nal or clinic. For women who have received no prenatal care and who present in labor, this time frame precludes the implementation of antiretroviral therapy during labor and delays the administration of antiretroviral agents to the newborn. In many cases, the delay exceeds the 48- to 72-hour period within which transmission might be reduced with treatment of the newborn. Finally, the availability of the OraQuick test might reduce the time that caregivers would need to receive antiretroviral agents after accidental sharps exposures, with the source being quickly shown to be HIV-negative. Anyone who has needed to take an antiretroviral “cocktail” for even 2 or 3 days can understand the potential savings in emotional stress and physical discomfort in such situations.

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BROAD ANTIRETROVIRAL DEFENSE BY HUMAN APOBEC3G THROUGH LEthal EDITING OF NASCENT REVERSE TRANSCRIPTS


Purpose of the Study. Innate intracellular antiretroviral defense mechanisms have been described. Viral infection requires that these lines of defense be overcome, and this task is usually accomplished by specialized viral proteins. The virus infectivity factor (Vif) protein of human immunodeficiency virus (HIV) is required to counter the antiretroviral activity of a protein expressed in human T cells, ie, APOBEC3G (apolipoprotein B messenger RNA-editing enzyme, catalytic polypeptide-like 3G, which is also known as CEM15). APOBEC3G family members have potent DNA-editing activity, triggering hypermutation in nascent DNA. The purpose of this study was to examine potential mechanisms of APOBEC3G effects.

Methods. In vitro experiments, the investigators measured the infectivity of wild-type and vif-deleted viruses, in the presence or absence of APOBEC3G. They then tested a series of point mutations, concentrating on residues of the catalytic site of APOBEC3G.

Results. When produced in the presence of APOBEC3G, Vif-defective virus was not infectious. The results of these studies demonstrated that APOBEC3G exerts its antiviral effects during reverse transcription, triggering lethal guanosine-to-adenosine hypermutation in the complementary retroviral DNA. It was also noted that APOBEC3G could act on a broad range of retroviruses, in addition to HIV.

Conclusion. APOBEC3G exerts its anti-HIV activity through lethal editing of DNA reverse transcripts.

Reviewer’s Comments. Immune cells have evolved a remarkable set of mechanisms to defend against microbial invaders, and microbes have coevolved to circumvent these defenses. APOBEC3G is a human factor produced in T cells that inherently inactivates retroviruses. However, as shown in this study, the HIV accessory protein Vif selectively inactivates APOBEC3G. An understanding of the mechanisms of viral infectivity and resistance has generated an increasing number of targets for interventions against HIV infection. For example, strategies aimed at limiting the activity of Vif might allow APOBEC3G to better accomplish its task of virus suppression.

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LONGITUDINAL ANALYSIS OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 RNA IN BREAST MILK AND OF ITS RELATIONSHIP TO INFANT INFECTION AND MATERNAL DISEASE


Purpose of the Study. Transmission of human immunodeficiency virus (HIV) via breastfeeding may occur throughout lactation. In developing countries, where >90% of HIV-exposed children live, safe alternatives to breastfeeding are not available. An understanding of the dynamics of breast milk virus levels and the correlation of breast milk virus levels with mother-to-child transmission is essential for the development of effective interventions.

Methods. A total of 648 breast milk samples were collected from 275 women enrolled in a clinical trial in Nairobi, Kenya, between 1992 and 1998. Antiretroviral regimens were not available to the women at the time of the study. Breast milk samples were analyzed for virus levels, and infants were monitored for up to 2 years, for assessment of HIV transmission.

Results. The average duration of breastfeeding was 21 months. Of the 275 women, 70 transmitted HIV to their infants and 205 did not. Greater maternal plasma viral loads, lower maternal CD4+ T cell counts, and detection of HIV DNA in maternal genital secretions were significantly associated with elevated breast milk HIV RNA levels. The median viral load in early milk was significantly greater than that in breast milk collected 14 days after delivery. Breastfeeding mothers who transmitted HIV had significantly higher breast milk HIV RNA levels and more consistent viral shedding, compared with mothers who did not transmit HIV.

Conclusions. The risk of infant infection through breastfeeding was increased by higher levels of virus in breast milk; levels were highest early after delivery.

Reviewer’s Comments. In developing countries, the rate of perinatal HIV transmission approaches 50%. This is dramatically higher than the 20% to 25% rate of transmission that was noted in developed countries before the initiation of perinatal antiretroviral therapy. It is now clear that breastfeeding is a significant factor in the transmission of HIV from mother to child and may be responsible for ≥30% of transmissions in developing countries. Unfortunately, safe alternatives to breastfeeding do not exist for most HIV-positive women. Provision of effective perinatal antiretroviral therapy, combined with safe alternative feeding methods, is required to significantly affect the extraordinary rate of HIV disease among children in the developing world.

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LETHAL T CELL IMMUNODEFICIENCY INDUCED BY CHRONIC COSTIMULATION VIA CD27-CD70 INTERACTIONS


Purpose of the Study. During human immunodeficiency virus (HIV) infection, CD4+ T cell levels decline. Studies suggested that this loss is less likely related to direct infection and killing of these cells than to exhaustion of the T cell pool induced by chronic immune activation. The purpose of this study was to determine, in an animal model, whether artificially induced chronic immune activation alone could result in clinically significant T cell deficiency.
Infectious Disease

RESPONSE TO SMALLPOX VACCINE IN PERSONS IMMUNIZED IN THE DISTANT PAST


Purpose of the Study. There is renewed interest in the use of smallpox vaccine, because of the potential for a bioterrorist attack. One obvious question relates to the current status of people who have been vaccinated in the past. This study sought to evaluate the use of diluted vaccinia virus for vaccination of previously vaccinated (nonnaive) participants.

Study Population. Eighty nonnaive participants, 32 to 60 years of age, were randomized to receive either undiluted or diluted (1:3.2, 1:10, or 1:32) doses of smallpox vaccine, in a single-blinded study. A comparison group of 10 vaccinia-naive participants, 18 to 31 years of age, received undiluted vaccine.

Methods. Participants were enrolled between April 1 and May 15, 2002, at the National Institute of Allergy and Infectious Diseases Vaccine and Treatment Evaluation Unit at St Louis University (St Louis, MO). Smallpox vaccine was administered through scarification, using 15 skin punctures in the deltoid region of the arm. Outcome measures included the presence of a major reaction, defined as a vesicular or pustular lesion or area of palpable induration surrounding a central lesion, after vaccination, measures of viral shedding, and antibody titers.

Results. Initial vaccination resulted in a major reaction for 64 of 80 nonnaive participants. Ninety-five percent of nonnaive participants had major reactions in the undiluted group, 90% in the 1:3.2 dilution group, 81% in the 1:10 dilution group, and 52.6% in the 1:32 dilution group. All of the vaccinia-naive participants (n = 10) experienced major reactions. Compared with vaccinia-naive participants, nonnaive participants had significantly smaller skin lesions (P = .04) and a significantly lower incidence of fever (P = .02). Preexisting antibody was present in 76 of 80 nonnaive participants. Antibody responses were significantly greater and occurred more rapidly among the non-naive participants, compared with the vaccinia-naive participants (P = .002 for day 28 and P = .003 for 6 months). Vaccinia-naive participants shed virus from the vaccination site 2 to 6 days longer and had significantly higher mean peak viral titers, compared with the nonnaive participants (P = .002).

Conclusions. Previously vaccinated persons could be successfully revaccinated with diluted (≤1:10) smallpox vaccine. Fewer adverse reactions were observed in this study among nonnaive participants, compared with vaccinia-naive participants, which might be attributable to immunologic memory.

Reviewer’s Comments. This is an excellent practical study addressing an important issue. Although we hope that widespread smallpox vaccination will not be necessary, these data should be useful for the design of whatever program might be necessary.

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EFFECT OF CONJUGATE PNEUMOCOCCAL VACCINE FOLLOWED BY POLYSACCHARIDE PNEUMOCOCCAL VACCINE ON RECURRENT ACUTE OTITIS MEDIA: A RANDOMIZED STUDY


Purpose of the Study. To determine whether pneumococcal conjugate vaccine can prevent acute otitis media (AOM) among older children who have experienced previous episodes of AOM.

Study Population. A total of 383 children (1–7 years of age) with ≥2 episodes of AOM in the year before entry were studied.

Methods. Children recruited from a Netherlands general hospital and tertiary care hospital were randomized to receive either 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide or hepatitis A or B vaccines, in a double-blind trial. The randomization was stratified into 4 groups according to age (12–24 months versus 25–84 months) and the number of prior AOM episodes (from parental reports, with physician confirmation) (2 or 3 episodes vs ≥4 episodes). All children were monitored, via parental diaries and clinical examinations, for 18 months for the recurrence of AOM. Cultures of middle ear fluid and nasopharyngeal swabs were performed to assess the association of pneumococcal serotypes with AOM after vaccination.

Results. Of the 383 children enrolled, 190 received pneumococcal vaccinations and 193 received control hepatitis vaccinations. A total of 474 episodes of AOM were diagnosed during the follow-up period after the final vaccination, with 275 recorded for 107 of the 186 children in the pneumococcal vaccine group (58%) and 200 recorded
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