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HIV-1 Super Infection

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1. Introduction

Human immunodeficiency virus type 1 (HIV-1) infection with more than one strain, termed dual infection (DI), encompasses both co and superinfection (SI). Co-infection is the acquisition of two viral strains during primo-infection, whereas SI is the infection with a second heterologous strains after primary infection or during the course of an established infection.

The first evidence that support HIV-1 DI, is the existence of numerous circulating recombinant forms, because recombination requires that a single cell is infected by two viruses. Recombination could arise inter-subtype (where viruses differ by ~30% in the viral envelope sequence) and intra-subtype (where viruses differ by only ~10% in the envelope). The first case of a intersubtype SI in a man, infected with a CRF01-AE recombinant form, who became superinfected with a subtype B strain was described by (Jost et al., 2002). Similar inter subtype cases have been reported by (Ramos et al., 2002). Intrasubtype cases, where the first and the second strain belong to the same B subtype, have been described (Altfeld et al., 2002; Pernas et al., 2006).

2. Detection

Different methods have been used to detect DI: restriction fragment length polymorphism (RFLP) (Ramos et al., 2002), multiregion hybridization assay (MHA), heteroduplex tracking assay (HTA), heteroduplex mobility assay (HMA) (Manigart et al., 2004), sequencing of single copy PCR amplifications (Salazar-Gonzalez et al., 2008), clonal sequencing followed by phylogenetic analysis (Pernas et al., 2006). All these methods are expensive, time consuming and require a laborious analysis.

Recently, new approaches to detect SI have been developed. Within population-based sequences multiple nucleotides are possible at a single position, which is called ambiguity codes. The presence of high number of ambiguous codes in the Viro-Seq HIV-RT sequence, vastly used for routine determination of resistance-associated mutations, has been applied to detect DI. In 16 out 37 patients, the existence of more than 34 ambiguous sites (34-99) in the Viro-Seq HIV-RT sequence revealed new cases of dual infections (Cornelissen et al., 2007). However, this method was less sensitive when compared to HMA (Rachinger et al., 2010) since minor variants present below 20-30% in the quasispecies population could not be detected in the sequence chromatogram. Because non synonymous positions are selected by

immune response or HAART, a new method focused on mixtures only in the synonymous positions (SM-index) was applied to discriminate between dually and single infection in highly-risk patients. To confirm the cases of DI, ultra-deep sequencing (UDS) was compared to the single genome sequence (SGS) method, considered as the gold standard method. In most of the samples, UDS identified minority variants that were not detected by SGS. Only in samples with very low viral load, SGS could detect minority variants more accurately than the UDS. These results showed that UDS could eventually replace SGS as the method for DI screening (Pacold et al., 2010).

The study of HIV-1 SI is highly dependent on the availability of the appropriate samples. Due to the high recombination rate in HIV (Jost et al., 2002), it is necessary to have samples close to the SI event, because after SI, recombinant strains could arise and mask the phylogenetic segregation of the clades. Serial sampling permits the detection of SI because it allows the identification of the resident strain; detect the appearance of the new strain and the emergence of recombinant strains (Gerhard M. Mloka, 2004; Pernas et al., 2006). Sometimes, soon after SI one of the virus strains overgrew the other which could no longer be detected (Templeton et al., 2009), and also the expression of one strain can vary with time (Kozaczynska et al., 2007; McCutchan et al., 2005).

Analysis of a second region in the HIV genome, that has permitted the detection of new cases of DI (Piantadosi et al., 2008), should be considered a standard approach for HIV SI detection.

We analyzed SI in an HIV-1 infected patient showing high-risk practices (Pernas et al., 2006). Viral quasiespecies were analyzed in *pol* and *env* genes in several plasma samples during the patient follow up. Analysis in *env* gene confirmed the existence of 3 different strains in the viral population, one of them a recombinant (Figure 1). The analysis of serial samples as well as the analysis of a second genomic region in *env* gene (Figure 1) has permitted the detection of SI and the identification of recombinant variants.

One important issue is how to discriminate between co-infection and SI. SI implies that the second infection can occur after the development of an immune response, suggesting that natural infection does not provide enough protection against SI; whereas co-infection occurs during primoinfection while the immune response is still not completely functional. To distinguish between these two events, the analysis of sequential samples is necessary. However it is not always possible.

In our group, we developed a method that permits the estimation of the dating time of viruses (Casado et al., 2000). The viral dating time is estimated by the use of a linear-correlation equation, previously developed on the basis of a large set of Spanish samples, that correlates the V3 nucleotide-sequence divergence to the Spanish-epidemic MRCA with the sampling time. Using this approach (Casado et al., 2007) we interpolated the year of the nucleotide sequence of each of the different patient clades (Table 1), were able to discriminate between co-infection and a SI in two LTNP patients, supporting the usefulness of the viral dating methodology. The years calculated for clades a and b for patient 1 were identical (1992), whereas those obtained for clades a and b for patient 2 was 1987 for clade a, close to the seroconversion time, and 1996 for cluster b (9 years later). The viral dating indicates that a SI had occurred in patient 2, whereas analysis of the first sample from patient 1 showed that he already was coinfecting, although a previous SI could not be ruled out.

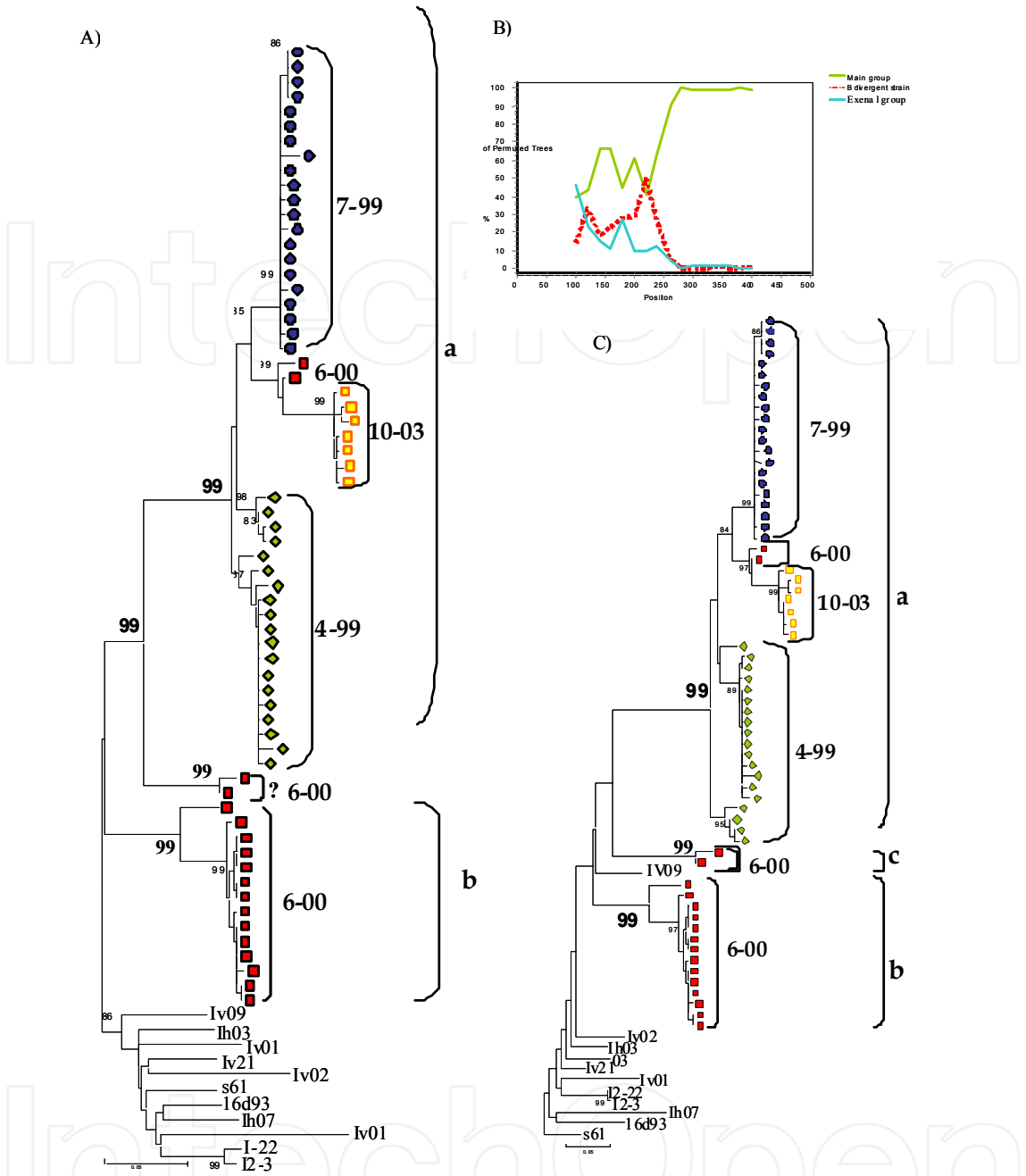


Fig. 1. **A).** Maximum likelihood tree of the sequence quaspecies derived from the C2-C5 region (501 nt) in the *env* gene. Clones were obtained at different time points 4-99♦, 7-99●, 6-00■ and 10-03■. Brackets in the right hand of the phylogenetic tree group the sequences corresponding to a , b and recombinant strain (?). Samples included as external group are designed by letters. **B)** Bootscan plot in the same *env* region of the virus marked with an ? in panel A. Main strain (—) and recombinant strain (···) and external group (—) are included in the analysis. In the first 240 nt the (?) virus showed an homology below 70% with the three compared viruses. **C)** Maximum likelihood tree of the first 240 nt from the C2-C5 region in the *env*. Brackets in the right hand of the phylogenetic tree correspond to a , b and recombinant (c?) virus. Samples designed with letters are reference Spanish strains. Bar represents 10 % genetic distance.

	First HIV-1+Test documented (year)	Genetic Distance to Spanish MRCA	Viral Dating
PATIENT 1	1986	6.9% ± 0.020% (a) 6.9% ± 0.019% (b)	1992 ± 3 (a) 1992 ± 3 (b)
PATIENT 2	1988	3.6% ± 1.4% (a) 9.2% ± 2.3% (b)	1987 ± 2 (a) 1996 ± 4 (b)

Table 1. Viral dating of dual infected LTNP patients.

3. Incidence

Although it is well establish that SI is frequent in HIV natural history, incidence studies have yielded contradictory results. Several studies found no evidence of HIV-1 SI, in a cohort of 718 HAART treated patients (Gonzales et al., 2003) nor in 37 injecting drug user patients who reported a high risk behaviour (Tsui et al., 2004). In contrast, three population-based studies found SI rates of ~5% which is similar to the primoinfection rate (Chohan et al., 2005). Other authors (Piantadosi et al., 2008) have found higher percentages of 7.7% per year, or even higher (17%) among 36 individuals (Piantadosi et al., 2007). Super-infection has been reported in every risk group, including men who have sex with men (MSM) (Campbell et al., 2009), heterosexual women (Templeton et al., 2009), and injection drug users (IDU) (Ramos et al., 2002; Yerly et al., 2004). Several cases of SI involving drug-resistant HIV-1 strains have been described (Ramos et al., 2002). Patients, inially infected with a drug-sensitive virus, has been superinfected with a resistant strain (Pernas et al., 2006; Smith et al., 2005) and vice versa (Koelsch et al., 2003). In another case, both viruses were drug-resistant (Brenner et al., 2004).

4. SI and immune response

Study about the role of the immune response in SI is limited. It is still unclear whether only the subset of individuals with a poor immune response are superinfected, or whether immune response during HIV-1 infection is in general inadequate to prevent infection. If SI is a common event, this implies that the immune response generated against HIV infection is not completely protective (Chohan, Piantadosi, and Overbaugh, 2010).

4.1 CTL response

SI has been observed in an individual who showed a cytotoxic acitvity (CTL) against the initial strain, but this response did not protect for SI with a second virus of the same (Altfeld et al., 2002) or different subtype (Ramos et al., 2002). Another case of SI in a patient who developed a high CTL response agaisnt the first virus has been described (Yang et al., 2005). Other authors have suggested that the ability of the SI strain to overcome the preexisting immune response, is related to its ability to rapidly recombine in regions under immune pressure (Streeck et al., 2008).

4.2 Neutralization antibodies response

Unlike CTL response, neutralization antibodies (NAbs) can prevent infection in animal models (Sealy et al., 2009), suggesting that this response might be able to prevent SI in humans. The lack of neutralizing antibody response was related with the predisposition to SI (Smith et al., 2006). On the contrary, a more extensive study showed that at the time of SI, there were not deficits in the Nabs response in the patients who became superinfected compared to the controls, concluding that NAbs elicited during natural infection was not sufficient to block infection (Blish et al., 2008).

5. DI and disease progression

Despite the varying disease progression rates, the majority of untreated HIV-infected individuals progress to AIDS in a period of around 10 years. In some of the HIV-1 dual infected patients, an accelerated disease progression has been observed. In a cohort of 34 patients, in the five individuals with dual infection, the progression to AIDS was very rapid (<3.4 years) (Gottlieb et al., 2004). SI with a dual tropic HIV-1 virus and rapid progression was reported (Gottlieb et al., 2007). In a cohort of HIV-1 subtype C infected female sex workers, DI was associated with an increase viral set point (Grobler et al., 2004). However is not clear whether SI leads allways to clinical progression (Fung et al., 2010).

6. SI in long term non progressor patients

It is very interesting to study SI in a special group of infected patients clasified as long term non progressor (LTNP) -a subset of HIV-positive individuals, who maintain high CD4+ T-cell counts without therapy for more than 15 to 20 years- or in LTNP-Elite controllers (EC) who are LTNPs maintaining undetectable viral loads. This group has attracted a lot of interest to disclose the factors contributing to the natural control of the viral replication. Viral control appears to be mediated by multiple mechanism including virological, host genetic and immune response factor:

a. Virological factors

Some studies supported that mutations or deletions in HIV functional proteins or in the accessory genes can lead to viral control like in the virus from the Sidney Cohort (Learmont et al., 1992). Recently, lower replicative capacity and reduced entry capacity in virus obtained from elite controller patients have been reported (Lassen et al., 2009). Other works attribute an important role to the impaired replicative capacity of *gag* (Miura et al., 2009) and *pol* regions obtained from these patients (Brumme et al., 2011). In addition, the presence of viruses with reduced replicative capacity in the initial stages of the infection has been described (Miura et al., 2010). In contrast, other authors did not find relevant deletions or defects after analyzing viral sequences from a large cohort of EC (Miura et al., 2007). Replication competent viruses, which replicated like standard laboratory strains “in vitro”, were obtained in 4 out of 10 ES patients, (Blankson et al., 2007). Similar results were obtained by (Lamine et al., 2007) discarding the role of virological factors in the disease control in these patients.

b. Host genetic

Host genetic polymorphisms mapping in the coding and the promoter regions of the co-receptor CCR5 have also been associated with protection against HIV-1 (Gonzalez et al.,

1999). However, the most relevant host factor associated with viral control in HIV infected individuals is the presence of certain major histocompatibility complex class (MHC) I group B HLA I alleles (Deeks and Walker, 2007). HLA B* 57, B* 27 and B* 58 haplotypes are consistently overrepresented in these patients (Fellay et al., 2009; Migueles et al., 2000).

c. Immune response

One of the most effective mechanisms to control HIV-1 infection is the CD8+T cell response. The effectiveness of the cytotoxic T-lymphocyte (CTL) response does not appear, however, to correlate to the number of the responsive cells but with its functionality (multiple cytokines secretion, degranulation, the ability to proliferate upon encounter with HIV antigens) which is higher in controllers compared to non controllers (Hersperger et al., 2011). The maintenance of a robust HIV-specific CD4+ T cell response, providing help to CD8+T cells, may also help to the long term control of HIV replication as has been recently described (Blankson, 2010).

Several investigations have studied if ECs have broadly neutralizing antibody (NAb) responses. It appears that this response is not present in most ECs and does not have a major protective role in the early or chronic phase of viral replication (Doria-Rose et al., 2010).

In the majority of the cases described in EC, SI is associated with loss of disease control. In a LTNP female sex worker, an abrupt decline in CD4T cells counts was associated to super-infection (Fang et al., 2004). In two elite controller patients, an accelerated rate of disease progression was observed after a documented super-infection (Clerc et al., 2010). Control of disease after infection by a *nef*-defective strain is lost after SI by a fully competent virus in a B*57 HIV-1 LTNP patient (Braibant et al., 2010). However, other reports have stated SI in patients without apparent clinical consequences. Recovery of viremic control after SI in a long term elite controller patient has been also described although viral load was higher after SI, which implies that the patient did not fulfil the definition of elite controller (Rachinger et al., 2008). For the first time, SI in a long term EC patient able to control both viruses and maintain undetectable viral loads for > 20 years has been reported (Casado et al., 2007). This patient presented strong immune response and viruses with low "in vitro" replicative capacity (Pernas et al, manuscript in preparation).

More studies of SI in people who control infection could be very useful in two ways:

- - Understanding why some EC patients lost viral control after SI while others maintain their EC status.
- - Analysis of SI in this group of patients could help to estimate the real incidence rate of SI in HIV natural infection, because in EC and LTNP patients there is no or very little viral evolution (Wang et al., 2003), consequently less recombinant forms appear and the detection of SI should be easier than in the patients with typical progression.

7. Conclusion

The study of SI is a very productive topic in HIV research because it provides useful information for different aspects of HIV infection. SI patients constitute an interesting group of patients to investigate the role of the immune response generated against HIV infection and to investigate which factors, including host genes, contribute to protection against new infections. Also, the study of the phenotypic characteristics of the infecting and super-infecting strains will produce very interesting information for HIV pathogenesis. Analysis of SI in LTNPs and EC patients could offer an excellent model for these studies. Moreover,

from the clinical perspective, detection of SI, with the potential pathogenic consequences, demonstrate the importance of reducing risky behaviors in HIV-1 infected individuals.

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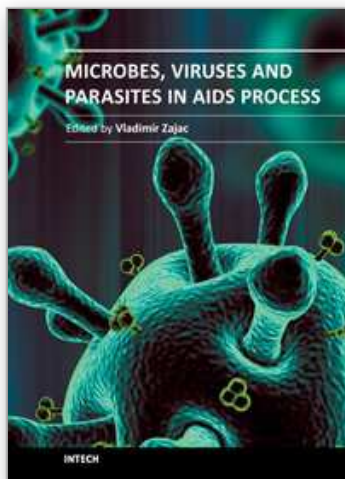
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The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases. Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa. Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally. It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

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