

## When do patients develop AIDS?

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The human immunodeficiency virus (HIV) is a retrovirus that infects cells of the human immune system, destroys and impairs their function. In the early stages of infection, the person has no symptoms. However, as the infection progresses, the immune system becomes weaker, and the person becomes more susceptible to so-called opportunistic infections. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS). It can take 10-15 years on average for an HIV infected person to develop AIDS. But some HIV infected patients are still asymptomatic after fifteen or more years of infection but some patients develop AIDS within two years.

This variation in the rate of disease progression is poorly understood and is caused by several factors such as viral reproductive abilities and immune proliferative abilities. An elegant explanation of this question was proposed by Martin A. Nowak in the early 1990s. He pointed out the possible importance of viral diversity due to high HIV mutation rate and created the viral diversity threshold theory. From the threshold theory proposed by Nowak downward, there is no study which can explain the questions about the asymptomatic phase.

Here we discuss on immune impairment effect of HIV to propose a new explanation for a variable length of the asymptomatic phase. We focus on a dysfunction of dendritic cells (DCs), which are crucial in the generation of adaptive immunity, caused by HIV infection. Several studies found that some DC populations are susceptible to HIV and a modulation of DCs by HIV infection leads to interference of their antigen presenting function. This implies that HIV disables DC's ability which may be relevant for optimal induction of HIV specific immune responses. It is also reported that HIV infected individuals have a significant decrease in the number of DCs compared with uninfected donors. A decreased number of DC was shown in late-stage patients, and more recently loss of DC was described in patients with high viral loads or in those with AIDS that develop

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opportunistic infection or cancer. These imply that a progression of HIV infection reflects loss of DCs, which would in turn impair generation of antiviral CTLs. Therefore we can consider the disease progression as increasing of immune impairment rate.

Let an increasing function  $\varepsilon(t)$  be a measure of impairment rate caused by a progressive decrease of DC abundance. Interestingly, we can obtain the impairment thresholds over an increase of  $\varepsilon$ ; “Risky threshold” ( $\bar{\varepsilon}$ ) and “Immunodeficiency threshold” ( $\varepsilon^*$ ). The

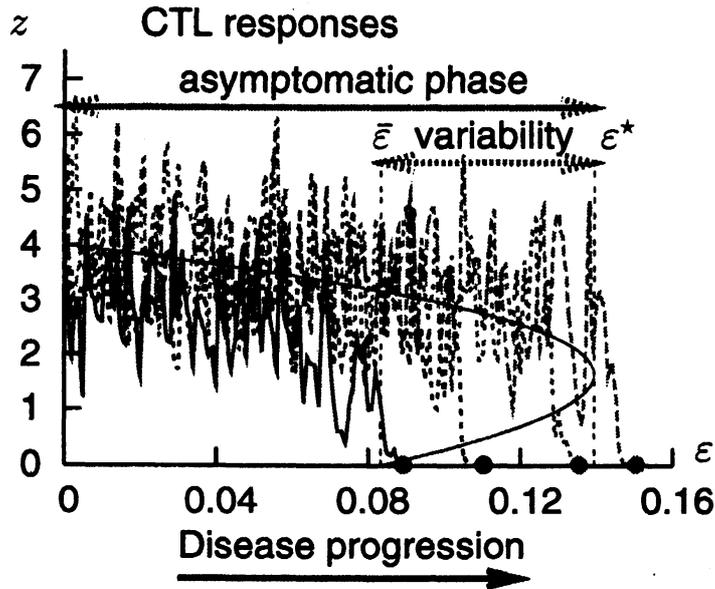


Figure 1: Four representative patterns of disease progression: In terms of our theory, we can conclude that a length of the asymptomatic phase is determined stochastically by the host and viral states between  $\bar{\varepsilon}$  and  $\varepsilon^*$ . We use a simple mathematical model:  $x' = \lambda - dx - \beta xy$ ,  $y' = \beta xy - ay - pyz$ ,  $z' = cxyz/(1 + \varepsilon(t)y + \xi) - bz$  where  $x$ ,  $y$  and  $z$  represent uninfected CD4 T cells, infected CD4 T cells and CTLs, respectively. Stochasticity can occur as a perturbation in the CTL proliferation  $cxyz/(1 + \varepsilon(t)y + \xi)$ , where  $\xi$  is a white noise measured by a normal distribution with mean  $\mu$  and variance  $\sigma$ . Variance is fixed at  $\sigma = 0.05$  in the process. Each path (red, blue, orange, green) is obtained as a sample of the process with mean  $\mu = 0.05$  (red),  $\mu = 0.03$  (blue),  $\mu = 0.0$  (orange) and  $\mu = -0.01$  (green). Positive mean value implies that perturbations are deleterious to the CTL proliferation on average. The white noise is incorporated with a different time scale; for every  $t = 10k$  ( $k = 0, 1, 2, \dots$ ), the value of  $\xi$  is updated. We assume that impairment on DCs accumulates with a very low rate during disease progression,  $\varepsilon(t) = 10^{-4}t$ , where  $10^{-4}$  is the rate of average impairment at which DCs are gradually impaired by HIV during infection.

former implies that immune system *may* collapse when the impairment rate of HIV ex-

ceeds the threshold value. The latter implies that immune system *always* collapses when the impairment rate exceeds the value. The increase of impairment rate, which represents a progression of the infection, boosts the probability of a development of immunodeficiency under some perturbations. Actually, in the infected individual, there are many perturbations which change the host and viral state during the course of HIV infection. For example, it is known that a mutation rate of HIV is higher than other viruses, the mutant virus can escape from the current immune pressures and also HIV populations switch their coreceptor from CCR5 to CXCR4 (which is more replicative than CCR5 virus) over the course of infection. These mutational events lead to some temporal increase of the virus load and decrease of immune responses. Further the emergence of drug resistance, the change of antiviral drug, the withdrawal of antiviral therapy and the infection of other virus also lead to some temporal changes in the infected individual. In terms of our theory, we can conclude that a length of the asymptomatic phase is determined stochastically by the host and viral states between  $\bar{\epsilon}$  and  $\epsilon^*$  (see Fig.1). The patients are usually robust for these perturbations because the HIV infected cells are always suppressed by CTLs if the disease progression does not exceed the risky threshold ( $0 < \epsilon < \bar{\epsilon}$ ). However, when the HIV infection progresses exceeding the risky threshold ( $\bar{\epsilon} < \epsilon$ ), the patients become sensitive to these stochastic perturbations. The most severe patients develop AIDS just after  $\epsilon$  becomes larger than  $\bar{\epsilon}$ ; lower numbers of CD4<sup>+</sup> T cells and CTLs caused by stochastic events result in immunodeficiency (red in Fig.1). While the most mild patients do not develop AIDS until the infection progresses exceeding the immunodeficiency threshold; viral load is well suppressed to low level by established CTL responses with higher numbers of CD4<sup>+</sup> T cells and CTLs (green in Fig.1). Thus the patients develop AIDS between  $\bar{\epsilon}$  and  $\epsilon^*$ .

## References

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