HIV-1 evolution and adaptation to the host during the course of infection
Gijsbers, E.F.

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SUMMARY

The clinical course of human immunodeficiency virus type 1 (HIV-1) infection is highly variable between individuals. Most patients show an average course of infection, with progression to acquired immunodeficiency syndrome (AIDS) approximately 8 years after infection in the absence of antiretroviral therapy. However, some patients show rapid progression within two years after infection or spontaneous control of infection for more than 20 years without the use of treatment. Prolonged survival after HIV-1 infection in so-called long-term nonprogressors (LTNPs) has been associated with the expression of certain human leukocyte antigen (HLA) class I alleles, such as HLA-B57/5801 and HLA-B27, and with strong cytotoxic T lymphocyte (CTL) pressure. However, the presence of a protective HLA allele does not guarantee a favorable course of the infection; about half of the HIV-infected patients carrying these HLA alleles exhibit a typical course of infection.

HIV-1 continuously adapts to the high selective pressure exerted by the immune system, which results in the frequent emergence of escape mutations in CTL epitopes. Although the escape mutations allow evasion of the CTL response, viral escape is not always associated with disease progression as some mutations come at a fitness cost, particularly when situated in conserved viral regions. The T242N mutation in the HLA-B57/5801-restricted TW10 CTL epitope in Gag has been demonstrated to decrease the viral replication capacity, which can explain the protective effect of this HLA type even after escape from CTL responses has occurred. Previously, it was described that virus isolates from HLA-B57/5801 LTNPs and progressors contained multiple CTL escape mutations, and that these escape mutations were not associated with disease progression. However, compensatory mutations within or flanking the TW10 epitope can partially restore replication capacity and viral isolates from HLA-B57/5801 progressors obtained late in infection showed better replication fitness than viral isolates obtained early in infection. In chapter 2, we compared Gag sequences from HLA-B57/5801 LTNPs and progressors to identify compensatory mutations that restore the replication kinetics of CTL escape viral variants. In sequences from HLA-B57/5801 progressors, frequent variation in the amino acid composition was observed at 5 positions in Gag (S126N, L215T, H219Q, M228I and N252H). The combination of these mutations restored the replication fitness of CTL escape HIV-1 variants, which may explain the differences in disease progression. The number of escape and compensatory mutations in Gag correlated with the replication fitness of biological HIV-1 variants isolated from HLA-B57/5801 patients, suggesting that the replication fitness of HLA-B57/5801 escape variants is restored by accumulation of compensatory mutations.

Variation in disease progression was also observed in three homosexual men from a proven homosexual HIV-1 transmission cluster. In chapter 3, we evaluated the effect of viral evolution in the capsid protein on replication fitness of viral variants obtained from these three patients. Viral Gag sequences from all three patients contained a mutation at position 242 (T242N or T242S), which has been associated with lower viral replication. Interestingly, HIV-1 variants from patients with a progressive clinical course of infection developed compensatory mutations within capsid that restored viral fitness, instead of reversion of the 242S mutation. Restoration of the viral replication fitness in these patients may have contributed to disease progression and might explain the differential clinical disease course in the three patients. In HIV-1 variants
from the third patient, an HLA-B57 elite controller, no compensatory mutations that restored the viral fitness emerged during follow-up.

Like HLA-B57/5801, HLA-B27 has been associated with prolonged AIDS-free survival after HIV-1 infection. Loss of control of viremia in HLA-B27 patients has been associated with CTL escape at position 264 in the immunodominant KK10 epitope in Gag. This CTL escape mutation has a high fitness cost and it has been hypothesized that this mutation is not viable on its own, but requires the presence of compensatory mutations before emerging. In chapter 4, we studied sequence evolution within HLA-B27-restricted CTL epitopes in the viral Gag protein during disease progression in four HLA-B27 positive patients. Sequence variation was predominantly observed in the immunodominant HLA-B27-restricted KK10 epitope and CTL escape mutations in this epitope were observed in sequences obtained from three out of four patients. The R264K mutation was observed in sequences from one patient and the R264G escape mutation in sequences from two patients. These CTL escape mutations were accompanied by their respective compensatory mutations S173A and E260D. Comparing viral sequences, a higher number of total mutations in Gag was observed for viruses containing the R264K escape mutation, which may represent additional compensatory mutations that increase replication capacity and impact disease progression.

Mother-to-child HIV-1 transmission pairs represent a good opportunity to study the dynamics of CTL escape and reversion after transmission in the light of shared and non-shared HLA alleles. In chapter 5, viral evolution and the dynamics of CTL escape mutations and reversion of these mutations after transmission from mother to child were studied. Inside CTL epitopes restricted by non-shared and shared maternal HLA alleles, only a limited number of reversions was observed, which suggests CTL escape mutations that have been transmitted did not come at a fitness cost or that the fitness cost had already been compensated for in the mother. The highest numbers of forward mutations in viral sequences from these children were found within predicted CTL epitopes restricted by HLA alleles inherited paternally, indicating that viral evolution in the children is at least in part driven by CTL responses restricted by paternal HLA alleles.

In the majority of new HIV-1 infections, outgrowth of a single viral variant is observed. Throughout HIV-1 infection the viral population diverges and viral diversity increases over time. In chapter 6, we investigated whether the degree of viral diversity in env early in infection, as determined by heteroduplex mobility assay (HMA) and sequencing, was predictive of the subsequent disease course in adult males who were infected through homosexual transmission. Viral diversity early in infection was an independent predictor of accelerated disease progression. It is likely that viral diversity can be restricted by both the humoral and cellular immune response as well as target cell availability, and it remains to be established whether viral diversity itself plays a causal role in the increased damage to the immune system or whether it is a reflection of immune pressure or other selective forces.

HIV-1 entry into target cells is mediated by binding of the viral envelope to CD4 and one of the coreceptors, CCR5 or CXCR4. The majority of HIV-1 infections is established by the outgrowth of viral variants that can only use CCR5 for entry. CXCR4-using viral variants (X4-HIV) emerge during the course of infection in at least half of patients infected with HIV-1 subtype B, and in the absence of antiretroviral therapy, the emergence of X4-HIV variants is associated with accelerated CD4+ T cell decline and an accelerated disease progression. In chapter 7,
the effect of the presence of X4-HIV before start of treatment on the subsequent response to combination antiretroviral therapy (cART) was studied. We observed that patients harboring X4-HIV variants at baseline showed a delay in time to achieve viral suppression below the viral load detection limit, which was independent of viral load at baseline. Although no differences were observed in the CD4+ T cell increase after treatment initiation between patients with or without X4-HIV at baseline, the absolute CD4+ T cell counts were significantly lower in patients harboring X4-HIV variants at all time points. This indicates that patients harboring X4-HIV variants initiated cART with lower CD4+ T cell counts, which might be a consequence of the accelerated CD4+ T cell decline associated with X4-HIV. Therefore patients may benefit from earlier treatment initiation to obtain a better reconstitution of the CD4+ T cell population.

Taken together, the studies in this thesis describe HIV-1 evolution during infection and the effect of viral adaptation on the course of infection and treatment response. Insight in the mechanisms of viral adaption to the host, and to a population over time, enhances our knowledge regarding the interaction between HIV-1 and its host.