SMALLPOX VACCINATION and the PATIENT WITH HIV/AIDS

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On September 23, 2002, the Centers for Disease Control and Prevention presented a detailed operational plan for implementing a large-scale smallpox vaccination (1). The purpose of this report is to review the CDC plan and the relevant issues as applied to persons with HIV infection and their providers. With regard to the CDC plan, the following points are emphasized:

- Smallpox vaccination will be voluntary.
- In the presence of an outbreak, everyone who has been in contact with a case or otherwise exposed is advised to get smallpox vaccine regardless of medical condition.
- In the absence of contact or other type of exposure, smallpox vaccination is not recommended for persons with HIV infection regardless of CD4 cell count.
- Persons with immune deficiencies, including AIDS, may develop severe complications from smallpox vaccination with generalized vaccinia or progressive vaccinia.
- For vaccination, medical screening must be done including HIV serology if requested, and vaccination should generally not be recommended for persons with contraindications including HIV infection unless they are case contacts. Screening should include voluntary rapid HIV testing if such tests are available and FDA approved.
- Severe reactions to the vaccine may be treated with Vaccinia Immune Globulin (VIG) and/or cidofovir; both are considered investigational requiring informed consent.
- If the HIV-infected person is not vaccinated and lives with someone who has been vaccinated, they should consider living apart to avoid contact vaccinia. The period of separation required should last until public health officials state there is no longer a risk, which is usually 14 days after vaccination or 18 days after contact with a smallpox case.
What is the expected outcome of smallpox in the absence of vaccination? The answer is unknown because smallpox was eradicated before AIDS was described. However, we do know that patients with CD4 counts <100-200/mm³ have major defects in both cell-mediated immunity and humoral immunity as indicated by susceptibility to opportunistic pathogens and reduced antibody response to vaccine antigens (2,3). Both humoral and cell-mediated defense mechanisms are considered important in containing variola (4). Since the mortality rate in unvaccinated immunocompetent patients with naturally acquired disease is about 30% in the general population, it is speculated that the mortality rate would be much higher in patients with HIV and this risk would correlate inversely with CD4 count; for those with AIDS or a CD4 count <200/mm³, the mortality rate is likely to be very high.

Would patients with HIV infection generate an immune response to smallpox vaccine? The experience with other vaccines is that serologic response is CD4 cell count-dependent. In general, antibody titers are nil or reduced with CD4 counts <100-200/mm³ for nearly all vaccines in common use including tetanus, hepatitis B, influenza, S. pneumoniae, polio (eIPV), and measles (2,3,5,6). Response rates are better or normal with CD4 counts >200/mm³ (5,6). The same applies to a large extent with cell-mediated immune responses based on the experience with PPD skin tests (6-8).

Will smallpox vaccine cause progression of HIV? Vaccines may stimulate an immune response including activation of CD4 cells that harbor HIV, thus increasing HIV viral load. The increase is generally <1,000 c/ml and lasts 2-6 weeks (9,10). This has not been problematic even in untreated patients or those receiving HAART using non-live microbe vaccines. However, vaccinia is a live virus vaccine, which may result in persistence of vaccinia infection that conceivably could cause persistent CD4 activation; in this case progressive vaccinia is probably a much greater concern as discussed below.

What are the risks of smallpox vaccine with HIV infection? Progressive vaccinia (or vaccinia necrosum) is THE risk (4,11). This is one of the most dreaded complications of vaccinia and is seen primarily in patients with compromised cell-mediated immunity such as patients with AIDS, organ transplants, cancer chemotherapy, chronic corticosteroids, hematologic malignancies, and combined immunodeficiency disorders; it has also been seen in some with hypogammaglobulinemia (4). The reaction consists of progressive enlargement of the primary site of inoculation and viremic spread to other sites with new disseminated lesions. The lesions show minimal local inflammation, biopsies confirm minimal lymphocytic infiltrates, and cultures of these distant sites yield vaccinia (4,12-16). This complication may occur after primary vaccination or revaccination (4,14,16) and is usually fatal. A possibly typical case has been described in a 19-year-old military recruit not previously known to have HIV infection who had a smallpox vaccination in May 1984 (16). This patient developed new satellite ulcers at the site of inoculation and then a widespread, disseminated pustular rash that yielded vaccinia on culture. The patient was treated with VIG and had a complicated course with both disseminated vaccinia and AIDS-related complications that culminated in death at 18 months post-vaccination. G. Zagury has also reported cell immunotherapy with recombinant vaccinia that resulted in “wide necrosis” at the site of subcutaneous/intramuscular injections resulting in death in three of eight AIDS patients; all three had CD4 counts <50/mm³ (17).

A case with analogous pathophysiology was noted in a 20-year-old college freshman who received live measles vaccine despite advanced HIV infection with prior P. carinii pneumonia and no detectable CD4 cells (18). This patient developed progressive pulmonary infiltrates ten months later that yielded the measles vaccine strain (Moratan strain) on lung biopsy. He was treated with IVIG and ribavirin, but had progressive disease and died five months later. There have been nine reported cases of disseminated BCG with six deaths in AIDS
patients following vaccination (19). These cases illustrate the hazard of disseminated disease following live microbe vaccinations in patients with late-stage HIV.

Is there a treatment for progressive vaccinia? The standard treatment is Vaccinia Immune Globulin (VIG) (4,12-16,20), although the experience is limited and somewhat variable. Availability of VIG is controlled by the CDC (404-639-3670); the usual dose is 0.6 mL/kg IM or about 40 ml that is usually given over 24-36 hours. Cidofovir has also been suggested based on in vitro activity vs. vaccinia (21,22) and activity in vivo in a rodent model (23). Nevertheless, clinical experience is nil for cidofovir treatment of vaccinia and related poxviruses with the exception of topical use for molluscum contagiosum (24). A study of immunodeficient mice challenged with cowpox showed cidofovir failed to prevent death (25). Perhaps the most important therapeutic intervention would be HAART combined with these other treatments.

How great is the risk of secondary spread of vaccinia to patients with HIV infection? Vaccinia causes an ulcer often with satellite lesions that shed the virus for about 10-14 days post-inoculation shedding occurs even through sealed bandages (11). The frequency of contact vaccinia is rare—about 2.6/100,000 with primary vaccination based on prior reports (26,27). These cases required close contact and rarely occurred outside the home except for a few hospital-related contact cases (11). Contact vaccinia in immunodeficient patients is a larger concern than these numbers indicate because the frequency may be substantially higher in immunodeficient patients and the consequences far greater. The implication is that vulnerable patients, including those with HIV infection, should be removed from direct contact with vaccine recipients until inoculation sites no longer shed virus (11). Recommendations include separate housing or, in the case of contact with vaccinated fellow workers, it could mean furloughing. The experience with varicella vaccine is possibly analogous since this also involves live virus that can be spread to contacts from inoculation sites, but here the consequences are far less devastating.

What will be the policy for HIV screening for vaccination? The CDC Guide states that HIV screening should be available if requested by the participant and that rapid tests for HIV should be considered if available and FDA approved. Potential problems with logistics of HIV testing as a contingency for smallpox vaccination is the need for informed consent for HIV serology and the delay in results using standard serologic methods. The only rapid test currently available that is FDA approved that could provide results in minutes is SUDS, but this test requires interpretation in a CLIA-certified lab. Several provider-read rapid HIV tests are under review by the FDA and these could simplify the process. Two of these tests (Oraquick and Reveal) have received “FDA-approvable” letters and FDA approval is expected soon. A major concern is the inadvertent vaccination of some of the estimated 300,000 patients with HIV infection who are unaware of their status; this includes the approximately 25,000 health care workers who may be prioritized for vaccination as first responders (11).

How much does the CD4 count matter? The CD4 count is the barometer for susceptibility to opportunistic infections and it would appear to be critical in defining the risk for both smallpox and progressive vaccinia. Nearly all complications of live vaccines in patients with HIV infection have occurred in those with CD4 counts <200/mm³. The commonly accepted threshold of susceptibility has always been 200/mm³ or 14%, which defines AIDS. Measles vaccine is considered safe in HIV-infected children with a CD4 count above 15%, and there is an ongoing trial of varicella vaccine in HIV-infected children also using a CD4 threshold of 15% to define safety. Based on these observations, many authorities would consider smallpox vaccination as clearly unsafe in those with a CD4 <200/mm³ or <14%. The problem is assumption of safety with a CD4 count >200/mm³ since there is no experience. The
CDC recommendations define risk by the presence of HIV regardless of CD4 count, presumably due to the lack of supporting clinical data with vaccinia. Nevertheless, this appears to be a critical variable that emphasizes the potential importance of disease stage and the utility of HAART in determining risk.

Does prior smallpox vaccination make a difference? Most Americans aged >30 years received smallpox vaccinations. These patients do not have detectable vaccinia antibody, but there may be persistent CMI protection and/or an amnestic response with revaccination (28,29). Neither of these observations is regarded as likely in the face of severe immunosuppression. Patients >30 years with early-stage disease or immune reconstitution seem likely to behave like immunocompetent persons with prior smallpox vaccination, although this is speculation.

REFERENCES


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