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HIV to AIDS – The Dynamics of HIV – 1 Infection

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In the course of 30 years since the discovery of HIV as the causative agent of AIDS we have made remarkable progress in understanding the biology and pathogenesis of the virus and the field of viral dynamics has been critical for understanding the details of progression of HIV infection to AIDS. A typical primary infection is characterized by high levels of viral titers in plasma [1,2] with concomitant decrease in the CD4+ T cell numbers. At the end of primary infection stage the viral titers decline due to depletion of $CD4^+$ T cells and partial immune activation [3,4]. Few months later the virus enters the chronic stage typified by a slow increase in the viral titers and gradual decrease in the $CD4^+$ T cell levels [3,4], immune activation, increased cell turnover and destruction of host immune system [5]. The final stage leading to AIDS and consequently to death is characterized by rising viral titers and decrease of $CD4^+$ T cells to a level where immune control over viral infection is lost [3,4].

Studying dynamics of HIV infection under suppressive Antiretroviral Therapy (ART) has offered substantial insights into the pathogenesis of HIV-1. Study by Mellors et al. [6] has revealed the importance of viremia where they showed that patients with higher viral load progressed to AIDS multiple folds faster than the patients with lower viral loads. Studies of decay of virus and productively infected cells (virus producing cells) under suppressive ART regiment using clinical assays with a detection limit of 50 HIV RNA copies/ml have shown that there are two phases of virus and productively infected cell decay [7-9]. A rapid first phase followed by a slow second phase which is accredited to long lived $CD4^+$ T cells or macrophages leading to a quasi-steady state level called set-point [10], where viral titer level and number of virus producing cells remains constant. This concept was called the steady state model. Based on the first phase and second phase decay half-lives it was indicated that prolonged ART could lead to the elimination of virus [11]. However development of single copy assays using real time RT-PCR capable of detecting as low as one HIV mRNA/ml [12] revealed two more phases of viral decay, a third phase with half-life ranging from 39 weeks to 69 weeks [13,14] and a controversial fourth phase with infinite half-life.

Due to subsistence of infected cells capable of making virus after several years (latency) elimination of HIV by ART was ruled out. Hence, it is clear that development of vaccine for prevention of infection is of utmost significance [15]. HIV establishes latency by integrating into the genome of a small fraction of resting $CD4^+$ T cells [16-19]. These latently infected cells cannot produce virus in the resting memory state but they can produce virus on activation [16]. The latent reservoir is maintained by homeostatic proliferation of these latently infected resting $CD4^+$ T cells. It is known that individuals on ART also have latently infected cells, this was demonstrated when HIV infected people on highly active antiretroviral therapy (HAART) regimen for more than year have seen resurgence of virus within two weeks of HAART interruption [20]. Activation of these latently infected reservoirs may occur via immune activation by some co-infection or vaccination. A new therapeutic strategy to lure out the virus from latently infected cells to successfully eliminate it using HAART is an area of extensive research and debate.

Although we acquired a lot of knowledge about HIV over the years, the exact mechanism of disease progression from primary infection to AIDS is still not known. Simple answer is that HIV infects $CD4^+$ T cells and kills and loss of these cells leads to AIDS. In reality it is more complicated than that, because $CD4^+$ T cell death in vivo is contentious. There are two possible mechanisms to kill productively infected cells 1. Viral cytopathicity 2. $CD8^+$ T cell/CTL responses. Another feature of the pathogenic infection is chronic immune activation and high levels of $CD4^+$ T cell killing which subsequently leads to immune exhaustion and damage of lymphoid tissue. Overall it is yet to be determined if the above mentioned mechanisms all together could lead to disease progression. As of now early HAART treatment for primary infection and immunotherapy plus HAART treatment for chronic infection seem to be the best interventions.

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