Eradication of helminthic infections may be essential for successful vaccination against HIV and tuberculosis

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The current epidemics of tuberculosis and acquired immunodeficiency syndrome (AIDS) (caused, respectively, by infection with *Mycobacterium tuberculosis* (MTB) and human immunodeficiency virus (HIV)) are a major cause for concern. No successful or effective anti-HIV vaccine has been yet developed, and Bacille Calmette–Guérin (BCG) has failed to confer protection against tuberculosis in developing countries. Nevertheless, apart from the use of social and educational measures, the only plausible way to overcome these epidemics is through mass vaccination.

An effective protective vaccine against MTB or HIV infection should generate a potent cellular immune response, which is dependent on a dominant T-helper type 1 (TH1) cellular response, rather than a T-helper type 2 (TH2) humoral immune response. These two cell types cross-regulate each other and thus cytokines produced by one T-helper subset can suppress the production and/or activity of the other.

Helminthic infections affect more than a third of the world's population, and have a similar geographical distribution to that of HIV and tuberculosis. In developing countries, children born in areas where intestinal nematodes are endemic harbour worms for most of their lives. Individuals with helminth infections are chronically immune-activated and have a very pronounced TH2 immune profile.

We have hypothesized that the chronic immune activation and TH2 immune profile caused by helminthic infections make the host more susceptible to HIV infection and less able to cope with it once infected. This may play a major role in the pathogenesis of AIDS in Africa (Bentwich Z et al. *Immunology Today,* 1995, **16**: 187–191) and account for the widespread tuberculosis in developing countries (Bentwich Z et al. *Immunology Today,* 1995, **201** 485–487). Furthermore, intestinal helminth infections may also compromise the generation of protective immunity upon vaccination for both HIV and tuberculosis.

This hypothesis is based on the following observations: several populations in Africa and South-east Asia have a pre-existent dominant TH2 cytokine profile and extremely high immune activation (e.g. Bentwich Z et al. *Clinical and Experimental Immunology,* 1996, **103**: 239–243); lymphocytes isolated from Ethiopian immigrants recently arrived in Israel had very impaired signal transduction and anergy following stimulation; there was a clear inverse correlation between immune activation in these Ethiopian immigrants and the capacity of their lymphocytes to proliferate and secrete chemokines following stimulation with tuberculin purified protein derivative (PPD) ($r = -0.58$, $P<0.002$); helminth-infected Ethiopian immigrants responded poorly to PPD skin test compared with such immigrants following deworming ($P<0.005$) (Borkov G. et al. *Journal of Clinical Investigation*, in press).

Why do the populations of developing countries exhibit such immune profiles? Though several factors could contribute to it, such as constant exposure to infectious diseases, poor hygiene and malnutrition, we have proposed that it is mainly a consequence of helminthic infections (e.g. Kalinkovich A et al. *Clinical and Experimental Immunology,* 1998, **114**: 414–421). This conclusion is largely based on the following evidence: the high prevalence of helminthic infections among the Ethiopian immigrants in Israel (>90% were infested with at least one parasite, while some had even 5 different parasitic infections); the immune profile of the Ethiopian immigrants returned to normal following the eradication of the helminthic infections; helminth eradication had also a clear effect on the HIV infection/disease, i.e. once their helminth infections had been eradicated the response of the Ethiopian immigrants to highly active antiretroviral treatment was similar to that of other Israeli inhabitants (Weisman Z et al. *Journal of AIDS*, 1999, **21**: 157–163); preliminary results of a study carried out in Ethiopia show that eradication of helminthic infections in people infected with both these and HIV is associated with significant decreases in HIV plasma viral load. Furthermore, HIV viral load was correlated with helminthic "load" (number of eggs found in stools of HIV and helminth-infected individuals).

The following observations further support our hypothesis: in Africa, faster progression to AIDS

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and increased HIV viral load occur in areas endemic for helminths; the increased HIV viral load in plasma found in individuals infected with leishmaniasis decreases following treatment of the latter; the poorest communities of Western Cape Province of South Africa, which are highly infested with helminths, have also one of the highest incidences of tuberculosis in the world.

In addition, *Schistosoma*-infected mice have an impaired TH1 response; selective inhibition of T-cell subsets is evidenced in filariasis, in which T-cells show antigen specific anergy, while antibody responses remain intact; and humans infected with *Schistosoma mansoni* have an impaired tetanus toxoid TH1 response.

A large number of candidate protective anti-HIV and tuberculosis vaccines are now being designed and tested. However, they may fail to be effective, especially where they are most needed, i.e. in South-east Asia and Africa, which have the highest incidence of MTB and HIV infections in the world, since the ability of the host to mount an immune response is greatly determined by the pre-existing state of the immune system. This has been clearly shown in TH2-dominant animals, which were not able to mount a cellular immune response against HIV envelope peptides, while the normal non-infected animals could do so. Thus, individuals with a pre-existing dominant TH2 profile may not be able to generate a TH1-type response. Since the majority of individuals afflicted with HIV and/or MTB infections live in developing countries, mostly in Africa and South-east Asia, it is highly important to develop vaccines and plan clinical trials taking into consideration their immune background.

Several key questions still remain to be answered in the context of developing vaccines against tuberculosis and HIV vaccines in developing countries. For example, can the pre-existent pronounced TH2 background be shifted to a TH0 or TH1 prior to vaccination, and thus facilitate the generation of cellular immunity by HIV or tuberculosis vaccines? Would eradication of helminths by itself be enough to transform the immune profile to a TH0, or allow easier manipulation towards a TH1 profile? What are the kinetics of the changes in the immune profile following eradication of helminth infection and the conditions necessary for them to persist? It is important to determine whether modulation of the immune response, e.g. by adjuvants, is possible in the presence of helminthic infections and following their eradication.

Clearly the efficacy of HIV and tuberculosis candidate vaccines will have to be tested in human field trials in Africa and Asia, in areas with a high incidence of HIV and MTB infections. However, potentially good vaccines may fail in such trials if they are tested under the current scenarios in developing countries. The failure of BCG vaccination in Africa and Asia to confer the same complete protective immunity against tuberculosis that it did in developing countries supports this assumption. It therefore becomes essential to take this major issue into consideration for development of any protective vaccine. The simplest and most effective way to do so is to eradicate helminthic infections before or during vaccination. Such eradication is important and has clear advantages and benefits in itself, regardless of the issue of HIV and tuberculosis vaccination, for growth retardation, impaired mental abilities, and capacity to cope with infections, anaemia, etc.

Treatment of helminthic infections is possible, relatively inexpensive and simple, and has already become a priority for public health in developing countries. Eradicating helminths in the context of the fight against HIV and tuberculosis is feasible, and may have additional far-reaching influences on health. We suggest that deworming would have a significant impact on the ongoing AIDS and tuberculosis epidemics, and more importantly, we believe that without eradication of helminths, HIV and tuberculosis vaccines may fail to confer protection in helminth-endemic areas. ■