# Co-Infection with HIV and *Mycobacterium tuberculosis*: Immunologic Interactions, Disease Progression, and Survival

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This article presents the hypothesis that co-infections accentuate the intrinsic immunopathology of HIV and thereby shorten the HIV disease free-interval and survival. Our published experience with *Mycobacteria tuberculosis* (Mtb) co-infection with HIV is reviewed. In this longitudinal study of the efficacy of isoniazid prophylaxis we present evidence that subclinical co-infections with *Mtb* shortened the interval for onset of HIV disease and survival and that treatment with isoniazid reversed this. Our preliminary data on lung immunopathology in active tuberculosis is presented in another paper in this issue by M Gloria Almeida and J Roberto Lapa e Silva who show that inflammatory host factors are expressed in the lung. Their expression in this millieu may mediate enhanced HIV replication. Lastly, we will review the data on the interactions between immune cells that trigger HIV replication in a model of how sexually transmitted diseases may enhance HIV transmission from men to women.

Over the last ten years, the paradox of how HIV infection results in the destruction of the immune system, as measured by the number of CD4+ T cells has recently been unraveled. Many hypotheses have been advanced, including the most extreme, that HIV does not cause AIDS. Our current understanding on the relationship between viral production and turn-over of CD4+ lymphocytes indicates that billions of virions and infected cells are destroyed every day (Wei et al. 1995, Ho et al. 1995a, Wain-Hobson 1995).

This vividly illustrates the very hostile environment created by the immune system. However, HIV counters by massive force of numbers. So long as a few progenies survive to continue replication HIV ultimately gains the upper hand when the immune system can not keep up with the shear numerical assault of HIV. Clinically this deadly combat is reflected by the clinical latency period, the calm before the storm of HIV associated illnesses and AIDS.

The accumulated data are provided by (i) longitudinal studies showing that overall viral load increases over months and years, (ii) progressive loss of CD4 lymphocytes being associated with increasing viral burden, (iii) much more virions and HIV-infected cells being evident than previously thought, and (iv) circulating virus detected in peripheral blood are viruses that have escaped from lymphoid organs, the site of HIV replication and destruction of the virus (Rasz et al. 1986, Simmonds et al. 1990, Panteleo et al. 1993, Embreton et al. 1993, Piatiak et al. 1993, Patterson et al. 1993, , Wain-Hobson et al. 1993, Connors et al. 1993, Cao et al. 1995). The most direct data were recently provided by two research groups (Wei et al. 1995, Ho et al. 1995a) These investigators demonstrated that the clearance of peripheral blood virions (between $10^8$ to $10^9$ viruses) is paralleled by turn-over of CD4 T cells (0.1 to 7 x $10^9$). Furthermore, a daily relative net loss of 0.02 to 0.2 x $10^9$ CD4 T cells accounts for a slow progressive depletion and the clinical latency of HIV infection.

In this setting of the immunopathology of HIV, we hypothesize that co-infection by other pathogens (eg, *Mycobacterium tuberculosis* and *Chlamydia trachomatis*) enhance HIV replication, tipping the balance in favor HIV and, thereby shortening survival and potentially enhance HIV transmission. Co-infections may enhance HIV replication by direct or by indirect mechanisms that trigger viral replication. Alternatively, co-infection may result in immune activation, suppression or immune cell depletion that further affect HIV replication or contribute to immunodeficiency. In this symposium, we will outline the indirect mechanisms by which

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co-infection enhance HIV replication. These factors are cytokines triggered during the immune response to the co-infection, reactive oxygen radicals, and cell-cell contact via the engagement of specific surface receptors. These factors trigger HIV replication or cell to cell transmission of HIV (Ho et al. 1995b, Lipton & Gendelman 1995, Bukrinsky et al. 1995).

Evidence that co-infection with *M. tuberculosis* shortens the interval for HIV disease progression and survival is provided by our published data in the *Lancet* of a cohort of Haitians who were randomly assigned to receive either isoniazid with vitamin B6 or vitamin B6 alone (Pape et al. 1993). Patients were not given anti-retroviral agents because this is not the standard of care available in Haiti. We showed that isoniazid was effective in preventing active tuberculosis. We further examined the potential effect of *M. tuberculosis* co-infection on the natural history of HIV. For this analysis, we excluded those who later developed tuberculosis. We found that isoniazid prophylaxis prolonged the HIV disease-free interval and survival. The prolongation of HIV disease free-interval and survival by isoniazid appeared comparable to that of anti-retroviral therapy.

We speculated that immunologic mechanisms triggered by co-infection with *M. tuberculosis* may adversely affect HIV disease progression and shorten survival. Containment of the bacilli one key feature of control of the infection. The containment of tubercle bacilli within a granuloma requires the generation of cytokines, including tumor necrosis factor-α (TNF-α) (reviewed in Pape et al. 1993). However, TNF-α is a potent enhancer of HIV replication, which may in this case increase viral burden leading to HIV-related diseases, AIDS and death. Isoniazid, by its ability to kill *M. tuberculosis*, obviates the host immune response to contain *M. tuberculosis* and thereby, lessens viral burden and prolongs HIV symptom-free interval and survival. Furthermore, the immune response during active tuberculosis has been shown to prime peripheral blood cells and enhance their susceptibility for HIV infection (Tossi et al. 1993).

Evidence that co-infection with sexually transmitted diseases can enhance HIV replication and potentiate transmission is provided by the recent *Journal of Experimental Medicine* article reporting an *in vitro* model of HIV transmission facilitated by *C. trachomatis* (Ho et al. 1995b). In this work, we found that neutrophils from HIV-seronegative donors induce HIV-replication from HIV-infected patients' mononuclear cells and cell lines. Furthermore, enhanced HIV replication was mediated by cell-cell contact and the generation of reactive oxygen radicals, because either partitioning of cells or removal of reactive oxygen radicals by superoxide dismutase and catalase abrogated the enhancement of HIV replication as well as the production of pro-inflammatory cytokines and HIV. In addition, engagement of surface ligand-receptors between cells has been shown to enhance HIV replication (Pinchuk et al. 1995). This *in vitro* model provides a biologic explanation for the increased risk for acquiring HIV infection when co-infected with an sexually transmitted disease. This may be related to the local recruitment of neutrophils by any sexually transmitted disease and the induction of infectious virus from mononuclear cells present in semen.

In summary, we presented longitudinal data on co-infection with *M. tuberculosis* contributing to enhanced HIV disease progression and shorten survival. We also delineated potential host factors that trigger production of infectious HIV and thereby, increasing sexual transmission of HIV. We speculate that co-infections mediate shorten HIV symptom-free time and survival by triggering increased HIV replication and viral burden that results in enhanced depletion of CD4 T cell and immunodeficiency. Co-infection with opportunistic infections is also the result of the immunopathology of HIV. Therefore, our research efforts should be directed at (i) evaluating effective prophylaxis or treatment for co-infections, (ii) delineating host factors that enhance HIV replication, and (iii) seeking novel strategies that interrupt the effects of these factors. Undertaking these research approaches will likely result in reducing HIV replication and viral burden and thereby increasing duration of symptom-free interval and survival in HIV-infected persons. Lastly, these approaches may also reduce HIV transmission and thereby limiting the scope of the HIV pandemic (Grosskurth et al. 1995).

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