Results. Twelve tumors were of B cell origin and expressed surface or cytoplasmic immunoglobulin. One tumor was a B cell–T cell composite. All 13 malignant B cell populations were positive for EBV-encoded RNA. Of the 11 bicalonal and monoclonal tumors, 4 appeared to arise from memory B cells, 5 seemed to be derived from somatically mutated non-memory B cells, and 2 had inactivated immunoglobulin heavy chain sequences, because of a stop codon and a large deletion causing an out-of-frame mutation.

Conclusions. PTLD can arise from atypical, post-germinal center, B cells that have failed selection into memory cells, like the monoclonal tumors of Hodgkin’s lymphoma, as well as from the antigen-selected memory cells that are usually colonized by EBV in immunocompetent individuals.

Reviewers’ Comments. Although the ages of the patients with PTLD were not reported in this study, young children receiving posttransplant immunosuppressive therapy are at increased risk for this disease, because they are more likely to be EBV-susceptible at the time of transplantation. The suggestion of a common initiation step in the pathogenesis of PTLD and Hodgkin’s lymphoma may lead to future diagnostic and therapeutic breakthroughs.

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HUMAN IMMUNODEFICIENCY VIRUS

FAILURE OF 1 WEEK ON/1 WEEK OFF ANTIRETROVIRAL THERAPIES IN A RANDOMIZED TRIAL

Purpose of the Study. Although highly active antiretroviral therapy (HAART) has dramatically improved the duration and quality of life of human immunodeficiency virus (HIV)-infected individuals, an increasing number of serious complications are being identified among patients who are treated with these agents for long periods of time. Strategies that reduce the total drug exposure among infected patients while maintaining the stability of HIV and T cell levels would be welcomed. Scheduled or structured treatment interruptions are being evaluated in an effort to decrease the costs and side effects of HAART.

Methods. In this study, 600 patients receiving successful HAART were randomized to either continuous therapy, CD4+ T cell count-guided therapy, or 1 week on/1 week off therapy.

Results. This report described the preliminary analysis of data for the 1 week on/1 week off arm. Of 36 evaluable patients, 19 had 2 successive HIV RNA plasma concentrations of >500 copies/mL after 1 week off therapy; those cases were classified as virologic failures. Most of the patients who experienced failure were receiving didanosine, stavudine, saquinavir, and ritonavir. Among those patients, there was no evidence of mutations suggesting drug resistance. Plasma saquinavir levels were within the expected range.

Conclusions. The 1 week on/1 week off schedule tested in this study showed an unacceptably high failure rate and was therefore terminated early.

Reviewer’s Comments. Early anecdotal reports suggested that HIV-specific immune responses were boosted after discontinuation of therapy. Clinical trials based on this concept were developed for both acute and chronic HIV infections. The most promising results were from studies involving subjects who were treated for acute HIV infections; specific T cell responses to HIV were enhanced after interruptions in therapy. Similar findings have not been demonstrated for patients with chronic HIV infections. The results of this study are certainly disappointing. However, the definition of virologic failure in this study was a rebound to ≥500 copies/mL. Current guidelines suggest that HIV RNA levels of ≤50 000 copies/mL, with stable CD4+ T cell levels, might be acceptable. The major concern with this approach would be the development of resistance to the antiretroviral therapy if repeated rebounds were allowed to continue in the off weeks. Studies of scheduled or structured treatment interruptions will continue. Perhaps a 2 weeks on/1 week off or 3 weeks on/1 week off schedule would limit the viral rebounds and still reduce the cumulative drug exposure for patients.

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USING POINT-OF-CARE TESTING TO MAKE RAPID HUMAN IMMUNODEFICIENCY VIRUS-1 TESTS IN LABOR REALLY RAPID

Purpose of the Study. The US Food and Drug Administration recently approved the OraQuick rapid human immunodeficiency virus-1 (HIV-1) antibody test (OraSure Technologies, Bethlehem, PA). The test is designed for point-of-care testing for HIV. The test is performed with a tiny amount of blood, and results are available within 20 to 30 minutes. Remarkably, this test is as sensitive and specific as the standard enzyme-linked immunosorbent assay for HIV-specific antibodies. The purpose of this study was to evaluate the differences in turnaround times between hospitals where obstetric staff members performed the rapid test at the point of care and a hospital where testing was performed in the hospital laboratory.

Results. During a 7-month period, 5771 women were evaluated in the labor and delivery areas of the target hospitals, and 514 met the criteria for rapid HIV testing. Of those, a total of 225 women were tested at 3 hospitals that used point-of-care testing and 155 were tested at a hospital that used the laboratory for the same test. Standard enzyme-linked immunosorbent assays confirmed 100% of the rapid test results. Three women were identified as being HIV infected; in those instances, antiretroviral therapy was administered during labor and delivery and/or administered to the neonate. The median turnaround time at the 3 hospitals that used point-of-care testing was 45 minutes (range: 30 minutes to 2.5 hours); the hospital that used the laboratory had a median time of >3.5 hours (range: 94 minutes to >16 hours; P < .0001).

Conclusions. The OraQuick rapid HIV-1 antibody test is a highly accurate measure of HIV risk, for use in a number of clinical settings. With the OraQuick test, hospitals can rapidly identify HIV-infected individuals. This study demonstrates that true point-of-care testing dramatically reduces the time needed for test result availability and allows clinical interventions in a timely manner.

Reviewer’s Comments. Same-day access to HIV test results could greatly reduce the number of adults who are tested but never return to the test site for their HIV test results. The availability of the OraQuick test also has the potential to reduce the already low incidence of perinatal HIV transmission. It currently takes days to obtain HIV antibody test results for individuals presenting to a hospi-
tal 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 antiviral activity of a protein expressed in human T cells, i.e., 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 this study was to examine potential mechanisms of APOBEC3G effects.

Methods. In in vitro experiments, the investigators measured the infectivity of wild-type and vif-deleted virions, 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.

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USING POINT-OF-CARE TESTING TO MAKE RAPID HUMAN IMMUNODEFICIENCY VIRUS-1 TESTS IN LABOR REALLY RAPID
Joseph A. Church
Pediatrics 2004;114;551

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