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HIV-1 Long-Term non-progression: More Open Questions than Answers

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Abstract

The reason for long-term non-progression is one of the most elusive of all of the open questions in AIDS research. This review summarises the available epidemiological and viro-immunological data, paying particular attention to the recent advances in the genetic correlates of non-progression. Despite the large number of contributions in this field, the classification criteria remain heterogeneous, and may present substantial obstacles when interpreting the results of ongoing studies.

Key words

HIV. Natural history. Long-term non progression.

One of the most striking characteristics of HIV-1 infection is its individual variability in terms of the time to progression towards AIDS[1-4]. Longitudinal studies have estimated that, in the absence of therapeutical intervention, the median incubation time of AIDS is 10 to15 years[1,5,6], and it has also been estimated that one out of four infected individuals remains AIDS-free for as long as 20 years after seroconversion[7].

Infectious disease is one of the most potent evolutionary factors for all living creatures, as our own species has experienced various times in the past. On the basis of these experiences, it seems likely that genetic variability is fundamental for conferring the best capacity for facing new pathogens and guaranteeing that at least some individuals survive to perpetuate the species. In this context, HIV-1 infection represents a particular challenge for a number of reasons: 1) It is a retrovirus capable of integrating itself within the host genome and perpetuating life-long infection; 2) The main target of the infection are T helper lymphocytes, the principal effectors of specific immunity; and 3) The genetic variability of the virus, its increase during each replicative cycle[8,9], further threatens host defences.

When planning strategies against any virus, and thus forecasting the future of an epidemic and its evolutionary cost for humanity, it is important to identify and characterise the subset of human beings most capable of resisting the infection.

The probable existence of individuals who escape infection despite repeated exposure to the virus[10] suggests that HIV-1 is no exception to the general rule, but we shall here concentrate on a different aspect of host resistance: the fact that there are some individuals who remain AIDS-free and retain relatively preserved immune functions for a long time after infection.

Since the early 1990's[2], a number of reports have described asymptomatic individuals whose CD4 cell counts remained within the normal range for several years. They were called long-term asymptomatics[2], long–term survivors[11] or long-term non-progressors (LTNPs)[12]. This privileged subset of people generally has a better immune response and greater control over viral replication than other HIV-1 infected patients[11].

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Nevertheless, there are still a number of open questions concerning their definition and classification, and even the main definition criteria (*i.e.* the duration of the asymptomatic period and the number of CD4 cells needed to be considered a long-term non-progressor) are interpreted and applied in quite different manners. The time threshold defining long-term non-progression in published studies varies from seven to ten years[13-16]. Furthermore, although some authors limit the definition of LTNP to people who maintain a positive CD4 cell slope[12,17], the majority include those who retain CD4 cell values above 500/µL regardless of the slope.

A further debate concerns the term 'non-progression' itself, which cannot be properly used in the case of individuals who, despite the absence of symptoms and the presence of relatively high CD4 cell counts, frequently present abnormal immune responses and variable degrees of viral replication[18,19].

How many long-term non-progressors are there?

The estimates of the real entity of the phenomenon obviously reflect the differences in classification. Of the 539 men enrolled in the seroconvertor cohort of the Municipal STD clinic of San Francisco, 42 (8%) were asymptomatic and had CD4+ cell counts > 500/µL ten or more years after seroconversion[13]. Considering a stable CD4+ cell slope as the definition criteria, Sheppard *et al.*[12] found a similar percentage of non-progressors (10%) during 78 months of follow-up of another seroconvertor cohort. However, although showing no net cell loss, these subjects had mean CD4+ cell counts that were approximately $400x10^6$/L lower than those of seronegative individuals. Studies of cohorts for whom the date of seroconversion is not known may lead to very different results despite the use of similar classification criteria. In the Vancouver Lymphadenopathy-AIDS study, only 1.8% of the recruited homosexual men met the definition criteria of long-term non-progression (CD4 cell count stable > 500/µL, and asymptomatic condition) after a median follow-up of 9.2 years[15], whereas 14.2% of the subjects in a Spanish haemophiliac cohort were classificable as LTNPs according to the same criteria after eight years of follow-up[16]. In a cohort of haemophiliacs recruited in Milan, 6.2% were LTNPs ten or more years after their first positive test for HIV-1[20]. Although it is possible that these differences are due to a higher risk of progression in different risk groups, is more probable that age at infection is a major source of difference, because it plays an important role in conditioning progression[21]. Furthermore, intravenous drug use does not seem to limit the possibility of meeting the LTNP definition criteria. Soriano *et al.*[22] have recently reported that the behavioural and epidemiological variables associated with non-progression in a Spanish cohort are male gender, young age, low cultural level, high alcohol intake, i.v. drug use, re-exposure to HIV, and HCV and CMV antibody positivity: These characteristics provide an accurate identity of intravenous drug users, the prevalent risk group in Spain. The criteria for non-progression were met by 103 of the 1956 subjects (5.3%) in the cohort.

The effect of different classification criteria has been highlighted in a recent paper published by the Italian Seroconversion Study Group[23]. Using four different definitions as LTNP[12-15], the percentage of subjects who could be defined as LTNPs varied from 2 to 4%. However, there was a little overlapping among the definitions: none of the subjects could be classified as LTNP according to all four definitions, and only 4 on the basis of three of them.

Moreover, regardless of the adopted definition, LTNPs actually appear to experience slower progression rather than permanently arrested infection. In a Milan cohort of asymptomatic subjects with more than 500 CD4+ cells/µL at enrolment, the cumulative probability of maintaining this status was 9.9% after seven years but only 4% after ten years of follow-up. However, all subjects showed a negative CD4+ cell slope[24]. In a recently published paper, the Australian long-term non-progressors study group reported a significant decline in the CD4 slope after enrolment in a considerable number of their LTNPs[19]. In the Resistant Host Prospective Study (r-HoPeS), which included asymptomatic individuals whose CD4 cell counts were > 500/µL after seven or more years of infection, and who had never been treated with antiretroviral drugs, we observed a clear inverse correlation between the duration of infection and CD4+ cell counts and slope. Moreover, the cumulative time-dependent probability of progression (defined as a reduction in the number of CD4 cells to < 500/µL) was 31% over a median follow-up of 554 days (unpublished data). Similar results have also been reported by other authors[22,25].

Taken together, this data suggests that the adopted definitions identify the right-hand tail of a normal distribution of progression rather than true non-progressors. So we need to ask ourselves about the real existence of LTNP. One good answer is offered by Petrucci *et al.*[23]: LTNPs exist as long as we define them.

Besides the limitation due to the relatively short follow-up available, it is probable that the currently adopted criteria (CD4 count, CD4 slope or both) are insufficient to distinguish different subsets of HIV-1 infected subjects destined to have different progression patterns. On the basis of recent findings[26], virologic and perhaps genetic parameters should be added to the classification criteria in order to achieve a better definition of LTNP and be able to predict real very slow (or 'non'-) progression. We can conclude, however, that long-term non-progression is a relatively rare phenomenon that can be observed in only a small percentage of infected subjects.

The virus or the host?

The reason for long-term non-progression is still unclear, and it has been alternatively attributed to a lower degree of pathogenicity of the viral strains involved[27,28] or to the characteristics of the host. The 'viral' hypothesis has been supported by the isolation of *nef*-deleted strains[27,29], but this finding regards only a minority of the cases who meet the definition of LTNP and is completely absent in several studies. Reduced variability in the *env* gene[30,31] and the presence of rare mutations in a domain crucial for the V3-loop structure[31] have also been associated with a more efficient host immune response.

A strong argument against a predominant role of attenuated strains in non-progression is the frequent finding of LTNP intravenous drug users with multiple re-exposures to HIV[22]. In my opinion, the presence of reduced viral genetic variability or defective viral strains is most likely a consequence of the pressure of a valid host immune response rather than the actual cause of non-progression. Such a response has been documented in a number of reports[32-34] and is apparently unaffected by behavioural factors because, as mentioned above, non-progression is reported in all risk groups without any significant differences between them. This efficient immune response is probably also responsible for the limited replicative activity of the virus and the low prevalence of syncitium-inducing strains reported in LTNP[20,32-37].

Non-progression and immunity

Among the immune mechanisms potentially involved in non-progression, the production of neutralising antibodies has been widely investigated[32,35,38-40]. The first data showing strong and broad neutralising activity against heterologous primary isolates in LTNP plasma[32] have not been confirmed in homologous isolates[38]. Moreover, other investigators have described a trend towards an association between a weak neutralisation of heterologous isolates and low viral load in LTNPs[39] and, more recently, a positive correlation between neutralising titres, CD4+ cell counts and T-cell function[40].

Another possible correlate of non-progression in LTNP is the maintenance of efficient anti-p24 antibody production[35]. The lack of *in vitro* anti-core antigen antibody production in progressors[41] prompted us to investigate whether the efficient *in vitro* production of specific anti-HIV-1 antibodies may be a correlate of non-progression. Against our working hypothesis, we found that anti-p24 antibody production by unstimulated PBMCs is significantly less frequent in LTNPs than in asymptomatic subjects with more recent infection[42], and that the *in vitro* production of anti-gp160 antibodies correlates with progression during follow-up and is a predictor of an increasing viral load[43]. Taken together, these results suggest that humoral response in LTNPs is more likely to be a correlate of viral reactivation in subjects with a relatively preserved immune response rather than a determinant factor for non-progression.

The data concerning the presence of efficient cellular immunity are more convincing and have been confirmed by several studies[26,34,44-46]. The majority of cases maintain an efficient cytotoxic T cell response specifically directed against the virus[44,45], type 1 cytokine production[34], and preserved specific T helper function[26]. Moreover, the percentage of CD8+ CD38+ cells in LTNPs is significantly lower than in progressors[34].

The cause of this favourable immunological profile is not known. A simplistic explanation attributes the better response and non-progression to a particularly favourable genetic pattern. In the case of HIV-1, however, the main targets of the virus are T helper lymphocytes, and the progressive impairment of the specific immune cell response may represent a consequence of the replicative activity of the virus and parallel disease progression. Therefore the fact that the preservation of some immune functions may represent a consequence of reduced virus replication due to other mechanisms rather than the cause of non-progression.

A recent report has claimed that ß-chemokines play a role in contrasting HIV-1 replication[47], and the identification of chemokine receptors as second receptors of HIV-1[48] has prompted a number of investigations of ß-chemokine production in LTNPs. The first data did not reveal any substantial difference in the *in vitro* production of RANTES, MIP-1α and MIP-1ß by PBMCs in LTNPs and progressors[19,51]. More recently, Scala *et al.* have reported increased chemokine production in cloned T cells from LTNPs[46], and significantly greater production of MIP-1α and MIP-1ß than in progressors has been observed in a larger group of LTNPs (Cocchi *et al.*, personal communication). Further studies are needed to clarify the role of this protective mechanism, its control *in vivo* and its relevance in non-progression.

LTNP and genetics

A number of studies have attempted to identify the genetic profile of non-progressors, but the results suggesting that non-progression is associated with certain major histo-compatibility complex (MHC) alleles[54-56] remain controversial[57]. Slow progression has also been associated with the absence of the complement C4 null allele[58], and with the presence of the TNFα C2 microsatellite allele[59]. On the contrary, a recent investigation designed to explore whether long-term non-progression was associated with a skewed T-cell receptor (TCR) Vß repertoire did not allow the identification of any significant difference in the expressed repertoires or in the expansion of a particular Vß family comparing LTNPs and other HIV-1 infected individuals[60].

A major issue in this field of research is the protective role of the different alleles against HIV-1 infection or its progression. Over a very short period of time, a lot of information has been produced concerning the effect on progression of the Δ32-deleted allele of the CCR5 gene[61], the 59029-G allele of

Table 1. *Prevalence of CCR5/ΔCCR5 in LTNP*

Authors	Year	Setting	(N)	LTNP (%)	Progressors (%)	HD %	p *
Cohen *et al.* [65]	1997	Bethesda	29	37.9	ND	21.7**	-
Eugen-Olsen *et al.* [66]	1997	Copenhagen	9	33.3	22.2	24.3	NS
Steward *et al.* [67]	1997	Sydney	64	35.9	12.6	18.4	.0005
Michael *et al.* [68]	1997	San Francisco	20	30.0	10.7	20.4	.02
Morawetz *et al.* [69]	1997	Lousanne/Milan	58	31.0	10.6	ND	.0001
De Roda Husman *et al.* [70]	1997	Amsterdam	23	48.0	9.0	ND	.001
Balfe *et al.* [71]	1998	London	45	42.0	26.0	15.0**	.1
Barker *et al.* [47]	1998	San Francisco	21	38.0	15.0	20.8	.12
Visco-Comandini *et al.* [72]	1998	Huddinge/Roma	23	30.0	8.0	20.0**	.1
Walli *et al.* [73]	1998	München	70	37.1	ND	15.8**	-
Galli *et al.* [74]	1998	Milan	68	23.5	9.8	10.7**	.03

* LTNP *vs.* progressors ND=not done NS=not significant HD=healthy donors
** statistically significant difference *vs.* LTNP

the CCR5 promoter[62], CCR2 64 I[63] and stromal-derived factor-1 (SDF-1)-3'A[64]. The CCR5 Δ32 deletion (Δ5) has been the subject of at least eleven studies published in two years[47,65-74] (Table 1).

According to the data obtained in large cohorts of HIV-1 infected subjects, which indicate that the heterozygous status may play a protective role against progression[61], the prevalence of Δ5 allele is significantly higher in LTNPs than in other groups of HIV-1 infected subjects in the majority of published surveys[67-70,74]. However, this prevalence varies markedly in different case series of LTNP (ranging from 23.5 to 48%). As a result of the differences in the distribution of the allele in different populations, the frequency of Δ5 is very low in non-Caucasian populations[61] and highest in Caucasian populations originating from Northern Europe. In the study reported in table 1, the frequency of Δ5 in healthy blood donors ranged from 10.7% in Milan to 24.3% in Copenhagen, thus clearly confirming its tendency to increase from South to North.

This relatively greater frequency is probably neither necessary nor sufficient to meet[47,65,69,74] or maintain[68] the currently used definitions of LTNP, although the introduction of more sophisticated classification criteria may change the situation. Furthermore, longer follow-up is needed before it can be determined whether Δ5 heterozygous LTNPs are really more protected against progression than their counterparts. In the majority of transversal studies, Δ5 heterozygous LTNPs did not differ from the others in relation to any of the studied parameters, including plasma viremia[47,65,67,74], with the exception of higher CD8+ T cell counts in the heterozygotes in one study[67] and significantly lower plasma viremia in another[73]. Nevertheless, the majority of LTNPs are infected with virus strains that are thought to use CCR5[34,37,71], and a recent study found that isolates from LTNPs maintain exclusive use of CCR5, whereas adaptation to the promiscuous use of CC and CXC coreceptors correlated with disease progression[75].

Of the other variants of chemokine receptor genes that have been associated with protection against HIV-1 progression, only the CCR2-64I mutation has so far been studied in LTNPs[76]. It has been reported that heterozygotes for this mutation are more frequent in LTNPs than in progressors (32.7 *vs.* 19.1% , p = 0.03), and the same has been found in the case of heterozygotes for both Δ5 and CCR2-64I (61.5 *vs.*. 29%, p = 0.0001). No association has been found between LTNP status and CXCR4 variants[77], but there are some intriguing data regarding a genetic variant of the CXCR4 ligand, stromal-derived factor 1 (SDF-1). An SDF-1 3'A homozygous state was found to be associated with protection against progression[64], but two recent reports suggest that it is related to accelerated progression[78-79]. Among the LTNPs studied by us, homozygosity for SDF-1 3'A is rare (2.3%) and the heterozygous subjects have a significantly higher viral load than wild-type gene homozygous subjects[80].

A French group has recently made an interesting advance in this field by cross-linking HLA and chemokine receptor alleles[81]. In this study, the frequency of ΔCCR5 was significantly higher in LTNPs, whereas that of CCR2-64I and SDF-13'A was not. The chance of LTNP was 15 times greater in the subjects who were heterozygous for Δ5 and homozygous for wild-type SDF-1. This increased to 36 times in the presence of the ß27 allele and the absence of DR6, and to 49 times in the presence of at least three of A3, B14, B17 or DR7.

Although greater studies are needed to define the putative genetic pattern of LTNP, the cross linking of different genetic markers seems to be a useful approach for developing our understanding on the causes of different progression patterns in HIV-1-infected patients.

Conclusions

The biological cause of non-progression in a minority of subjects with HIV-1 infection remains unknown, but genetic studies and the definition of the immunological profiles of subjects with different genetic patterns seems to be the most promising ar-

eas for future investigations. Furthermore, prospective studies are beginning to enable us to identify the predictors of progression in this particular subset of patients. Perhaps surprisingly, plasma viremia (generally low in LTNPs) does not seem to be the best predictor of further progression since the Australian prospective study[19] found that high ß2-microglobulin values but not plasma viral load were predictive.

In our own LTNP case file, progression is not significantly associated with plasma viremia but is associated with the level of intracellular unspliced transcripts, thus suggesting that this precocious indicator of virus replication is a more sensitive predictor of progression in LTNPs.

Finally, despite the number of investigations currently being carried out, the high degree of dishomogeneity in the classification criteria may endanger the interpretation of the future results. Furthermore, given that criteria restricted to clinical data and CD4 cell counts are probably insufficient, there is an urgent need for consensus on a more stringent definition of LTNP.

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