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Clinical Relevance of HIV-1 Superinfection

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1. Introduction

Over time a single patient can be infected by multiple intra- or intersubtype human immunodeficiency viruses type 1 (HIV-1) strains. These so-called dual infections are divided into co-infections and superinfections. HIV-1 co-infection is described as a second infection taking place before measurable HIV-1 antibody production by the immune system (seroconversion) and HIV-1 superinfection is defined as a second infection occurring after seroconversion. Here the focus lays on superinfections, which have implications for HIV-1 transmission, treatment and vaccine development (Gottlieb et al., 2004). Moreover superinfections can give rise to HIV-1 circulating recombinant forms (CRF); this significantly increases the global epidemiology (Gottlieb et al., 2007). Also due to these recombination events, two different drug resistant HIV-1 viruses could lead to multi drug resistance or even to more pathogenic viruses (Gottlieb et al., 2004, Blackard et al., 2004, Fernandez Larrosa et al., 2006).
Another important issue that is not extensively surveyed in literature is the clinical relevance of HIV-1 superinfection, as most descriptions rely on case reports and not on controlled cohort studies. The individual cases differ in severity, as several superinfected patients with rapidly progressive HIV-1 disease have been described since 2002, but superinfection cases were also found by coincidence in long-term non-progressors (LTNPs). These patients were able to control HIV-1 disease before and sometimes also after the superinfection event. So it is not resolved yet how superinfection affects disease progression in general and, if any, specific host or viral factors are involved. In this chapter, first an overview will be given of HIV-1 superinfected patients from several studies, with regard to HIV-1 disease progression. Disease progression is indicated by an increase in the HIV-1 plasma viral load, a decrease in the CD4+ T-cell count, acquired immunodeficiency syndrome (AIDS) related events and/or the start of antiretroviral treatment. These outcomes are compared to values of disease progression for single HIV-1 infected patients, resulting in an indication of the clinical relevance of HIV-1 superinfection.

2. Experimental studies with multiple lentivirus strains

An in vitro HIV-1 superinfection system for the analysis of viral dynamics and production of pseudotypes was used by Fernandez Larrosa et al. (2006). In vitro superinfected cells showed higher cell mortality, favoured viral spread and enhanced viral replication compared to non-superinfected cells. The results suggest that HIV-1 superinfection could

result in progressive disease, as viral replication, a marker of pathogenicity, is enhanced after superinfection. A second study also showed that superinfection of cells infected with a defective HIV-1 virus, with a second replication-competent strain, results in the production of highly cytopathogenic HIV-1 particles (Iwabu et al., 2006).

In an in vivo cat model, both co- and superinfection compared to monoinfection with the related lentivirus feline immunodeficiency virus (FIV) increases neuroinflammation and subsequent neurodegeneration in the cat brain, also indicating enhanced pathogenicity (Afkhami-Goli et al., 2009).

A mathematical model of the within-host dynamics of HIV superinfection suggested that only superinfection with a fitter strain will lead to faster progression to AIDS (Fung et al., 2010). Probably, the HIV-1 superinfections in patients that are clinically detected are productive superinfections that indeed largely occur with fitter strains (Kozaczynska et al., 2010). Superinfections with less-fit strains may go unnoticed in vivo due to a low or localized replication of the less-fit strain. Another computer simulation study suggested that regulated superinfection of single cells might increase HIV-1 fitness through recombination (Leontiev and Hadany, 2010). Enhanced viral fitness is often associated with increased replication and pathogenicity. If different strains superinfect single cells, adaptation of HIV-1 could be more optimal than if only a single strain is present. Superinfection should be regulated so that competition for host resources does not result in less virions produced per cell as compared to single infected cells. If that happens, superinfection will not increase viral fitness. However, the authors speculate that HIV-1 is able to regulate superinfections by multiple virions. Indeed, this phenomenon is called superinfection resistance (SIR), and has been observed for many retrovirus infections (for a review, see: Nethe et al., 2005). SIR can be induced by simply down-regulating the virus receptor on the cell surface, but more complex retroviruses, such as HIV, often carry accessory genes specifically involved in resistance to superinfection of an already infected cell.

Thus, the few in vivo (FIV), in vitro (HIV-1) or in silico (HIV-1) studies that have been performed with lentiviruses with emphasis on growth characteristics, suggest that infection with multiple strains results in enhanced replication capacity, fitness and pathogenicity.

3. Disease progression in HIV-1 single infected patients

3.1 Markers of disease progression

Accepted indicators for HIV disease progression, especially in the post-ART (antiretroviral therapy) era, are increases in the plasma viral load and/or decreases in the CD4+ T-cell count below a certain limit (Mellors et al., 1997), although these markers are not clearly correlated (Rodríguez et al., 2006), and should preferentially be combined (Mellors et al., 1997). Korenromp et al. (2009) collected and analysed longitudinal viral load and CD4+ T-cell count data from untreated HIV-1 infected patients included in 30 studies and 16 cohorts, from the moment of seroconversion. The plasma viral loads of these patients ranged between 3.7 $\log_{10}$ and 5.6 $\log_{10}$ copies/ml, with an overall median of 4.4 $\log_{10}$ copies/ml. No significant change was seen in this median viral load for over 8 years. Mean CD4+ T-cell counts decreased from 600 to 360 cells/µl in 8 years. This is in agreement with the typical progression to AIDS in untreated HIV-1 infected patients within 8-10 years after infection (Gottlieb et al., 2004). However, the course of infection is variable; with approximately 5% of HIV-1 infected patients developing AIDS within 3 years, whereas up to 12% of the infected patients remain free of AIDS for over 20 years (Mellors et al., 1997).

The viral setpoint, e.g. the plasma viral load level stabilization after the acute infection period, has been found to be highly predictive of the rate of disease progression (Geskus et al., 2007). However, another study found that setpoint and disease progression are only linked in patients of European descent, and not in Africans (Müller et al., 2009).
Nowadays, HIV-1 disease progression until the occurrence of an AIDS-defining event or death from AIDS as a clinical end-point is replaced with CD4+ T-cell count decline to a certain level (mostly the level that indicates start of ART) or the start of antiretroviral treatment. Treatment is currently initiated in most western countries when CD4+ T-cell levels are below 350 cells/μl.

3.2 Disease progression profiles among risk groups

HIV-1 incidence varies among risk groups. Some risk groups in the western world, for example men having sex with men (MSM) and intravenous drug users (IDUs), have a high risk of acquiring HIV-1. The route of infection could be related to the type of initial immune response, which could theoretically influence the pattern of disease progression.
Pehrson et al. (1997) compared the disease progression parameters for HIV-1 infected MSM and IDUs, using the criteria of AIDS defining events and death from AIDS as endpoint markers. They observed a significant lower HIV-1 disease progression for IDUs. A similar outcome was found in an Italian study of 1078 HIV-1 seroconverters, were IDUs began antiretroviral therapy significantly later than homo- or heterosexual patients, even when corrected for CD4+ T-cell counts (Dorrucci et al., 1997). Such a difference in disease progression between MSM and IDUs was not seen in 12 European cohorts, where only a higher pre-AIDS mortality was obvious for IDUs (Prins and Veugelers, 1997). A similar outcome was seen in the Swiss Cohort Studies, where a uniform mortality risk was found among the sexes and risk groups, with only an increased risk of death for IDU without CD4+ cell depletion at entry, also probably not attributable to HIV-1 infection (van Overbeck et al., 1994). In homosexual men from different continents, no differences were found in time to development of AIDS, and also year of infection (before or after 1985) did not affect disease progression (Biggar, 1990). Adults with haemophilia infected through blood transfusion progressed slower towards AIDS than homosexual men before the introduction of ART due to the highly increased risk of Kaposi's sarcoma in the latter group (Biggar, 1990).
Overall, an age-related effect was seen whereby younger age at seroconversion was mostly beneficial (Biggar, 1990; Rosenberg et al., 1994; Collaborative Group on AIDS Incubation, 2000). However, perinatally infected children were found to have a much lower survival in the pre-ART era than children infected post-natally from breastfeeding (Marston et al., 2011).
Gender differences between men and women have also been reported, with women generally having lower initial HIV-1 plasma viral loads independent of exposure group, e.g. heterosexual or IDU (Rezza et al., 2000) or within an IDU cohort (Sterling et al., 2001), but this difference was not associated with lower disease progression rates (Sterling et al., 2001).
Concluding, disease progression profiles after HIV infection do generally not differ within and between risk groups. HIV-1 infected individuals do show variation in progression over time depending on the specific host characteristics, which includes age at seroconversion. For a review on this topic with similar conclusions, see: Hessol and Palacio (1996).

3.3 Disease progression in relation to HIV-1 subtype

HIV-1 group M is a highly variable virus. By now 9 subtypes (named A-D, F-G, J-K) are circulating worldwide accompanied by at least 48 described CRF's (circulating recombinant forms) and numerous URF's (unique recombinant forms) (Hemelaar et al., 2011). Distribution of these virus strains is variable, with all strains being present in Africa, but specific strains dominating epidemics on other continents. For an overview of the geographical distribution of HIV-1 strains in 2000-2007, see: Hemelaar et al. (2011).

It is reasonable to assume that HIV-1 isolates differ in their pathogenicity. Indeed, attenuated circulating virus strains that promote long-term disease free survival have been described, e.g. a nef-deleted strain found in Australia among blood-product recipients (Deacon et al., 1995). It is less clear if subtypes in general also differ in their capacity to induce AIDS, irrespective of host genetics. Most studies, mainly in African women, that describe a difference indicate that subtype D induces faster disease progression, especially when compared with subtype A (Kanki et al., 1999; Kaleebu et al., 2001; Vasan et al., 2006; Baeten et al., 2007; Kiwanuka et al., 2008). One Swedish/African study found similar rates of disease progression among persons infected with either subtypes A, B, C or D (Alaeus et al., 1999), in line with an Israeli study that showed no differences in progression between Ethiopian immigrants infected with subtype C and Israeli homosexual men infected with subtype B (Galai et al., 1997). In contrast, Singaporese seroconverters infected with CRF01_AE had an increased rate of CD4+ T-cell decline and a shorter time to initiation of ART than their non-CRF01_AE infected counterparts (Ng et al., 2011).

Env-V3 loop variation within a subtype can also affect disease progression, as Brazilians infected with a variant subtype B strain (B'-GWGR motif) had a lower progression towards AIDS and a lower chance of experiencing AIDS-defining events than Brazilian patients infected with the US/European subtype B strain (B-GPGR motif) (Casseb et al., 2002; de Brito et al., 2006).

Concluding, it is not unlikely that some subtypes, primarily subtype D and possibly CRF01_AE are more pathogenic than other HIV-1 subtypes, but generally subtypes do not differ appreciably in disease-inducing potential. However, when comparing disease progression in cohorts, it would be advisable to mainly evaluate patients infected with a certain subtype or recombinant form.

3.4 Disease progression in relation to host genetics

Infection of a host species by a pathogen is counteracted first by the innate and secondly by the adaptive immune system. The immune system of vertebrates has evolved into a highly variable gene complex, so that immune responses between individuals can differ depending upon the specifically inherited alleles.

Genome-wide association studies have suggested that the major genetic variation associated with control of HIV infection in humans is found in the Major Histocompatibility Complex (MHC) located on chromosome 6 (Fellay et al., 2007; International HIV Controllers Study, 2010). Decreased disease progression and lower plasma viral load at setpoint have been associated with carrying MHC class I alleles HLA-B*2705, HLA-B*5701/02/03 and HLA-B*5801 (reviewed by Goulder and Watkins, 2008, for a specific study, see: Altfeld et al., 2003). Rapid disease progression and high plasma viral load at setpoint is found in individuals carrying HLA-B*1801, HLA-B*3502/03, or HLA-B*5802 alleles. However, it has been observed that HIV-1 strains are escaping from HLA-B pressure (Goulder et al., 2001;

Cornelissen et al., 2009). Immune escape had already been described for individual patients, but more importantly, it is now also visible in the general epidemic.
Specific HLA alleles differ in their distribution worldwide, so that HIV disease progression related to HLA variation can differ not only between individuals, but also between populations. In a Swiss cohort study, a lower average CD4+ T-cell decline was seen for patients from African descent compared with Europeans (Müller et al., 2009). Earlier in a UK cohort, it was already observed that African descent was associated with lower plasma viral load after correction for CD4+ T-cell counts, compared with European ancestry (Smith et al., 2003). However, an earlier in-depth analysis of published studies did not reveal obvious differences in progression towards AIDS-defining events in correlation with race or ethnicity (Hessol and Palacio, 1996). Probably, in a certain population advantageous and disadvantageous alleles are generally more or less balanced, and other cofactors are also of importance. Therefore, although the inherited HLA type is important for the individual patient with regard to disease progression, ethnicity itself is no indicator for (loss of) control of HIV replication.
Variation in other genes is also implicated in disease progression rates, be it delayed or accelerated (reviewed by Fellay, 2009). Especially polymorphisms in the chemokine receptors CCR2 and CCR5 promoter regions have been found to be influential, as is the CCR5-Δ32 variant that is only present in Caucasians. In a large study on HIV controllers, the only variation outside the MHC-I regions that was significantly associated with control of infection, were polymorphisms in CCR2/CCR5, albeit only in European samples (International HIV Controllers Study, 2010).
Concluding, host genetic variation is important in HIV-1 disease progression, but it is not practically possible to compare only individuals with a similar genetic make-up. Also, viral factors are important, making disease outcome in the individual patient a trade-off between host and viral genetics. Besides, HIV might be in the process of circumventing adverse host factors, as is ongoing for some HLA-B alleles. Another important issue is the level of expression of a certain trait, e.g. how well functions the adaptive immune system, and the balance between traits is of importance. Consequently, one has to recognize that host (and viral) genetics influence disease progression, but is complicated in practice to draw firm conclusions, even when genetic information would be entirely available.

4. Clinical progression and HIV-1 superinfection

4.1 HIV-1 superinfection: Introduction

In the earlier days of the epidemic, many were sceptic about the existence of HIV-1 superinfections, e.g. a re-infection with an unrelated HIV-1 strain after seroconversion. For some time, it was assumed that infection with HIV would protect against such a second infection. Recombinant strains observed already early in the epidemic were explained as having been generated by HIV co-infection during the acute, early phase of the infection when the adaptive immunity is not fully developed, or be the ultimate result of long-term evolution (Gonzalez et al., 2003).
The first reported HIV-1 superinfection was detected in an MSM who experienced an acute retroviral syndrome in 1998 after infection with a CRF01_AE strain, and who was superinfected with a HIV-1 subtype B strain in 2001 (Jost et al., 2002). In the same year a second HIV-1 superinfected patient was described, another MSM who controlled initial HIV-1 infection after supervised ART interruption (Altfeld et al., 2002). Although many

researchers did not find HIV-1 superinfections when examining their diverse cohorts (Tsui et al., 2004; Diaz et al., 2005), many others did, so that the concept of HIV-1 superinfection being a regular event was gradually accepted. For example, Hu et al. (2005) identified two superinfected individuals amongst 80 HIV-1 infected Thai IDUs with a sample available 12 months after seroconversion, and concluded that superinfection is not an uncommon event. In several cohorts, especially in Africa, sometimes high incidences of HIV-1 dual infections were found (Manigart et al., 2004; Chohan et al., 2005; Piantadosi et al., 2007), so that the authors reached conclusions similar to Hu et al. However, most studies do not report on clinical progression of the superinfected individuals, leaving the question whether or not HIV-1 superinfection is harmful to the individual patient.

4.2 Superinfection cases with rapid clinical progression

Gottlieb et al. (2004) found amongst 34 HIV-1 positive patients, 4 patients who were co-infected with HIV-1 (3 MSM and one African female sex worker) and one MSM who was intrasubtype superinfected with HIV-1 subtype B. He had a rapid CD4+ T-cell decrease after initial infection and became superinfected approximately 1 year after seroconversion (Gottlieb et al., 2007). Antiretroviral treatment was initiated half a year after superinfection. In these five patients, a CD4+ T-cell count of <200 cells/μl was reached <3.1 years after seroconversion and AIDS-defining events occurred <3.4 years after seroconversion. Due to the rapid disease progression in HIV-1 dually infected patients, including a superinfected patient, compared with single infected patients; the authors suggested a general association between dual infection and HIV-1 disease progression.

A fast progressing MSM, reaching an AIDS diagnosis within 1.5 years from primary infection and infected with two unrelated HIV-1 populations early in infection, had already been reported in 1997 (Liu et al., 1997). It was, however, in this study unclear whether the source partner had a dual infection or whether the second HIV-1 population in this patient originated from a second source.

Published reports on rapid disease progression after HIV-1 superinfection are rare, and only one of them concerns an actually confirmed superinfection (Gottlieb et al., 2004). In single HIV-1 infection cases, rapid progression to AIDS is also infrequent, and estimated to occur in only 5% of patients.

4.3 Superinfection cases with markers of increased clinical progression

The first case of superinfection to be described involved an MSM with initial CRF01_AE infection who acquired a subtype B superinfection when interrupting his ART regimen (Jost et al., 2002). The superinfection was accompanied by transient fatigue and fever, a rebound in the plasma viral load remaining at 200,000-400,000 copies/ml and a steady decline of the CD4+ T-cell count. ART was resumed four months after the rebound in plasma viral load.

In a Swiss IDU cohort, two CRF11_cpx superinfections after initial subtype B infection were found in chronically infected patients that had low viral loads without antiretroviral treatment for years (Yerly et al., 2004). In both patients, a Caucasian female and an African male patient, HIV-1 superinfection was associated with an acute retroviral syndrome, stably increased viral loads and a significant decrease of the CD4+ T-cell counts.

Three HIV-1 superinfection cases were reported from a North American Acute Infection and Early Disease cohort of HIV infected patients (Smith et al., 2004). The superinfections occurred within 6-12 months from primary infection, and were associated with a

unfavourable change in disease markers. Within 6 months of superinfection, the plasma viral loads of these 3 patients increased with a mean of 1.6 $\log_{10}$ copies/ml and the CD4+ T-cell count decreased with a mean of 132 cells/µl. Two of the three individuals were initially infected with a drug resistant HIV-1 strain and became superinfected with a wild-type strain. The third individual was initially infected with a wild-type strain and became superinfected with a drug resistant strain (see also: Smith et al., 2005). In all individuals the superinfecting strain was fitter than the initial infecting strain, so that a change in antiretroviral susceptibility was seen. In two individuals the wild-type superinfecting strain masked the initial drug resistant strain.

A similar observation was published by Koelsch et al. (2003), were a male patient initially infected with a subtype B drug-resistant strain was superinfected with a wild-type subtype B strain four months later. After primary infection, the patient had a low viral load of around 6000 viral RNA copies/ml at setpoint, in line with the finding that drug-resistance mutations often decrease viral fitness (see: De Luca, 2006). After superinfection, the viral load increased sharply to 200,000 copies/ml and CD4+ T-cells declined steadily from 792 cells/µl at enrolment to ± 500 cells/µl four months post-infection (immediately before superinfection) till 283 cells/µl eleven months post-infection (approximately 7 months after superinfection), suggestive of increased disease progression.

Drug-resistant virus strains have also been identified in further superinfection cases. An MSM first infected with a multidrug resistant HIV-1 subtype B strain was superinfected 10 months later with another multidrug resistant subtype B strain from a new partner (Brenner et al., 2004). The first infection was associated with low viremia: 1305 copies/ml decreasing to undetectable levels without antiretroviral treatment four months after infection. Superinfection was associated with a rise in the plasma viral load from undetectable levels to 13,888 copies/ml. CD4+ T-cell counts were not documented during that time, although they were very high after the acute infection phase (1200 cells/µl).

In a cohort of female South African sexworkers infected with HIV-1 subtype C, many intrasubtype dual infections were observed during primary infection (Grobler et al., 2004). It was unclear how many of these dual infections could be attributed to early superinfections. Dual infection was significantly associated with an elevated viral setpoint compared to the single infected patients. No superinfections were detected in any patient during follow-up.

A triple HIV-1 infection in a Dutch MSM was reported by van der Kuyl et al. (2005). In March 2001 the patient was diagnosed with an HIV-1 subtype B infection. His plasma viral load was then approximately 3.4 $\log_{10}$ copies/ml and his CD4+ T-cell count was around 850 cells/µl. Retrospective analysis showed that he became superinfected with another subtype B strain in October 2002. His plasma viral load was then 4.5 $\log_{10}$ copies/ml with a CD4+ T-cell count of 550 cells/µl. No medical symptoms were reported by the patient around the time of the first superinfection. However, in July 2003, the patient presented with acute fever and an increased plasma viral load of 6 $\log_{10}$ copies/ml and a decreased CD4+ T-cell count of 300 cells/µl. Analysis of the viral genotype indicated that he was again superinfected, this time with a CRF01_AE strain. After the second superinfection, the plasma viral load stabilized at an increased level while the CD4+ T-cell counts continued to decrease. Therefore, ART was initiated in June 2005, two years after the second superinfection.

An African female barworker, who was initially infected with a HIV-1 ACD recombinant strain, became superinfected 6 till 9 months after seroconversion with an AC recombinant strain. At that time, the plasma viral load was 5.6 $\log_{10}$ copies/ml (McCutchan et al., 2005), while CD4+ T-cell counts were unavailable. Six months after seroconversion, the patient

showed recurring short episodes of malaise, fever, cough, diarrhoea and had moderate weight loss, symptoms indicative of an acute HIV infection. Genotyping indeed indicated that a superinfection with an AC recombinant strain had occurred around that time. Three months after superinfection a setpoint value of 4.8 $\log_{10}$ copies/ml was maintained, while CD4+ T-cell count declined from 482 cells/µl to 377 cells/µl 24 to 30 months after primary infection, suggestive of increased disease progression.

An Asian-American MSM presenting with an acute HIV-1 infection syndrome was found to be infected with a multi-drug resistant HIV-1 subtype B strain, of which he controlled viremia after the acute infection period (Yang et al., 2005). His viral load was 1000 copies/ml, and his CD4+ T-cell count rose above 600 cells/µl after an initial decline to 396 cells/µl). However, before he could reach long-term non-progressor status, he was superinfected 4 months later with a distinct, drug-sensitive subtype B strain. Viremia immediately rose to 30,000-40,000 copies/ml with a concomitant decline in CD4+ T-cell counts to 450 cells/µl. Ten months after the first infection CD4+ T-cell counts decreased further to <400 cells/µl.

Smith et al. (2006) described 3 superinfected homosexual male patients from the USA and compared them to 11 control patients primarily to analyse (neutralizing) antibody profiles. Over the study period (6 months after first antibody measurement), viral loads (ΔHIV RNA) showed a significant increase ($p=0.02$) in the superinfected patients compared to the control group, but there was no statistically significant difference ($p = 0.29$) in the CD4+ T-cell count reductions (ΔCD4) between the groups.

Reports describing increased disease progression, mainly inferred from rising plasma viral load or decreasing CD4+ T-cell counts, but not always in combination, are more common. In some cases, increasing plasma viral load can be attributed to re-infection with a virus that has higher replication capacity, e.g. in the case of infection with a drug-sensitive virus after primary infection with a drug-resistant strain. Also, in other cases with enhanced progression, superinfection could have occurred with a fitter strain. Possibly, cases with increased disease progression are more easily detected, as patients suddenly presenting with adverse clinical characteristics are more likely to be scrutinized.

4.4 Superinfection cases with low or normal clinical progression

HIV-1 superinfection events in IDU's which did obviously not result in enhanced disease progression were reported from Thailand (Ramos et al., 2002). In October 1996, a female patient was found to be infected with the recombinant strain CRF01_AE. She became superinfected with HIV-1 subtype B, probably 3-6 weeks after initial infection. Her plasma viral load varied within 2 logs (mean 4 $\log_{10}$ copies/ml), while the CD4+ T-cell counts remained around 500 cells/µl, only dropping below this number once. A second, male patient was identified with an initial HIV-1 subtype B infection in August 1996. He became superinfected 5-9 months later with strain CRF01_AE and experienced fluctuating viral loads between 3.7 $\log_{10}$ and 4.9 $\log_{10}$ copies/ml for 3 years. His CD4+ T-cell counts remained >500 cells/µl. Both patients showed at the time before superinfection limited or absent specific T-cell and antibody immune responses (see also: Promadej-Lanier et al., 2009).

Analysis of a Swiss IDU cohort revealed three subtype B/CRF11_cpx co-infected patients and a transient subtype B superinfection in an initially CRF11_cpx infected female individual in a cohort with recent HIV infection (Yerly et al., 2004). No symptoms were associated with the transient superinfection, and both the plasma viral load and CD4+ T-cell counts were stable in this patient.

Manigart et al. (2004) reported 2 superinfected women out of 147 HIV-1 infected commercial sex workers in a cohort from Burkina Faso. In November 1999 the first woman was found to be single infected with CRF02_AG. In samples from January 2001 onwards, a second virus strain, CRF06_cpx, was always present. Plasma viral load levels increased till July 2001, with a steady decline thereafter. A second woman was found to be HIV-1 seropositive with a CRF02_AG infection in March 2000 and a plasma viral load of around 55,000 copies/ml. A subsequent superinfection with CRF06_cpx occurred before November 2000 with a tripling of the plasma viral load in the November 2000 sample. Thereafter, her plasma viral load decreased to 11,000 copies/ml. Unfortunately, she was lost to follow-up after she died in 2001 from obstetric complications.

A superinfected Kenyan female sex worker from the pre-antiretroviral therapy period was presented by Fang et al. (2004). In February 1985, this patient from Nairobi tested HIV-1 seropositive and was, retrospectively, found to be infected with a subtype A strain. In April 1992, at least 7 years after primary infection, she presented an acute febrile illness with chills and had a greatly decreased CD4+ T-cell count (<100 cells/µl) compared with a measurement in March 1991 (794 cells/µl). A superinfection with a subtype C strain was suspected but due to a lack of samples, only in later samples from 1995 and 1997 subtype C sequences could be detected from subtype A/C recombinant strains that had already been formed then. The patient never received antiretroviral treatment. From 1994, symptoms indicating the onset of the AIDS phase, e.g. weight loss, tuberculosis and cryptococcal infection appeared and she died in 1998, e.g. over 14 years after her primary HIV-1 infection (Fang et al., 2004). In this cohort of sex-workers, mean survival was 4.4 years, and surviving over 10 years was rare, suggesting that this woman had a remarkably slow disease progression despite an HIV-1 superinfection in the chronic phase of the infection.

Also from Kenya, but now from its second-largest city Mombasa, three additional superinfection cases in a cohort of intermediate risk heterosexual women were described during the 1993-2000 period (Chohan et al., 2005). During follow-up, none of these women received antiretroviral therapy. All three women were inter-subtype superinfected with HIV-1; two women were infected with a subtype D strain and became superinfected with an subtype A strain, while the third women was infected with a subtype C strain and was superinfected with an A/C recombinant strain. The first patient experienced a superinfection 264-385 days after primary HIV infection. Follow-up was done for 2282 days (> 6 years), and during this time her plasma viral load was high (≈ 6 $\log_{10}$ copies/ml), but stable, with no obvious increase at the estimated time of superinfection. The second woman experienced an HIV-1 superinfection 303-591 days after primary HIV infection. She was followed for 2069 days (> 5.5 years), during which her plasma viral load was stable at 5 $\log_{10}$ copies/ml. The third woman became superinfected between 101-485 days after primary HIV infection. During follow-up (1262 days ≈ 3.5 years), her plasma viral load rose from a very low level of 1.7 $\log_{10}$ copies/ml at day 485 to the modest level of 4.1 $\log_{10}$ copies/ml at end-point. It is possible, however, that in this patient, viraemia continues to rise after the 3.5 years of follow-up. But even then, this patient cannot be classified as a fast progressor.

From the same Kenyan cohort, 7 additional HIV-1 superinfection cases were reported two years later (Piantadosi et al., 2007). Four of these women were inter-subtype superinfected, while the other 3 were superinfected with a second strain of the same subtype. The women were superinfected as early as around 2 months after primary HIV infection to as late as 5

years after seroconversion. Plasma viral load changes were measured before and after the superinfection moment, and were either similar or modestly increased in the subjects. Only one of the intra- and one of the inter-subtype infected women showed a 1.5 $\log_{10}$ increase in her plasma viral load. CD4+ T-cell counts measured at the first moment after superinfection ranged between 553-628 cells/µl for 3 patients, between 296-309 cells/µl for 2 other patients, and were not available for the two remaining women. Unfortunately, no CD4+ T-cell counts were available from earlier moments. The two patients with the lowest available CD4+ T-cell counts had both been superinfected around 2.5 years from their primary HIV infection moment, suggesting that the relatively low CD4+ T-cell counts were not necessarily due to an already advanced disease stage. Four patients had viral load data for more than 2 years after superinfection (range 2.1-5 years). In all four, including a patient with 309 CD4+ cells/µl, the plasma viral load was stable at around 5 $\log_{10}$ copies/ml. The other patient with <300 CD4+ T-cells/µl after superinfection also had a stable viral load after approximately one year of follow-up. So, in this female African cohort, HIV-1 superinfection was not correlated with plasma viral load increases. In 2008, two more superinfected women from this cohort were described (Piantadosi et al., 2008). One woman was intrasubtype superinfected with two subtype A strains, and also showed no significant plasma viral load increases after more than 3.5 years of follow-up, although her viral load had increased from 4.3 $\log_{10}$ copies/ml to 4.9 $\log_{10}$ copies/ml directly after superinfection. The other patient, infected with a subtype D strain, did however show continuous plasma viral load increases in the three years after superinfection with a subtype A strain. On the other hand, the plasma viral load of this patient was already increasing during the mono-infection period.

Pernas et al. (2006) described a Spanish HIV-1 triple infected patient who was an IDU but also had unprotected heterosexual contacts. In 1987 this patient became infected with a subtype A HIV-1 strain. Antiretroviral treatment was started in 1996 due to strongly declining CD4+ T-cell counts. Plasma viral load data were only available from 1998 onward. The patient was poorly compliant, and treatment was interrupted several times voluntarily. In 1999, twelve years after primoinfection, the patient was found to have been superinfected, probably at the same moment, with both a subtype B and a subtype C strain. The superinfecting strain B had several drug resistance mutations in the pol gene. After the superinfection moment, the patient's viral load increased steadily from 4.2 $\log_{10}$ copies/ml directly after superinfection till 5.3 $\log_{10}$ copies/ml in 2001. His CD4+ T-cell count decreasing accordingly; from approx. 280 cells/µl directly after superinfection till 55 cells/µl in February 2003.

Patients with no obvious increased disease progression after HIV-1 superinfection have been mainly reported from cohort studies examining viral diversity in general. It is remarkable that most non-progressors described above are women (15 women versus 2 males in the mentioned studies). However, this probably has to do with the time-frame of the studies. Female sex-workers in Africa have probably been exposed to repeated HIV-1 infections from the start of the epidemic due to their risk behaviour. The male cohorts examined mainly consist of MSM from Europe and the USA. In this risk group, risk behaviour, and thus risk exposure sharply diminished after HIV-1 diagnosis before the availability of ART (Rachinger et al., 2010). In line with this reduced risk behaviour, no HIV-1 superinfections were reported from MSM cohorts before the year 2000 (Gonzalez et al., 2003; Rachinger et al., 2010).

4.5 Superinfection cases in long-term non progressors

Long-term non progressors (LTNPs) are HIV-1 infected patients who control viral replication without anti-retroviral therapy to low levels and have stable CD4+ T-cell counts in the normal range for over 10 years. Only a minor group of HIV-1 infected patients are LTNPs (Deeks et al., 2007; Canducci et al., 2009). An even smaller LTNP subgroup is constituted of the so-called elite HIV controllers. Elite HIV controllers are atypical HIV-1 infected patients who have continuous undetectable viral loads of <50 copies/ml, and no decline in CD4+ T-cell count for at least 10 years, also without the help of antiretroviral therapy (Deeks et al., 2007; Clerc et al., 2009).

Casado et al. (2007) reported two HIV-1 infected LTNP patients, who remained in control of their HIV-1 infection even after a potential superinfection. The patients were an IDU who was HIV-1 infected for at least 18 years and an MSM who was infected for at least 20 years. Both had CD4+ T-cell counts of >500 cells/ml, remained asymptomatic and antiretroviral therapy naïve. In time, the IDU had multiple peaks in the viral load and a slow decrease in CD4+ T-cell count whereas the MSM had undetectable viral loads and a steady CD4+ T-cell count. The time of HIV-1 infection for both patients was estimated based on the genetic distance to a reconstructed most recent common ancestor. These calculations suggested that the IDU was most likely co-infected with two HIV-1 subtype B strains, but a superinfection could not be ruled out, and that the MSM became HIV-1 subtype B superinfected 9 years after initial infection. Both patients did not show any indications for faster disease progression after long-term follow-up, suggesting that here a putative superinfection is not associated with progressive HIV-1 disease. However, the presumed superinfection event is based on nucleotide distance estimation, and not on actual sampling, so that the superinfection could in reality be a co-infection and vice versa. Still, no increased disease progression is seen in these two LTNP's, whether or not they have been co- or superinfected.

A haemophiliac harbouring two separate clusters of replication-competent HIV-1 subtype B strains was controlling his HIV-1 infection without antiretroviral treatment and with > 90% of plasma viral load measurements being below 400 copies/ml (Lamine et al., 2007). The patient received contaminated blood products, most likely on distinct occasions. He was thus possibly superinfected, but did not experience disease progression after more than 10 years of follow-up.

An HIV-1 elite controller who showed HIV-1 viremic control before and after superinfection was described from The Netherlands (Rachinger et al., 2008). The patient, an MSM, was diagnosed HIV-1 positive in 1991. His viral load was under the detection limit of the assays used then, and the CD4+ T-cell counts were > 600 cells/µl from 1996 onwards. In May 2005, the plasma viral load of the elite controller increased. In April 2006, the viral load peaked at 25,000 copies/ml. Sequence analysis of the 2006 sample showed that a superinfection with another subtype B strain had occurred. Indeed, the patient reported unprotected sexual intercourse with a new partner at that time. HIV-1 RNA levels continued to decline again till around 1000-2000 copies/ml during November 2006 – March 2008, suggesting that the former elite controller was regaining control of his HIV-1 viremia. CD4+ T-cell counts, however, were slowly declining to 480 cells/µl in March 2008 (approximately 2 years after superinfection), suggestive of disease progression. Two other patients, the source partner and a second partner that had been infected with the same virus strain, showed rapidly decreasing CD4+ T-cell counts and high viral loads. Therefore, this specific virus strain is not attenuated. Host factors are important in controlling infection, and indeed, the index patient was shown to carry the protective HLA class I B*5701 allele.

However, not all (initial) controllers of HIV viral replication are able to control a second HIV infection. Streeck et al. (2008) described a HIV–controller who rapidly lost control due to an HIV-1 superinfection. The patient, expressing the protective HLA-B27 allele, had at initial infection a peak viral load of 5.7 $\log_{10}$ copies/ml and a CD4+ T-cell count of approximately 900 cells/µl. He controlled viral replication as early as 22 days after infection with a plasma viral load well below 10,000 copies/ml, most likely due to his rapidly increasing CD8+ T-cell immune responses. However after 1.4 years, the viral load increased to 5.6 $\log_{10}$ copies/ml followed by a steady decrease in CD4+ T-cell count. Three years after initial infection (1.5 years after superinfection) the CD4+ T-cell count was below 300 cells/µl. Phylogenetic analysis of viral sequences showed that the patient was superinfected with a distinct subtype B HIV strain. The superinfecting strain dominated the blood plasma for the following 3 years with no control of viral replication.

Clerc et al. (2010) also showed that elite controllers are not exempt from HIV-1 superinfection and risk of disease progression. Two HIV-1 infected IDU elite controllers contracted an HIV-1 superinfection and subsequently experienced progressive disease. In 1996, a Swiss woman was tested positive for HIV-1 infection with a subtype B strain. For over 6 years, she had undetectable plasma viral loads and CD4+ T-cell counts >800 cells/µl. However in July 2002, she presented with a syndrome of high fever, general weakness and multiple adenopathies. A viral load of 5.9 $\log_{10}$ copies/ml was measured with a decreased CD4+ T-cell count (600 cells/µl). A diagnosis of acute retroviral syndrome was made due to superinfection with a CRF11_cpx strain. In August 2007 she started with antiretroviral therapy, as her CD4+ T-cell count was then as low as 240 cells/µl, and had already been around the 400 cells/µl level from January 2005 onwards. After the superinfection moment, the plasma viral load had always been high.

An African male IDU patient with the protective HLA B*81 allele was tested HIV-1 subtype B positive in March 1999. His viral load was undetectable and he had normal CD4+ T-cell counts. In October 2002, he showed fatigue, general weakness and multiple new adenopathies. His plasma viral load was then 5 $\log_{10}$ copies/ml and the CD4+ T-cell count decreased from 1225 to 674 cells/µl. Also this patient was superinfected with a CRF11_cpx strain and showed HIV-1 disease progression. After superinfection, the plasma viral load remained high at around 5 $\log_{10}$ copies/ml, while CD4+ T-cell counts dropped below 400 cells/µl. Nineteen months after the HIV-1 superinfection event the patient died from a drug overdose and was lost to follow-up.

A homosexual male patient infected with an attenuated HIV-1 subtype B strain that lacked the *nef* gene lost control of HIV-1 replication when he was subsequently superinfected with a wild-type subtype B strain (Braibant et al., 2010). The patient had been included in a French long-term nonprogressors cohort after 10 years of seropositivity with 5 years of stable CD4+T-cell counts >600 cells/µl. However, in March 1999, almost 4 years after inclusion in the cohort, plasma viral load increased progressively to 10,350 copies/ml and CD4+ T-cell counts declined <600 cells/µl, necessitating the start of antiretroviral therapy. Retrospective analysis showed that the patient had been superinfected with a wild-type subtype B strain around the time of inclusion in the controller cohort. Although control of HIV-1 replication was lost by this patient after superinfection, disease progression was relatively slow, e.g. 4 years after superinfection, CD4+ T-cell counts were still around 500 cells/µl, and plasma viral load was only slowly increasing till ±10,000 copies/ml.

LTNPs and elite controllers are not free from HIV-1 superinfection. This should come as no surprise, because although these atypical patients are able to control replication of HIV, they are fully susceptible to infection with the virus. How viral control is achieved is not completely clear. Favourable HLA-B types are associated with control, as are infections with low-replicating virus variants. In the latter case, re-infection with a more competent strain could easily result in loss-of-control. If the adaptive immune system is controlling the virus, there is a possibility that control will not be lost or can be regained after superinfection. From the above described patient cases, it is clear that all hypothetical situations exist in real life, but that control is more often lost than recovered.

5. Conclusion

The course of an HIV-1 infection in humans varies greatly. From rapid progression to AIDS within a few years to control of viral replication for more than 20 years: it all exists. The studies presented above indicate that patients who get infected with a second HIV-1 strain follow similar divergent tracks of disease progression: from rapid to no obvious progression. Assigning HIV-1 superinfection cases (leaving out the questionable cases) into progression or non-progression categories results in 20 cases immediately exhibiting markers of disease progression versus 21 cases that do not, e.g. in 50% of cases HIV-1 superinfection results in an accelerated loss of viral control. However, larger studies, e.g. case-control studies, are needed to assess the effect of HIV-1 superinfection upon disease progression in a controlled way, as most reports published have low numbers of superinfected patients.

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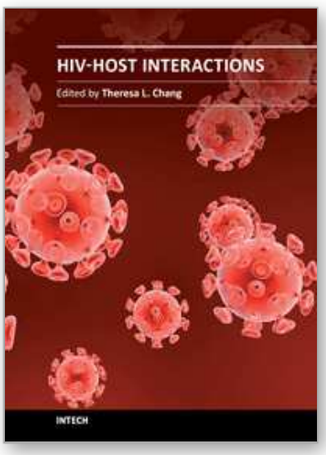

HIV-Host Interactions

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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and Trichomonas vaginalis on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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