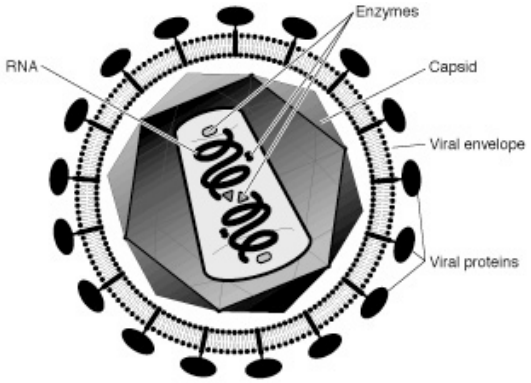
BIOE 301 LECTURE 10
MITALI BANERJEE

A VACCINE FOR HIV

HIV

AIDS



Structure of Human Immunodeficiency Virus (HIV)

Visit wikipedia.org to learn more about tests done to see if someone is HIV+

ELISA

Western Blot

Which test would you do first?

HAART

Visit wikipedia.org and learn the mechanism of action of the five classes of antiretroviral drugs.

(1) Reverse transcriptase inhibitors (RTIs)

(2) Protease Inhibitors (PIs)

(3) Fusion Inhibitors

(4) Integrase inhibitors

(5) Entry inhibitors

Read the included article from *Science* magazine about a DNA vaccine for HIV and answer questions to make sure you understand important points.

***Science* 20 October 2000:**
Vol. 290. no. 5491, pp. 463 - 465

AIDS:
Enhanced: Preventing AIDS But Not HIV-1 Infection with a DNA Vaccine

Xuefei Shen and Robert F. Siliciano

Individuals infected with human immunodeficiency virus-1 (HIV-1), the cause of AIDS, develop strong immune responses against the virus but never completely eradicate the infection. The extraordinary mutation rate of HIV-1, its ability to evade immune responses by establishing a latent (silent) infection, and the progressive destruction of the CD4+ T helper cells [HN2] that it infects all contribute to the inability of the immune system to completely destroy this virus. These characteristics also complicate the development of vaccines to prevent HIV-1 infection. Indeed, it is currently unclear whether it will be possible to develop a vaccine that can actually prevent infection. Nevertheless, an important study by Barouch et al. suggests that vaccine-induced immune responses may control the virus effectively enough to prevent clinical disease even if they fail to prevent or eradicate infection.

Most vaccines against viruses prevent infection by inducing antibodies that stop the virus from infecting host cells. It is difficult to induce antibodies to HIV-1 that serve this protective role. This is a reflection of the enormous variation in the HIV-1 envelope (env) protein and the failure of most antibodies that recognize this protein to neutralize the virus. For these reasons, investigators developing vaccines to protect against AIDS have concentrated on boosting the response of CD8+ cytolytic T lymphocytes (CTLs). These lymphocytes provide resistance to infection with HIV-1 by inducing lysis of virally infected cells. Numerous studies implicate virus-specific CD8+ CTLs as crucial players in the control of HIV-1 replication...

... Barouch and colleagues use a similar animal model to determine whether vaccine-induced immune responses, especially CTL responses, could prevent infection or ameliorate the course of disease. In this case, the virus used to infect rhesus monkeys was a chimeric simian/human immunodeficiency virus (SHIV) consisting of the SIV genome containing the HIV-1 env gene instead of the SIV env gene. Rhesus monkeys were immunized with a vaccine that contained DNA encoding the SIV gag and HIV-1 env proteins as well as human interleukin-2 (IL-2), a cytokine that enhances the immune response. Although immunized monkeys developed CTL responses that could be readily measured, they were not protected against intravenous challenge with a large dose of a highly pathogenic form of SHIV. However, the pattern of infection and the course of disease were altered markedly compared with control monkeys receiving a sham DNA vaccine. Sham-immunized animals generated only weak CTL responses after infection and showed high levels of viral replication and a rapid loss of CD4+ T cells. There was clear disease progression in the control monkeys, and half of them died within 140 days of being exposed to SHIV. In contrast, monkeys immunized with optimal doses of the vaccine had a slightly blunted initial increase in virus levels in the blood (viremia) and then developed potent secondary CTL responses, with gag-specific CTLs comprising an astonishing 18 to 40% of the circulating CD8+ T cells. Most important, these animals showed suppression of viral replication to low or undetectable levels with stable CD4+ T cell counts. There was no evidence of clinical disease, and all immunized monkeys survived for at least 140 days. The magnitude of the CTL response induced by vaccination correlated with the degree of suppression of viral replication after challenge with SHIV. Neutralizing antibody responses could not be detected before challenge and appeared in some infected animals only when the viremia had already been partially controlled. These results strongly suggest that a vaccine-induced increase in the number of CTLs was responsible for the control of viral replication (although the part played by neutralizing antibodies and nonspecific innate immune effector responses modulated by IL-2 cannot be excluded).

One of the most interesting aspects of this study is that optimal vaccine-induced immunity required the inclusion of IL-2--in the form of either a

recombinant divalent IL-2-immunoglobulin fusion protein or the genes encoding such a protein. The idea of including cytokines as immune response promoters (adjuvants) grew out of work with tumors where locally delivered cytokines have been identified as potent stimulators of an antitumor immune response. The IL-2-immunoglobulin fusion protein incorporated into the Barouch et al. vaccine presumably provides the second signal needed to drive the proliferation and differentiation of virus-specific CTLs (the first signal is provided by the gag and env antigens).

When interpreting the results of Barouch and colleagues, it is important to keep in mind that the authors have used an animal model in which there is very rapid depletion of CD4+ T cells in control infected monkeys that are not immunized. In six of eight sham-immunized animals, the depletion of CD4+ T cells was almost complete by day 20. Thus, there is not the prolonged asymptomatic period characteristic of HIV-1 infection in humans. In a model infection where so many critical events happen in the first 20 days, the advantages of a vaccine-induced "head start" may be more dramatic than in an infection that progresses less rapidly. Additional studies will be needed to determine whether the same beneficial effects will be observed in vaccinated humans.

The findings of Barouch et al. shed new light on what can be reasonably expected from the candidate AIDS vaccines that are currently under development. If the results can be generalized to immunization of humans with HIV-1 vaccines, then we can expect to have vaccines that do not prevent infection with HIV-1 but nevertheless have a significant effect on the course of the disease, potentially improving the quality of life and the life-span of infected individuals. According to the most recent estimates by the Joint United Nations Programme on AIDS (UNAIDS), about 5.4 million people became infected and about 2.8 million died of AIDS in 1999. If vaccine-induced CTL responses allow long-term suppression of viremia to undetectable levels, the rate of transmission and number of AIDS deaths could be substantially decreased.

This is especially important in countries where effective drug therapy is not readily available. In the United States, the introduction of highly active antiretroviral therapy (HAART)--triple drug therapy consisting of two reverse transcriptase inhibitors and a protease inhibitor--has resulted in a substantial decrease in deaths from AIDS. However, eradication of the virus does not appear to be possible, and HIV-1-induced immune responses may decline in patients on long-term HAART because of decreased antigenic stimulation. Thus, there has also been tremendous interest in the idea that therapeutic vaccination might be combined with anti-HIV-1 drug treatment. With the enhanced immunity engendered by vaccination, it is possible that infected individuals immunized while on HAART will eventually be able to contain the low level of persistent virus even in the absence of drugs, as the immunized animals in this study appear to be able to do.

Q: What makes the development of a vaccine that *prevents* HIV infection unlikely?

Q: What is the *animal model* used to study vaccine-induced immune responses for HIV in humans? What are some problems with this animal model?

Q: What are *cytokines*?

Q: What does it mean to combine a *therapeutic vaccine* with with anti-HIV drug treatment?

Visit wikipedia.org and learn about the six principles of medical ethics:

(1) Beneficence

(2) Non-maleficence

(3) Autonomy

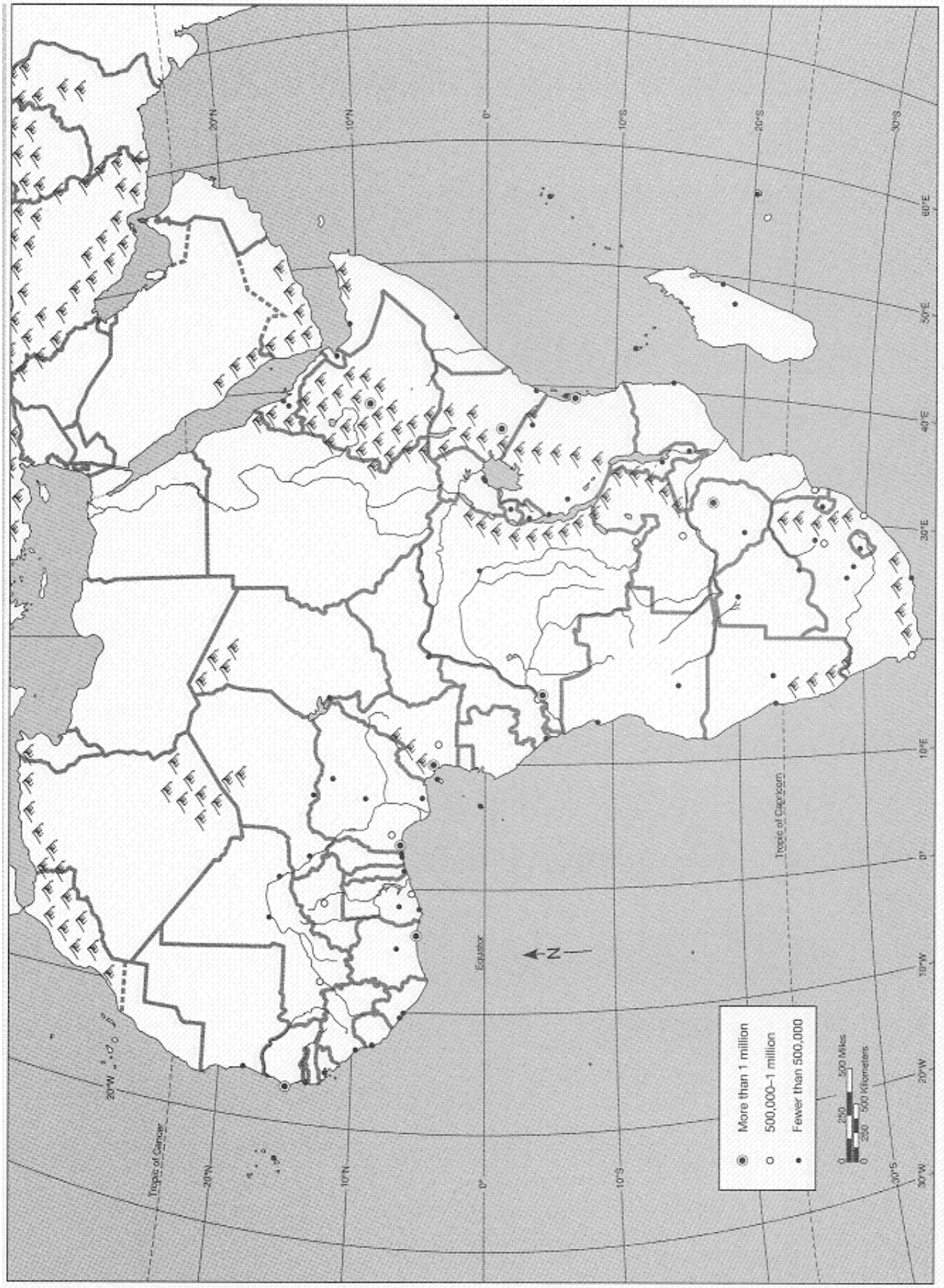
(4) Justice

(5) Dignity

(6) Truthfulness/Honesty

Now read about the Tuskegee syphilis study to prepare for the discussion during Lecture 11. What are the problems with the experiment? Which priniciples of medical ethics did the scientists violate?

Familiarize yourself with sub-Saharan Africa by labeling the map with country names. This geography may be unfamiliar to many students, and so this exercise is included for its importance in visualizing the setting of the HIV epidemic.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Fewer than 500,000
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0 250 500 Kilometers
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Equator
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