹

3.2.4 Host factors influencing disease progression

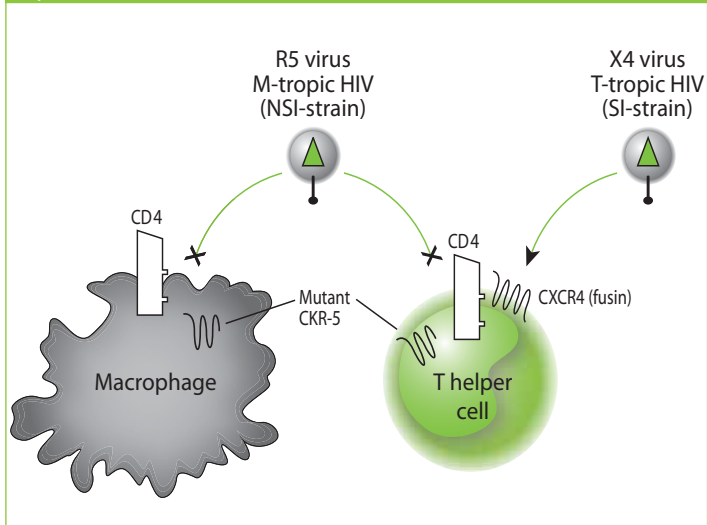
Chemokine protein and chemokine receptor polymorphisms

Genetic polymorphisms of multiple chemokine receptors, chemokine proteins and related cytokines have been demonstrated to influence both HIV transmission and HIV disease progression (Table 3.2). The first reported polymorphism was CCR5Δ32. This polymorphism encodes for a CCR5 molecule that contains a 32-base-pair deletion and is not expressed on the cell surface.

The absence of CCR5 is the basis for the resistance of some individuals to infection with R5 viruses (Figure 3.2).¹⁰² However, homozygotes for CCR5Δ32 can be infected with HIV isolates which use other co-receptors.¹⁰³ Cell-surface expression of CCR5 is reduced in heterozygotes (CCR5Δ32/WT) and this is thought to be the basis of delayed progression to AIDS in these subjects. Mutations can also occur in the

promoter region of the CCR5 gene. Mutations in CCR2-64I are also associated with delayed disease progression.¹⁰⁴ Another chemokine that binds to CCR5, CCL3 is also relevant to disease progression. Lower CCL3L1 copy number is associated with higher susceptibility to HIV infection and disease progression.¹⁰⁵

Figure 3.2 Mutation of CCR5 (mutant CKR-5) prevents surface expression of CCR5 and leads to resistance to infection with R5 virus



Source: French MR, Stewart GJ, Penry R, Levy JA. How HIV produces immune deficiency. In: Stewart G (editor) *Managing HIV*. Sydney: Australasian Medical Publishing Company, 1997:27. Used with permission NSI = non-syctium-inducing; SI = syctium-inducing; CCR5 = coreceptor molecule used by macrophage-tropic strains of HIV to enter CD4 cells, also known as CC-CKR5 and CKR5; CXCR4 = coreceptor molecule used by T cell-tropic strains of HIV to enter CD4 cells, formerly known as fusin.

Table 3.2 Chemokine protein and receptor and related polymorphisms known to influence HIV disease progression

	Mutation		Influence on natural history		Putative effect
	Site	Codon	Transmission	Disease progression	
Chemokine protein					
SDF1	3'UTR	SDF1-3A'	decrease MTCT ⁵⁵	decrease ⁵⁶	? block CXCR4
RANTES	Promoter	G4	increase ⁵⁸	decrease ⁵⁸	? increase RANTES
Chemokine receptor					
CCR5	Promoter	59029 G		decrease ⁵⁹	decreased promoter activity
		CCR5P1		increase ⁶⁰	
CCR5	ORF	59356 T	increase MTCT		
		CCR5Δ32	decrease ^{52,79}	decrease ⁸⁰	
CCR2	ORF	CCR2-64I		decrease ^{54,81} delayed progression to AIDS then accelerated progression ⁸⁵	Linked with CCR5 promoter polymorphism, ⁵⁴ however mechanism undefined Once X4 virus is selected disease progression is accelerated. ⁸⁵
Related cytokines					
IL-4	Promoter	IL-4 589 T		decrease ^{86,87} increased acquisition of X4 phenotype, associated with delayed progression to AIDS and then accelerated progression	? increased IL-4 production with resultant decrease CCR5 and AIDS then increase CXCR4 expression
IL-10	Promoter	IL-10 5'A	increase ⁸⁸	increase ⁸⁸	decreased IL-10 inhibition of HIV

IL = interleukin; MTCT = mother-to-child transmission; ORF = open reading frame; RANTES = regulated on activation, normal T cell expressed and secreted; SDF = stromal-derived factor; UTR = untranslated region.

3 Natural history of HIV infection

HLA alleles

A number of HLA alleles have been shown to impact on the natural history of HIV. The following HLA types are associated with decreased rates of disease progression: HLA B27, HLA B51 and HLA B57. People with HLA B57 are less likely to present with acute asymptomatic HIV illness and are more likely to have broader and stronger HLA B57 restricted anti-HIV immune responses.¹⁰⁶ People with HLA B57 who do not maintain HIV specific responses against a specific HIV nef epitope, HW9, are more likely to have progressive disease than HLAB57 people who maintained such responses.¹⁰⁷

Gender differences

Some studies have demonstrated that women develop AIDS at higher CD4 cell counts than men.¹⁰⁸ However, this difference may be explained by decreased access to care rather than biological effects. Conversely, other studies have demonstrated that, for a given CD4 cell count, women have up to 0.3 log₁₀ lower plasma HIV viral load than men.¹⁰⁹ This difference is most apparent in the four years following seroconversion.¹¹⁰ After this time, women experience greater rises in plasma viral load. This late rise in viral load in women may account for the lack of gender differences in disease progression observed in other cross-sectional studies.¹¹¹ The underlying mechanisms for these observed differences remain undefined. No gender differences have been demonstrated in clinical progression following seroconversion.¹¹²

Viral factors

Multiple viral factors have been associated with altered HIV disease progression including deletion of certain viral genes; coreceptor usage; viral subtype and replicative capacity. Viral factors which were associated with slower progression rates included attenuated viruses such as nef-deleted isolates.¹¹³ People with dual tropic (or mixed R5 and X4) viral populations progressed to AIDS 3.8 times more rapidly, independent of CD4 cell count and viral load, than those with only R5 isolates at baseline.¹¹⁴ Viruses, which use the CXCR4 coreceptor, are more pathogenic than other strains: they form syncytia (giant, multinucleated cells) *in vitro* and were previously described as syncytium-inducing variants. In contrast, R5 viruses are less pathogenic than X4 viruses: they do not form syncytia *in vitro* and were previously termed non-syncytium-inducing variants. Transmission of X4 strains, which occurs rarely, is associated with accelerated disease progression. A recent case of acquisition of a dual tropic, multidrug resistant isolate with high replicative capacity was reported to be associated with rapid disease progression.¹¹⁵ The viral coreceptor usage changes from R5 to X4 in up to 40% of patients during the course HIV disease. A coreceptor switch changes the viral phenotype and is associated with acceleration in CD4 cell loss and disease progression.¹¹⁶ Subjects with syncytium-inducing (X4) variants are seven-times more likely to progress to AIDS over a 30-month period. In the 60% of individuals who do not demonstrate a change from R5 to X4, it is unclear why there is accelerated disease progression, but this may be secondary to a change in affinity for CD4 or co-receptors.

Viral subtype is an independent predictor of HIV disease progression. Women with the Brazilian variant of subtype B HIV infection had a faster progression of HIV disease than women with other subtype B variants.¹¹⁷ People with subtype A HIV infection have slower rates of disease progression relative to

subtype D and other subtypes.¹¹⁸⁻¹²⁰ Viral subtypes may also differ in their capacity to be transmitted. Subtype C is associated with increased vaginal shedding.¹²¹ Viral replication capacity has been shown to be associated with CD4 cell decline but not to viral load. People infected with viruses with high replicative capacity were more likely to have faster rates of CD4 cell decline independent of plasma viral load.¹²²

GB virus-C

The flavivirus GB virus-C (GBV-C), previously designated hepatitis G, may have a protective effect on HIV disease progression.¹²³⁻¹²⁵ People with GBV-C co-infection have reduced mortality, increased survival post-AIDS and lower plasma viral loads compared with people with HIV without GBV-C infection. Increases in CD4 cell counts have been demonstrated in some,¹²⁶ but not all studies of people with HIV/GBV-C co-infection.¹²³ As GBV-C and HIV share transmission routes, co-infection is common and has been demonstrated in between 16 - 40% of people with HIV in the USA. This compares with a prevalence of GBV-C in 2% of volunteer blood donors and 20% of intravenous drug users in the USA.^{127,128} *In vitro* studies have demonstrated that GBV-C inhibits HIV replication by inducing the production of chemokines, which may inhibit HIV replication and reduce the expression of coreceptors on the surface of T-cell.^{129,130} This is in keeping with the observation that persistent infection is required for delayed progression as people who clear GBV-C infection have higher mortality rates than those with persistent infection.⁴⁷ At present a causal relationship has not been proven.

Other predictors of HIV disease progression

Behavioural factors, drug-use behaviour, and intercurrent STIs are not associated with an increase in disease progression,¹³¹ although certain behaviours have been associated with a poorer response to cART. The mode of acquisition of HIV infection does not influence HIV disease progression rates.¹³²

3.3 Serious non-AIDS events

The causes of death in people with HIV infection have shifted from traditional AIDS-related illnesses to serious non-AIDS events since the introduction of cART. The most common of these are: atherosclerotic cardiovascular disease, non-AIDS-defining malignancies, liver disease and renal disease.¹³³ There is a gradient of risk, which reduces with increasing CD4 count. Fatal liver disease and fatal non-AIDS malignancies are more common in people with lower CD4 counts.^{134,135} However, people with high CD4 cell counts remain at risk of serious non-AIDS events. The risk of serious non-AIDS events in people with HIV infection is greater than for people without HIV after accounting for other risk factors such as smoking.

The exact mechanisms underlying the increased risk of serious non-AIDS events associated with HIV-induced immunodeficiency remain to be defined. Immune activation, as previously described, is a marker of HIV disease progression and a key determinant of CD4 depletion. People who cease antiretroviral therapy have an increased chance of developing serious non-AIDS events and also experience increased levels of immune activation.¹³⁶⁻¹³⁸

Early randomised data suggest that antiretroviral therapy may decrease the risk of serious non-AIDS events in people with CD4 counts > 350/μL.¹³⁹ HIV infection also results in an inflammatory response, which has been demonstrated to activate the

coagulation system.¹⁴⁰ Increased D-dimer levels have been related to cardiovascular disease in people without HIV infection and may be relevant to cardiovascular risk in people with HIV infection on cART.¹⁴¹

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