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EDITORIAL

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Why Brazil should not be a site for AIDS vaccine trials

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In the last eight years more than 15 immunogens that were candidates for a vaccine against HIV/AIDS were tested, in a limited way, on small groups of individuals, with the goal of establishing whether vaccines are safe and capable of stimulating immune responses. The results of these preliminary trials with different antigens indicate merely fleeting protection and dubious effectiveness against the strains of HIV in circulation in the regions tested (07,13,14).

The search for an explanation of how HIV causes AIDS (15) showed a variety of pathogenic mechanisms participating in direct or indirect ways in the course of the HIV infection.

First there are effective humoral and cellular responses that limit the viral replication, the positive T helper CD4 cells tend to decrease and cells like the macrophages begin to transport great quantities of the HIV to the lymph nodes. Human cellular proteins like HLA DR, HLA class I, and beta-2-microglobulin are in the gp 120 of the HIV and interact with the cellular receptors of the T4 lymphocytes and the cells presenting antigens like the macrophages(1).

When it is cytopathic, the HIV virus directly destroys the infected cells. However the other half of HIV isolates are non-cytopathic and use different indirect mechanisms to compromise and/or destroy infected and non-infected cells: 1. Apoptosis (10) - abnormal induction in mature T cells (lymphocytes T, CD4+ and CD8+) of the programmed cell death, by indirect via using the gp 120 immune complex, HIV at a distance, and even non-infected CD4+ lymphocytes, or by direct action of infected CD4+ lympocytes upon non-infected activated T lymphocytes* ; 2. Specific immune response of cytotoxic T lymphocytes against HIV-infected cells; Autoimmune response caused by viral antigens with homology toward cellular antigens (03) or by the presence of HLA-DR' on the surface of the HIV envelope (01).

The components of the immune response that promote protection against HIV are not established (06,13). Protecting activities are attributed to the neutralizing antibodies and the cytotoxic T cells (06). These protective components are fleeting, as they are substituted by or simultaneous with dysfunctional mechanisms of the immune system, autoimmunity and even cell death (06,07,13,15).

The majority of vaccines against HIV infection and AIDS were manufactured in the developed countries from syncytia-producing viruses (cytopathic strain), and maintained in laboratories for long periods of time (07). Besides the notable genetic variability of HIV from person to person, and from region to region, it is more easily transmitted when the HIV variantis a non-syncytia-inducing virus (07) i.e., is a non-cytopathic strain. Thus, incompatibility between the vaccine products that are being tested and the HIV strains in circulation in different populations is a constant problem.

Only through a thorough understanding of the structure, composition, and infection mechanisms of the various HIV strains, and a complete understanding of the protective immune response and the physiopathology of the different stages of the HIV infection will it be possible to discover vaccines or immunomodulators that will be able to protect human beings (02,04,07,13). The presence of HIV in lymphocytes, macrophages, and dendritic cells expands the population of infected cells (13,15), and various interactions take place with the normal cells of the human organism. These interactions are uncontrolled and often unpredictable, sometimes producing untoward

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reactions like dysfunction, destruction and autoimmune destruction instead of protective responses (13,14,15). The fundamental problem with the vaccines being tested and the immunomodulators proposed is that while they may intensify mechanisms that are favorable to immunological protection, they might instead actually provoke destruction or derangement of the immune system, or merely be innocuous and ineffective (02). On the other hand, immunosuppressorial drugs like corticosteroids, cyclosporin, and pentoxiphylline (11,12) show partially favorable results in certain cirumstances with HIV infection. Marked regional antigenic differences among different HIV strains must also be considered.

The negative results presented by HIV vaccinologists at the Sixth Annual Conference on "Advances in the Development of Vaccines for AIDS", (which took place in November of 1993 in Alexandria, Virginia, sponsered by the National Institute of Allergies and Infectious Diseases, or NIAID), were very close to what was expected beforehand. These discouraging results in the preliminary trials with HIV vaccines caused dismay showed the need for immediate review of the large-scale efficacy trials. Certainly unsafe or ineffective products should not be tested on a massive scale.

The negative results were attributed to the differences between the existing vaccines, which were developed from viruses that were adapted and maintained in laboratories, and those viruses that are in circulation in the different populations tested (04).

The need for review of the plans for large-scale tests of vaccines, in the face of these unfavorable results, has been causing delays and provoking apprehension among the vaccine manufacturers, as companies like Genentech and others have stocked more than 200,000 doses to use in Third World countries (04). The World Health Organization, through the head of the AIDS vaccine development, Jose Esparza, contends that large- scale trials in developing countries will providee more information than 1000 lab experiments, although Jose Esparza recognizes the lack of interest by the manufacturers in tailoring specific vaccines from strains that circulate mainly in Third World countries (04).

The damaging impact that a mass vaccination could provoke in the population of the Third World countries chosen as testing sites must be considered with great care. The eventual positive benefits resulting from the development of an efficient vaccine against AIDS would not eliminate the risks of the tests. The candidate AIDS vaccines and an eventual succesful vaccine against AIDS are and will be the exclusive property of the pharmacuetical companies that develop them (14). The strengthening of the medical and scientific infrastructure of the participating countries, high HIV infection rates, lower operational costs, and a weaker tradition of human rights and social control are other arguments presented in favor of the trials (08,14).

In order for the developing countries to obtain an anti- HIV/AIDS vaccination of 90% efficiency, it would be necessary to vaccinate 75% of the adults and adolescentes in order to obtain stabilization of the prevalence of HIV infecton. If however the vaccine used has only 50% efficiency, the prevalence over the course of 20 years could multiply up to four times (09). Less efficient vaccines would have even worse results.

If we consider as an example the price of the vaccine for hepatitis B in poor countries, we conclude that efficient vaccines are not always available or affordable, due to elevated costs. Thus, Third World countries test vaccines from the First World on a large scale (08), assume the risks of this procedure, and benefit with the strengthening of a few chosen medical/scientific institutes, but then are subject to unbearable prices, at least for their weaker economies, due to the lack of international regulatory mechanisms (14), and are also obligated to use products of inferior quality, because of the incompatibility between the strains existing in their population and those that generate the vaccine products, which will be unlikely to protect their populations from the devastating menace of HIV/AIDS infection.

It is fit therefore to pose the following questions for discussion and reflection:

1. Is it fair that citizens in developing countries be subjected to risks associated with vaccine products with doubtful preliminary results and with no guarantee of indemnification of possible damages caused?

2. Will it be a fair deal to submit our populations to the risks of mass vaccinations and find ourselves in the same situation as with the vaccination for Hepatitis B, with inaccessible prices?

3. Why won't citizens of the First World also be submitted to these large scale trials? After all, these vaccines were produced from European and American variants of HIV, and will be sold and preferentially applied there.

We anxiously await the Brazilian government take a stand in defense of our population.

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