HAART and response to the pneumococcal vaccine in HIV-infection.

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A. Study purpose and rationale

Treatment of infection with the human immunodeficiency virus (HIV) has changed dramatically over the past two years; currently, many believe that the standard of care consists of two reverse transcriptase inhibitors (e.g. zidovudine plus lamivudine) and one protease inhibitor, such as indinavir (1). This combination regimen, known as "highly-active anti-retroviral therapy" (HAART) has been linked to lower levels of viremia (as measured by HIV RNA, the "viral load") and increases in the number of circulating T-helper lymphocytes (CD4+ cells) (2), as well as declining morbidity and mortality attributed to HIV infection and AIDS (3). The mechanisms that underlie this improvement are unclear, but it is probable that improvements in lymphocyte function result in increased ability to defend against infection.

Infection with *Streptococcus pneumoniae* (pneumococcus) is common among persons with HIV infection; in one series, pneumococcal bacteremia was approximately 100 times more common in HIV-infected individuals than in uninfected age-matched controls (4). Current guidelines call for immunization with the polyvalent pneumococcal vaccine (5), which contains the polysaccharide antigens of the 23 serotypes of pneumococcus responsible for approximately 90 per cent of infections in humans (6). Despite these recommendations, many HIV-positive persons do not receive the vaccine (7), as there is doubt about its efficacy in the HIV-infected population (8).

Currently, no epidemiologic studies have been published to support its use in this group of people, and some studies have demonstrated a lack of immunoglobulin (Ig) response to the vaccine among persons with HIV, especially those with more advanced disease (9, 10). These findings, however, are not uniform, with at least one study showing that the Ig-response to the vaccine was not significantly different between an HIV-positive and HIV-negative cohorts (11). The applicability of these studies today is suspect because they were carried out before 1996, and the appearance of two important advances in the care of patients with HIV. These studies correlated response to the vaccine with the CD4+ cell count; the viral load is considered a more reliable index of the stage of disease than the CD4+ count (12). The efficacy of the vaccine in large populations of HIV-infected individuals should soon be known: a large, randomized, double-blind, placebo-controlled trial of the vaccine in HIV-positive Africans was recently completed (13).

Given the low cost and low incidence of adverse reaction to the vaccine, it would probably be unethical to carry out such a trial in the United States (14). The question of when to give the vaccine, however, remains unanswered; the studies cited above (9,10), recommend giving the vaccine when the CD4+ cell count is high (i.e. soon after the diagnosis of infection with HIV). A 1991 study suggested giving the vaccine four weeks after the initiation of monotherapy with zidovudine, then the only anti-retroviral in wide use (15). Many patients seen at the CPMC Infectious Disease Clinic have low CD4+ cell counts and high viral loads at the time they begin HAART. Because of this, they might be expected to have a poor response to the pneumococcal vaccine. In addition the response to the vaccine might be more robust after three to four months of HAART[1].

[1] Detailed studies of immune function in patients who have received combination therapy for HIV have revealed two phases of change. The first, which occurs during the first three to four months of therapy, is characterized by a rapid rise in the number of circulating lymphocytes due to the cessation of viral replication. The second phase, thought to occur from the third month to after the twelfth month, involves an increase in the diversity of lymphocytes, permitting immune response to a wider variety of antigens. See WG Powderly, *et al.*, reference number 1.

In this investigation, we propose to examine whether HAART results in an improved response rate to the pneumococcal vaccine. Specifically, we intend to study whether the proportion of responders is higher if the vaccine is given after four months of HAART than if it is given before HAART is begun.

B. Study design

The study is a longitudinal, randomized cohort observation. HIV-positive persons with low CD4+ cell counts (less than 200 per cubic millimeter) would be randomly assigned to one of three groups. The first group would receive the vaccine on day number one of HAART. The second group would receive the vaccine after four months of HAART. The third group would receive the vaccine twelve months after beginning the treatment. In addition, a group of HIV-negative controls would be vaccinated. The control group would be matched to the test (HIV+) groups by age, sex, and ethnicity.

All subjects would have 10 cc of blood drawn before and after vaccination. Serum would be separated by centrifugation, and serum levels of IgG directed against five representative antigens contained in the vaccine would be measured by ELISA. The persons performing these measurements will be blinded to the group assignments. The percentage of responders in each group would be compared; responders will be defined as persons who have a two-fold increase in the concentration of IgG directed against the five antigens. Non-responders will be offered repeat vaccination.

C. Study procedures

For members of the HIV-positive test groups, approximately 10 cc of blood will be drawn at the time that blood is drawn for routine clinical analysis. No additional venipuncture is anticipated, as persons receiving HAART undergo routine venipuncture as part of their clinical care. The pneumococcal vaccine is recommended by the American College of Physicians (5), and thus is frequently administered to persons with HIV. Members of the control group would receive the vaccine for free and have 10 cc of blood drawn just prior to and one month after vaccination. They would be compensated for their participation.

D. Study drugs

No experimental drugs will be used in this investigation. The vaccine used will be one of the commercially available polyvalent vaccines.

E. Medical devices

No experimental medical devices will be used in this investigation.

F. Study questionnaires

No specific questionnaire will be used during this investigation; participants will be asked about adverse reactions at the time of follow-up venipuncture.

G. Study subjects

120 consecutive HIV-seropositive patients seen at the CPMC Infectious Disease Clinic with CD4+ cell counts of less than 200/mm^3 will be enrolled. Potential participants will be identified by their primary physicians prior to the initiation of HAART. Persons having received retroviral therapy in the prior six months will be excluded, as will those who have received the pneumococcal vaccine in the past

10 years. Inclusion of minorities and women: the CPMC Infectious Disease Clinic cares for many women and persons who are members of ethnic minority groups. It is likely, therefore, that women and minorities will be well represented in the study.

20 control subjects will be matched by age, sex, and ethnic background to the test groups. Persons who have received the pneumococcal vaccine in the past 10 years will be excluded.

H. Recruitment of subjects

Potential subjects will be identified by their primary physicians in the CPMC Infectious Disease Clinic. Patients will be approached independently by and investigator and asked to participate in the study.

Potential control subjects will be recruited by advertisements placed in CPMC buildings and the vicinity.

I. Confidentiality of study data

All subjects eill be assigned anonymous numerical identifiers. Subjects' names and medical record numbers will not be used in correspondence or publication materials.

J. Potential conflicts of interest

None.

K. Location of the study

Subjects and controls will be cared for at the CPMC Infectious Disease Clinic, where they will have their blood drawn and where they will receive the vaccinations.

L. Potential risks

There is minimal potential risk to the study subjects and controls, as no experimental medicines or procedures will be used, and the volume of blood drawn will be minimal. Members of the test groups will continue to receive normal clinical care.

M. Potential benefits

There is no potential benefit to the study subjects, as no additional interventions are planned. The potential benefit to society is that the most appropriate time to administer the vaccine to HIV-infected persons may be better understood.

N. Alternative therapies

Patients could elect not to participate and receive the pneumococcal vaccine according to their clinicians' judgment.

O. Compensation to subjects

There will be no compensation to the members of the test groups; all testing will be included with their clinical care. Control subjects will be compensated $25.

P. Costs to subjects

No additional costs will be incurred by the subjects as all testing will be included as part of routine clinical care.

Q. Inclusion of minors

Minors will not be included.

R. Radiation or radioactive substances

The use of radiation or radioactive substances is not anticipated.

S. References

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