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# Cyclosporin A in combination with HAART in primary HIV-1 infection

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**ABSTRACT: HAART is the cornerstone of HIV therapy, and has significantly reduced morbidity and mortality associated with HIV disease. The institution of HAART during the primary HIV-1 infection has a more profound influence on the ultimate pattern and rate of disease progression than therapy commenced later on. However, it also well demonstrated that HAART alone is not able to eradicate the virus, unless over a life-long period of time. There is therefore the need to develop alternative strategies aimed at modulating the immune responses in order to achieve the long-term control of HIV even once HAART is discontinued. Among immunomodulant agents, cyclosporin A in combination with HAART might play a role in the treatment of people with primary HIV-1 infection. (J Biol Regul Homeost Agents 2000; 14: 79-81)**

**KEY WORDS:** *HAART, Primary HIV-1 infection, Cyclosporin A, Immune-based strategies, Immunosuppression, HIV eradication*

## INTRODUCTION

The introduction of HAART has considerably improved the prognosis of HIV infection (1), having significantly reduced, since 1996, morbidity and mortality associated with HIV disease (2-4). Despite this achievement, several pieces of evidence indicate the presence of persistent residual virus replication even in highly active antiretroviral therapy (HAART)-treated subjects with an effective control of HIV replication (i.e. below 50 RNA copies/ml) (5-10). These results have seriously questioned the possibility to eradicate the virus within the previously estimated time-frame, i.e. 2 to 3 years (11). Based upon most recent data, eradication of HIV might be achieved only after a life-long therapy (12). Clearly, this is not clinically feasible because of the wide range of physical and psychological morbidities associated with long-term HAART. Furthermore, the cellular compartment, composed of latently-infected memory CD4+ T cells containing replication-competent virus (5-7), that allows the virus to escape both antiviral therapy and the immune response, might also play a role in the persistency of residual virus replication, thus explaining rebound of plasma viremia back to baseline levels once therapy is discontinued. Of note, this pool of cells originates very early in the natural history of the infection. As a matter of fact, the institution of HAART as early as 10 days following contamination, does not efficiently prevent the formation of this pool.

In this scenario, alternative strategies are welcomed, particularly in the setting of the primary infection, when the mutual interactions between host factors and virus factors determine both the pathogenesis of HIV infection and the rate of disease progression (13, 14). Furthermore, start of treatment at the time of the peak of viremia during primary HIV-1 infection is accompanied by the preservation of both CD4 and CD8 T cell HIV-specific responses (15). Therefore, HAART during this stage has a more profound influence on the ultimate pattern and rate of disease progression than therapy commenced later on.

Even in PHI, HAART is the cornerstone of HIV therapy. However, particularly intriguing is the possibility to modulate the response to HIV during PHI with immunomodulants that, alongside potent antiretroviral therapy, can down-regulate the heightened state of immune activation, which is a common feature during this phase of the infection. Indeed, the rationale for this approach is the role of specific and non specific immune activation in HIV infection and replication at the single cell level and in tissues (13, 16-18). This strategy might reduce the "set point" of early viral load and also lower the pool of latently infected cells that are the major determinants of the natural history of HIV disease (1).

In this context, the use of immunomodulatory agents, such as cyclosporin A (CsA), might be beneficial. CsA is a potent immunosuppressive agent that suppresses T cell activation by inhibiting interleukin (IL)-2 release and IL2 dependent T cell proliferation and differentiation (19). It is also able to block quiescent T lymphocytes in the $G_0$ phase or at the beginning of the $G_1$ phase, thus likely reducing the number of proliferating cells capable of supporting viral replication. CsA effects are specific and reversible, with no effect on phagocytic function. Therefore, CsA in combination with HAART might suppress HIV replication, prevent the dissemination of the virus, restore both


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CD4+ T cell counts and a correct CD4/CD8 ratio, and preserve HIV-specific T cell responses.

CsA has been previously tested *in vivo* in clinical studies of patients at different stages of disease and recipients of HIV-infected transplants. These studies produced conflicting results. Of note, no adequate antiretroviral therapy was administered to these patients, and truely detrimental effects were observed only in late stage of disease. Some recent experimental data indicate that the transcription factor NF-ATc is a positive regulator of HIV-1 infection in resting CD4+ T cells *in vitro*, since NT-ATc-transfected cells are fully permissive for HIV replication even in the absence of any other stimulus (20-22). These findings emphasize the potential role of CsA in HIV therapy. In fact, CsA blocked HIV replication by 58% (22) and led to a diminution of the levels of fully reverse transribed genomic HIV-1 DNA; moreover, in primary CD4+ T cells, NF-ATc expression was well correlated with the levels of HIV replication and the inhibitory effect of CsA was equally active (22). CsA therefore inhibits NF-ATc pathways and prevents the early events after full transcription, such as nuclear import of viral DNA in resting CD4+ T cells (21, 22). Based upon these observations, CsA might be an attractive tool in primary HIV infection.

Furthermore, as far as the effects of immune activation in tissues are concerned, a recent set of data (23) emphasizes the potential importance, yet not proven, of continuous virus production even during HAART because of local bursts of immune activation that occur asynchronously in varying sites of inflammation. Therefore, according to this hypothesis, some virus replication would persist at any given moment because of local sites of activation supporting HIV replication at varying instants. Finally, in a study carried out on monkeys acutely infected with SIV, CsA induced a significant, albeit transient, reduction of proviral DNA and p27 antigenemia, and delayed the typical decline of the CD4/CD8 ratio (24).

Overall, these data provide support for the rationale to design strategies that, along with the use of potent antiretroviral therapy, inhibit the heightened state of cellular activation.

In this context, in a pilot study carried out at the Divisions of Infectious Diseases in Lausanne and Milan, 8 patients with primary HIV infection have been treated with CsA in combination with HAART, and followed for at least 36 weeks. CsA was discontinued after 8 weeks in all patients, while HAART was continued. This approach induced a remarkable effect on plasma viremia levels. Furthermore CD4 percent and count values increased substantially in a very short period of time (2 to 7 days), suggesting the engagement of a phenomenon of T cell redistribution from the lymphoid tissue into the bloodstream induced by CsA in combination with HAART. It is conceivable that the reduction of cell activation along with the remarkable inhibition of the inflammatory cytokine pathways exert an immediate and potent effect on cell sequestration in lymphoid tissue. Furthermore, CD8 percent and counts decreased rapidly and, consequently, a dramatic increase of the CD4/CD8 ratio occurred during the first week of therapy. These quantitative changes in the T cell subsets were more marked than those observed in a group of patients with primary HIV infection treated with HAART alone. Interestingly, these results were maintained over time even after the discontinuation of CsA (at week 8). Furthermore, analysis of HIV-specific CD8 T cell responses prior to and following treatment with CsA in combination with HAART clearly demonstrated that these responses are not blunted by the use of CsA, persisting during and after treatment with CsA. Finally, no significant CsA-related adverse events occurred in any of the 8 patients enrolled in this pilot study. Of note, the suggestion that CsA could be oncogenic by itself *in vitro* (25) does not find support in a very large cohort of CsA-treated patients with rhemathoid arthritis (26). It is however conceivable that a very short use (8 weeks or shorter) of CsA does not add a significant oncogenic risk.

Overall, *in vitro* and *in vivo* clinical studies support the design of therapies that combine immune downregulation and HAART in primary HIV-1 infection. This approach can ultimately exert a major impact on the long-term course of HIV infection and warrant the design of a randomized controlled trial, comparing the use of potent antiretroviral therapy either in combination with CsA or alone during primary HIV-1 infection.

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