Smallpox Vaccination and Patients with Human Immunodeficiency Virus Infection or Acquired Immunodeficiency Syndrome

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Smallpox vaccination strategies are evolving rapidly and have important implications for human immunodeficiency virus (HIV)–infected persons. Cell-mediated immunity is important for controlling both smallpox and vaccinia. For smallpox, the concern is a substantial increase in the associated mortality rate, which is 30% among healthy persons. For smallpox vaccination, the concern is progressive vaccinia, which is usually lethal but relatively uncommon. The risks associated with both smallpox and vaccinia viruses probably correlate with CD4 cell count, and, as a corollary, the best protection against infection with each is presumably immune reconstitution. It appears that all vaccinations will be voluntary, with 2 recommendations: (1) HIV-infected persons will be advised to decline preemptive vaccination, and (2) in the event of a bioterrorism attack involving smallpox, HIV-infected patients with exposures will be advised to receive vaccine.

On 23 September 2002, the Centers for Disease Control and Prevention (CDC; Atlanta, GA) presented a detailed operational plan for implementing large-scale smallpox vaccination [1]. The purpose of this report is to review the CDC’s plan and the relevant issues as applied to HIV-infected persons and their providers. The following points are emphasized in the CDC’s plan:

- Smallpox vaccination will be voluntary.
- In the presence of an outbreak of infection, everyone who has been in contact with a case or who has otherwise been exposed is advised to receive smallpox vaccine, regardless of their medical condition.
- In the absence of contact with an infected person or other types of exposure, smallpox vaccination is not recommended for persons with HIV infection, regardless of CD4 cell count.
- Persons with immunodeficiencies, including AIDS, may develop severe complications due to smallpox vaccination, such as generalized vaccinia or progressive vaccinia.
- Before vaccination, medical screening with serological testing for HIV infection should be done, if requested. Vaccination generally should not be recommended for persons with contraindications, including HIV infection, unless there is a smallpox attack. Screening should be done with informed consent and may include the rapid HIV test.
- Severe reactions to the vaccine may be treated with vaccinia immunoglobulin (VIG) and/or cidofovir. Both are considered investigational and require informed consent for use.
- If a vaccine candidate has a household contact with HIV infection, this represents a contraindication to the vaccine because of the possibility of contact vaccinia. The alternative is living apart. The period of separation required should last until public health officials state that there is no longer a risk, which is usually 10–20 days after vaccination.

The following are relevant additional points about smallpox vaccination and patients with HIV infection.

What is the expected outcome of smallpox in the absence of vaccination? The answer is unknown, because smallpox was eradicated before AIDS was first described. However, we do know that patients with CD4 cell counts of <100 cells/mm$^3$...
to 200 cells/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]. Because the mortality rate among unvaccinated immunocompetent patients with naturally acquired variola major is 10%–30% in the general population, it is speculated that the mortality rate would be much higher among patients with HIV infection, and this risk would correlate inversely with the CD4 cell count. For patients with AIDS or a CD4 cell count of <200 cells/mm³, the mortality rate is likely to be very high.

**Would patients with HIV infection generate an immune response to smallpox vaccine?** Experience with other vaccines indicates that the serological response depends on the CD4 cell count. In general, antibody titers are nil or reduced in persons with CD4 cell counts of <100 cells/mm³ to 200 cells/mm³ for nearly all vaccines in common use, including vaccines against tetanus, hepatitis B, influenza, *Streptococcus pneumoniae*, polio (enhanced inactivated poliovirus), and measles [2, 3, 5, 6]. Response rates are normal or better in persons with CD4 cell counts of >200 cells/mm³ [5, 6]. To a large extent, the same applies to cell-mediated immune responses, as determined on the basis of experience with purified protein derivative (PPD) skin tests [6–8].

**Will smallpox vaccine cause progression of HIV infection?** Vaccines may stimulate an immune response that includes activation of CD4 cells that harbor HIV, thus increasing the HIV load. The increase generally is <1000 copies/mL and lasts 2–6 weeks [9, 10]. This has not been problematic, even in untreated patients or in patients receiving HAART who receive non–live microbe vaccines. However, smallpox vaccine is a live virus vaccine, and administration may result in persistence of vaccinia that conceivably could cause persistent CD4 cell activation; in this case, progressive vaccinia is probably a much greater concern, as discussed in the next paragraph.

**What are the risks of smallpox vaccine associated with HIV infection?** Progressive vaccinia (or vaccinia necrosis) is the risk [4, 11]. This is one of the most dreaded complications of vaccinia. It is seen primarily in patients with compromised cell-mediated immunity, such as patients with AIDS, organ transplant recipients, patients who undergo cancer chemotherapy, those who receive long-term corticosteroid therapy, patients with hematologic malignancies, and patients with congenital immunodeficiency disorders; it has also been rarely seen in some patients with agammaglobulinemia [4]. The reaction consists of progressive enlargement of the primary site of inoculation and viremic spread to other sites with 10–20 cutaneous lesions. The lesions show minimal local inflammation, biopsy confirms minimal lymphocytic infiltrates, and cultures of specimens 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 possible typical case was described in a 19-year-old military recruit who was not previously known to have HIV infection and who underwent smallpox vaccination in May 1984 [16]. This patient developed new satellite ulcers at the site of inoculation and then developed a widespread, disseminated pustular rash, specimens of which yielded vaccinia on culture. The patient was treated with VIG and had a complicated clinical course that included both disseminated vaccinia and AIDS-related complications, which culminated in death 18 months after vaccination. A review of this case, which preceded HIV serological testing, suggested that ~300 other military recruits with HIV infection had been vaccinated without incident. Zagury [17] has also reported cell immunotherapy with recombinant vaccinia that resulted in “wide necrosis” at the site of subcutaneous and/or intramuscular injections, resulting in death for 3 of 8 patients with AIDS. All 3 of the patients who died had CD4 cell counts of <50 cells/mm³.

A case with analogous pathophysiology was noted in a 20-year-old college freshman who received live measles vaccine, despite having advanced HIV infection with prior *Pneumocystis carinii* pneumonia and no detectable CD4 cells [18]. This patient developed progressive pulmonary infiltrates 10 months after vaccination, and a lung biopsy specimen yielded the measles vaccine strain (Moratan strain). He was treated with intravenous immunoglobulin and ribavirin, but he had progressive disease and died 5 months after vaccination. There have been 9 reported cases of disseminated bacille Calmette-Guérin disease occurring after vaccination among patients with AIDS, 6 of whom died [19]. These cases illustrate the hazard of disseminated disease in patients with late-stage HIV infection after receipt of live microbe vaccine.

**Is there a treatment for progressive vaccinia?** The standard treatment is VIG [4, 12–16, 20], although it has never been studied in a controlled trial. Availability of VIG is controlled by the CDC (telephone number, 404-639-3670). The usual dose is 0.6 mL/kg administered intramuscularly, or ~40 mL usually given over 24–36 h. Cidofovir has also been suggested on the basis of its in vitro activity against vaccinia [21, 22] and in vivo activity in a rodent model [23]. Nevertheless, there is no clinical experience with cidofovir treatment of vaccinia or of infections due to related poxviruses, with the exception of topical use for treatment of molluscum contagiosum [24]. A study of immunodeficient mice challenged with cowpox showed that 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 that often involves satellite lesions that shed the virus for ~10–14...
days after inoculation. Shedding occurs even through sealed bandages [11]. The frequency of contact vaccinia is rare—approximately 2–6 cases per 100,000 persons who undergo primary vaccination, as determined on the basis of prior reports [26, 27]. These cases required close contact and rarely occurred outside of the home, except for a few hospital-related contact cases [11]. Progressive vaccinia from contact vaccinia was very rare in the 1960s, but it could be more frequent now because there are more immunodeficiencies, including HIV infection. 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]. The recommendation is to avoid vaccination if a household member has HIV infection. For health care workers who provide HIV care, it could mean furloughing or reassignment until the scab dislodges.

What will be the policy for HIV screening for vaccination? The CDC operational plan states that screening for HIV infection should be performed if it is requested by the participant, and rapid tests for HIV infection should be considered if they are available [1]. Potential problems with the logistics of HIV testing as a contingency for smallpox vaccination are the need for informed consent for serological testing for HIV infection and the delay in results of tests performed with use of standard serologic methods. A major concern is the inadvertent vaccination of some of the estimated 300,000 patients with HIV infection who are unaware of their status, including ~25,000 health care workers who may be prioritized for vaccination as members of the hospital-based smallpox response teams [11].

How much does the CD4 cell count matter? The CD4 cell 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 associated with live vaccines in HIV-infected patients have occurred in patients with CD4 cell counts of <200 cells/mm³. The commonly accepted threshold of susceptibility has always been 200 cells/mm³ (or 14%), which defines AIDS. Measles vaccine is considered to be safe in HIV-infected children nevertheless, this appears to be a critical variable that emphasizes the potential importance of disease stage and the usefulness of HAART in determining risk.

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

References