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Commentary

Long term non-progressor (LTNP) HIV infection

The human immunodeficiency virus (HIV) infection is a dynamic process and has a variable rate of progression in infected people. Despite the varying disease progression rates, the majority of HIV-infected individuals eventually progress to AIDS. According to the rate of progression, HIV infection may be divided into three major types: *(i)* rapid progression, where AIDS develops within 3 years of infection; *(ii)* intermediate progression, where AIDS develops slowly between a span of 3 and 10 years after seroconversion; and *(iii)* long-term non progression (LTNP) where HIV infected people maintain high CD4+ and CD8+ T-cell counts and remain therapy naïve[1]. The group of HIV positive long term non-progressors comprises less than 5 per cent of the total HIV population. Different studies have used different duration to define long term non-progressor which makes comparison difficult. Some studies have used >8 years duration to define non-progressor while others have used >10 years[2,3]. As viral load testing became available, long-term non-progressor were further divided into two groups - one showing low detectable plasma viraemia (<5000 HIV-RNA copies/ml), termed long-term non-progressors; second group showing plasma HIV-RNA values persistently below 50 copies/ml, and termed "elite" or "natural controllers".

Transition from long-term non-progressive infection to progressive HIV-1 disease presents an opportunity to investigate pathogenesis and planning treatment and vaccine strategies. Studies have tried to identify host, genetic and viral factors which may be useful to predict progression. Effectiveness of antiretroviral therapy (ART) in delaying progression and preventing opportunistic infections has been established beyond doubt. However, the point during the course of HIV infection at which ART is best initiated in asymptomatic patients remains unclear. According to consensus, at present initiation of therapy is best guided by CD4 cell count, a marker of immune status, rather than on viral load, a marker of virologic replication[4]. In one systematic review, the authors have concluded that there is evidence of moderate quality that initiating ART at CD4 levels higher than 200 or 250 cells/µl reduces mortality rates in asymptomatic, ART-naive, HIV-infected people. However, for patients with advanced clinical AIDS defining symptoms, it is recommended to start treatment regardless of CD4 count[4].

Host and genetic factors

The genetic factors which influence the rate of progression from HIV to AIDS can be broadly divided into three categories: *(i)* genes encoding cell-surface receptors or ligands for these proteins; *(ii)* genes within human leukocyte antigens (HLA) that regulate host immune response to infection; and *(iii)* other cytokine or immune response genes.

The most widely studied marker, the CD4 positive T lymphocyte count, is perhaps the best single indicator of stage of illness. Serum factors such as neopterin and beta-2 microglobulin, alone and in combination with CD4 cell counts, have been shown to have good predictive value. Pereyra *et al*[5] reported that CD8+ T cells from both elite and viraemic controller groups preferentially target Gag over other proteins in the context of diverse HLA class alleles. They found significantly more CD4 and CD8 T cells in "elite controllers" that secrete interferon-gamma and interleukin-2 and lower level of HIV-neutralizing antibodies. Individual responses were heterogenous and none of the parameter was uniquely associated with the ability to control viraemia[5]. There was an increased risk of progression within 4 years of study entry in individuals with detectable effector cytotoxic

T-lymphocyte (CTL) activity, higher plasma levels of HIV-1 RNA, higher beta(2)-microglobulin levels, and higher immune complex dissociated p24 antigen levels at enrollment[6].

Studies have shown that heterozygosity at HLA class I loci (HLA-A, HLA-B and HLA-C) is strongly associated with resistance to progression to AIDS and has a progressive effect. HLA-B*81:01 and B*39:10 alleles have been found to be associated with viraemic control in HIV-1 subtype C infection. Both alleles restrict the TL9 epitope in p24 Gag, and CTL mediated escape mutations in this epitope have been associated with an *in vitro* fitness cost to the virus[7]. The haplotype B*35-Cw*04 has also been shown to be associated with rapid progression to AIDS which helps the virus to escape activity against HIV-1. It has been predicted that HLA-B*27 and HLA-B*57 exert a protective effect to progression to AIDS in HIV-1 infected individuals[8].

Viral factors

Amino acids 25 to 36 in HIV-1 nef have been reported to be important both for several well-defined *in vitro* functions of nef and for the pathogenicity of HIV-1 in humans. Nef proteins derived from LTNPs and slow progressors (SPs) were found to be defective or far less capable of enhancing viral replication and/or viral infectivity. The sizes of the deletions in the nef/LTR (long terminal repeat) region increased progressively during the follow up period[9].

In another study[10], researchers compared the replication rates of recombinant reporter viruses carrying envelope proteins from LTNPs to control viruses from patients with similar CD4 count and viral load. In this study none of the eight LTNPs showed the 32-base pair deletion in the *ccr5* gene while HLA-B*5701 and HLA-B*27 alleles were detected in one LTNP each, respectively. Although Env sequences from LTNPs differed from those of controllers with respect to the length of variable domains and the number of N-glycosylation sites, these differences were not statistically significant and did not lead to differences in infectivity of recombinant reporter viruses[10]. In a meta-analysis, no significant association was found between defective/disrupted *nef* genes and disease progression as reported by earlier studies[11]. Ideally, long-term follow up with sequences from different disease stages is required to avoid other potential confounding effects of the disease process on the mutation rate[11].

In this issue, in a study from Andhra Pradesh, India, Radhakrishna *et al*[12] have reported 26 HIV perinatally infected paediatric long-term non-progressors who were followed up for 5 years to study factors affecting disease progression. Most of the studies done so far are in adults and from other countries. In this study, the authors have monitored their CD4 count, noted the morbidities and tried to see correlation. However, they could not study their genetic or viral factors. It will be interesting to study the viral sequencing and genetic factors in these long-term non-progessors. The LTNPs in this study were defined as individuals who have been living with HIV for at least 7 to 12 years and have stable CD4+ counts of > per µl, no HIV-related diseases, and no previous antiretroviral therapy. Case definition used in present study is different from other studies. Previous studies have used 8 or 10 years period for defining LTNP. Authors have shown an association between opportunistic infections and decline in CD4 count, and have also described various morbidities seen in these children as they have progressed from long-term non-progressor to long-term progressor[12].

Most investigators interested in determining the mechanisms of virus control in these individuals have assessed specific host factors. These studies were cross-sectional in nature, making it difficult to determine if a given host response is a cause of virus control or a consequence[13]. Although none of the study design is optimal, collective data support a central role for potent HIV specific CD8+T cells and to a lesser degree CD4+T cells in maintaining the virus control[14].

These studies indicate that there are multiple factors that play a role in disease progression. Results are not consistent regarding virus or host factors studied till date. Perinatally acquired HIV infected children are now surviving into adolescence. Study of these long-term non-progressors may help in better understanding of disease progression.

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References

1. Zeller JM, McCain NL, Swanson B. Immunological and virological markers of HIV-disease progression. *J Assoc Nurses AIDS Care* 1996; *7* : 15-27.
2. Ashton LJ, Carr A, Cunningham PH, Roggensack M, McLean K, Law M, *et al*. Predictors of progression in long-term nonprogressors. Australian Long-Term Nonprogressor Study Group. *AIDS Res Hum Retroviruses* 1998; *14* : 117-21.

3. Grabar S, Selinger-Leneman H, Abgrall S, Pialoux G, Weiss L, Costagliola D. Prevalence and comparative characteristics of long-term nonprogressors and HIV controller patients in the French Hospital Database on HIV. *AIDS* 2009; *23* : 1163-9.

4. Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. *Cochrane Database Syst Rev* 2010; (3): CD008272.

5. Pereyra F, Addo MM, Kaufmann DE, Liu Y, Miura T, Rathod A, *et al*. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. *J Infect Dis* 2008; *197* : 563-71.

6. Keoshkerian E, Ashton LJ, Smith DG, Ziegler JB, Kaldor JM, Cooper DA, *et al*. Effector HIV-specific cytotoxic T-lymphocyte activity in long-term nonprogressors: associations with viral replication and progression. *J Med Virol* 2003; *71* : 483-91.

7. Ntale RS, Chopera DR, Ngandu NK, Assis de Rosa D, Zembe L, Gamieldien H, *et al*; the CAPRISA 002 Study Team. Temporal association of HLA-B*81:01 and HLA-B*39:10-mediated HIV-1 p24 sequence evolution with disease progression. *J Virol* 2012; *86* : 12013-24.

8. Chatterjee K. Host genetic factors in susceptibility to HIV-1 infection and progression to AIDS. *J Genet* 2010; *89* : 109-16.

9. Carl S, Daniels R, Iafrate AJ, Easterbrook P, Greenough TC, Skowronski J, *et al*. Partial "repair" of defective nef genes in a long-term nonprogressor with human mmunodeficiency virus type 1 infection. *J Infect Dis* 2000; *181* : 132-40.

10. Antoni S, Walz N, Landersz M, Humbert M, Seidl C, Dittmar MT, *et al*. Genetic and biological characterization of recombinant HIV type 1 with Env derived from long-term nonprogressor (LTNP) viruses. *AIDS Res Hum Retroviruses* 2007; *23* : 1377-86.

11. Pushker R, Jacqué JM, Shields DC. Meta-analysis to test the association of HIV-1 nef amino acid differences and deletions with disease progression. *J Virol* 2010; *84* : 3644-53.

12. Radhakrishna M, Durga K, Rao RK, Reddy DM, Kondapi AK. Factors associated with conversion of long-term non-progressors to progressors: A prospective study of HIV perinatally infected paediatric survivors. *Indian J Med Res* 2013; *138* : 322-8.

13. Deeks SG, Walker BD. Human immunodeficiency virus controllers: mechanisms of durable virus control in the absence of antiretroviral therapy. *Immunity* 2007; *27* : 406-16.

14. International HIV Controllers Study, Pereyra F, Jia X,McLaren PJ, Telenti A, de Bakker PI, Walker BD, Ripke S, *et al*. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science* 2010; *330* : 1551-7.