Herpes Group Viruses and HIV Infection

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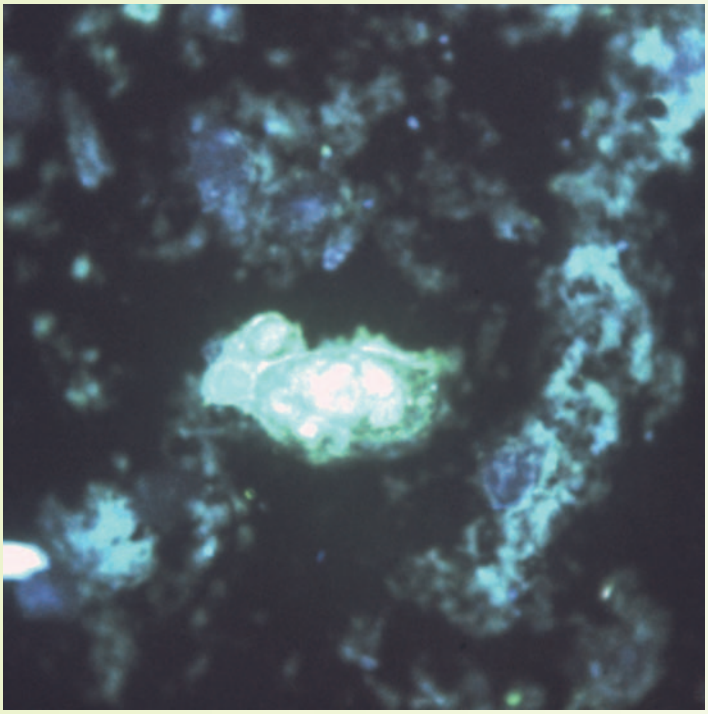
The name herpes comes from the Greek *herpein*—"to creep." Members of the *Herpesviridae* family have been identified in a variety of animals and they all share certain features, including an ability to establish latency following primary infection, as well as a potential to reactivate and cause further disease.

Herpesviruses have large genomes and contain approximately 35 virion genes—all of which encode a number of enzymes involved in nucleic acid metabolism, DNA syntheses, and protein processing—making them a complex group of viruses. The Herpesviruses are widely separated in terms of genomic sequence and proteins, but all are similar in terms of virion structure and genomic organization.

Of the 100 or so herpesviruses known to infect animals, eight are known to establish infection and cause disease in humans. These human herpesviruses can be divided into three sub-families: *Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae*.

In the *Alphaherpesvirinae* subfamily are the following: simplexvirus (herpes simplex virus 1 [HSV-1] and 2 [HSV-2]) and varicellovirus (varicella-zoster virus [VZV]). "Alpha herpes viruses are the most aggressive," Dr. Balfour said. "They will infect a large variety of cell types and tissues and can reproduce very quickly. In turn, they have been the favorite targets of antiviral chemotherapy."



Photomicrograph of HSV-2 in a Genital Smear Using Immunofluorescent Technique

It is well known that sexual transmission of HIV is facilitated by the presence of genital ulcer disease, including the common HSV-2 infection.

Source: CDC Public Health Image Library

In the *Betaherpesvirinae* subfamily: cytomegalovirus (CMV) and roseolovirus (human herpes virus 6 and 7 [HHV-6 and HHV-7]). "These viruses are much more selective in the tissues and cells they infect," added Dr. Balfour. "They are harder to grow in the laboratory and are much more difficult to treat."

In the *Gammaherpesvirinae* subfamily there is lymphocryptovirus (Epstein-Barr virus [EBV]) and human herpesvirus 8 (HHV-8, also known as Kaposi's sarcoma-associated herpes virus [KSHV]).

To review each of these viruses, even as they relate to HIV infection, would be an enormous undertaking. In turn, PRN recently asked Dr. Henry Balfour, Jr., to crystallize some of the most recent data related to HSV, VZV, CMV, and EBV, in the context of HIV infection, and the direction of research we can expect to see in the near future.

"Recent clinical and basic science research findings do impact the management of these infections in HIV-infected persons," Dr. Balfour said. "With HSV-2, we've learned more about its effect on transmission of HIV. With VZV, new data are available regarding the use of the chickenpox vaccine in people with HIV. CMV research is also telling us more about the use of CMV viral load as a marker of disease progression in HIV-infected patients, even those responding well to antiretroviral therapy. There is also the issue of quantitative EBV virology, which could have a number of implications for HIV-positive patients at risk for complications associated with this infection."

HSV-2 and HIV Transmission

It is well known that sexual transmission of HIV is facilitated by the presence of genital ulcer disease, including the common HSV-2 infection. In discussing the impact of prevalent and incident HSV-2 infection upon the acquisition of HIV, Dr. Balfour focused on data published last year in the *Journal of Infectious Diseases*, involving the search for HSV-2 antibodies in stored serum samples from a cohort of 2,732 HIV-negative patients attending four clinics in Pune, India (Reynolds, 2003).

Incident HSV-2 infection was defined as serologically "recent" if a negative HSV-2-specific antibody result could be documented within the previous six months. Incident HSV-2 infection was defined as serologically "remote" if greater than six months had elapsed since the last negative test result. Prevalent HSV-2 infection was defined as the percentage of patients positive for HSV-2 at entry.

Of the 2,732 individuals enrolled, 2,260 were male, 463 were female, and 9 were eunuchs. The prevalence of HSV-2 at enrollment was 43%. The HSV-2 incidence was 11.4 per 100 person-years, and the HIV incidence was 5.9 cases per 100 person-years.

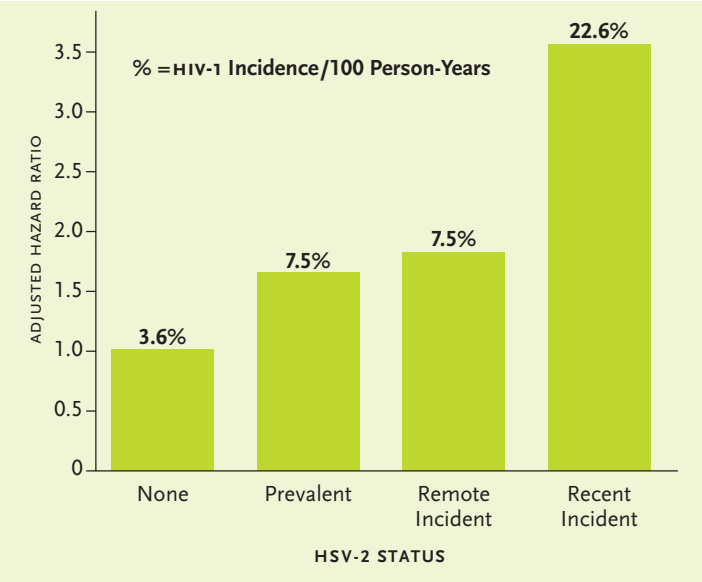


FIGURE 1. HIV Incidence in Patients with Prevalent and Incident HSV-2 Infection

In a study conducted in Pune, India, the incidence and prevalence of HSV-2 infection and subsequent HIV infection were evaluated using stored serum samples from a cohort of 2,732 HIV-negative patients attending four public health clinics. Incident HSV-2 infection was defined as serologically "recent" if a negative HSV-2-specific antibody result could be documented within the previous six months. Incident HSV-2 infection was defined as serologically "remote" if greater than six months had elapsed since the last negative test result. Prevalent HSV-2 infection was defined as the percentage of patients positive for HSV-2 at entry. The prevalence of HSV-2 at enrollment was 43%. The HSV-2 incidence was 11.4 per 100 person-years, and the HIV incidence was 5.9 cases per 100 person-years. As is illustrated in this figure, the HIV incidence was 3.6 per 100 person-years among persons without evidence of HSV-2 infection, 7.5 per 100 person-years among persons with prevalent or remote incident HSV-2 infection, and 22.6 per 100 person-years among persons with recent incident HSV-2 infection. A conclusion of this study was that individuals experiencing incident HSV-2 infections are at the greatest risk of HIV acquisition, compared with individuals not infected with HSV-2 or who have prevalent HSV-2 infection—a compelling argument for stepped-up efforts to manage and prevent HSV-2 infection in individuals at risk for HIV infection.

Source: Reynolds, 2003. Reprinted with permission of *The Journal of Infectious Diseases* and the University of Chicago Press.

The HIV incidence was 3.6 per 100 person-years among persons without evidence of HSV-2 infection, 7.5 per 100 person-years among persons with prevalent or remote incident HSV-2 infection, and 22.6 per 100 person-years among persons with recent incident HSV-2 infection.

The interaction between clinically apparent or self-reported genital ulcer disease and HSV-2 serostatus was also investigated. Of the 217 individuals with serologic evidence of incident HSV-2 infection, 51 (23%) had a genital lesion documented at the same visit at which seroconversion was demonstrated. Using a proportional hazards model, the investigators found that the presence of asymptomatic prevalent HSV-2 infection conferred an adjusted hazard ratio for HIV infection of 2.14 (compared with no genital ulceration and negative results of serologic testing for HSV-2). Symptomatic prevalent HSV-2 infection conferred an adjusted hazard ratio of 5.06.

In short, this study demonstrated that individuals experiencing incident HSV-2 infections are at the greatest risk of HIV acquisition, compared with individuals not infected with HSV-2 or who have prevalent HSV-2 infection. The individuals with serologic evidence of recent incident HSV-2 infection had the highest HIV incidence, illustrating that recent infection with HSV-2 is independently associated with HIV acquisition.

Dr. Balfour pointed out that some recent *in vitro* studies have helped to explain the association between HSV-2 and HIV. First, some studies have demonstrated that HSV-2 infection may increase the risk of HIV acquisition through the influx of susceptible, host CD4+ cells to the infected area. Studies have also demonstrated that HSV-2 has the ability to enhance HIV replication. In the Pune study, the investigators suggested that the elevated risk of HIV acquisition among individuals with exposure to recent incident HSV-2 may reflect a more vigorous immune response in individuals who are immunologically naive to HSV-2. In turn, further studies examining the local immune response to incident HSV-2 infection may help explain the elevated risk of HIV acquisition that is associated with exposure to incident HSV-2.

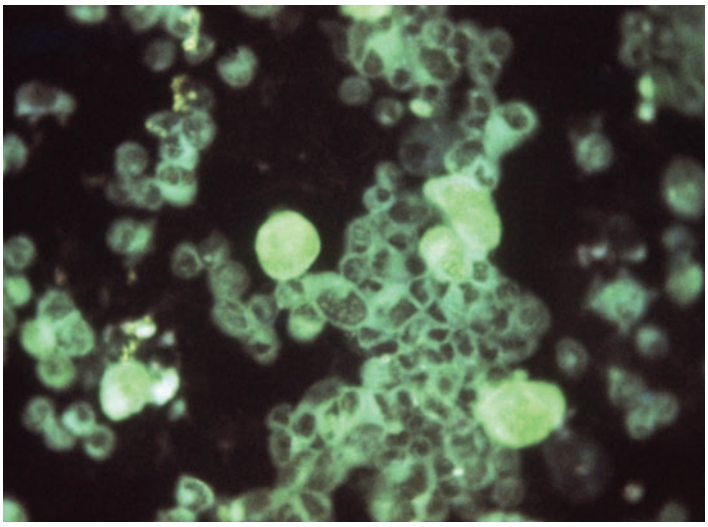
"We definitely need to see more data from studies like this," Dr. Balfour commented. "But there are some take-home implications for clinicians to think about. We clearly need to be more aggressive in terms of treating HSV-2 infection. Even in some patients with asymptomatic infection, there is viral shedding that seems to confer some risk of acquiring HIV infection." As for preventing HSV-2 with the use of a vaccine, Dr. Balfour explained that the issue is wide open. "The development of herpes vaccines, particularly genital herpes vaccines, has been checkered with a lot of pitfalls and some qualified successes. But we're still hoping for a breakthrough."

VZV: The Utility of Vaccination in HIV/AIDS

VZV IS THE CAUSATIVE AGENT OF BOTH VARICELLA (CHICKENPOX) AND zoster (shingles). HIV-infected adults and children are at risk for developing severe illness from either varicella or zoster. Progressive primary varicella, a syndrome in patients who have previously had chickenpox, is associated with persistent new lesion formation with systemic dissemination and may be life-threatening in HIV-infected patients. Zoster recurrences, particularly in HIV-infected patients, can be frequent and extensive.

A VZV vaccine—a preparation of the Oka/Merck strain of live, attenuated varicella virus—has been approved in the U.S. for use in immune-competent individuals to reduce the risk of primary VZV infection. However, the incorporation of the VZV vaccine into the routine care of HIV-infected, VZV-naive children and adults has been slow, due to fears surrounding the use of a live vaccine in this population. Fortunately, encouraging data have emerged regarding the safety and efficacy of the VZV vaccine in HIV-positive children and adults.

In a study published in 2001, investigators at the University of Colorado School of Medicine evaluated the safety and immunogenicity of the VZV vaccine (two doses) in 41 HIV-positive, varicella-naive children in the early stages of HIV disease (CDC stage N1 or A1) (Levin, 2001). Aside from some mild local and systemic reactions, the vaccine was well tolerated. Vaccination had no effect on the clinical stage of HIV or viral load. CD4+ cell percentages and absolute CD4+ cell counts were marginally decreased four weeks after the first vaccination, with levels returning to prevaccination levels within eight weeks. Two months after the second dose of the vaccine, 60% of vaccine recipients had anti-varicella antibody in their serum, and 83% had a positive lymphocyte proliferation assay



Photomicrograph of CMV in a Specimen of Human Embryonic Lung Using Immunofluorescent Technique

Cytomegalovirus (CMV) infects between 50% and 85% of adults in the United States by 40 years of age. In HIV-positive patients with compromised immune systems, the loss of CMV-specific CMI can lead to active CMV replication and dissemination of the infection and, ultimately, to end-organ disease.

Source: CDC Public Health Image Library

(LPA) response to varicella antigen. "These responses are less than what we would normally see in HIV-negative children, but they are encouraging numbers nonetheless," Dr. Balfour said.

Similar findings were reported in a controlled study of the safety and immunogenicity of vzv vaccination in HIV-infected adults previously infected with vzv (Brady, 2002). Thirty-six patients whose CD4+ counts had never fallen to below 400 cells/mm^3—all of whom were on stable antiviral therapy for at least three months prior to study entry—were randomized to receive two doses of vzv vaccine or placebo separated by 12 weeks. An additional 15 HIV-negative controls were enrolled and received two doses of the vzv vaccine for comparative purposes.

Nineteen patients were randomized to vaccine and 17 to placebo. Adverse events were reported in 47.4% of the subjects after the first injection in the vaccine group, compared with 64.7% of subjects after the first injection in the placebo group. Adverse events were less common after the second injection, with 23.5% in the vaccine group and 17.6% of subjects in the placebo group reporting symptoms. All systemic and local adverse events were mild. There were no significant changes in the CD4+ cell counts or HIV-RNA levels in the vaccine group.

Assessments of immune response to the vaccine were made at week 24. Responders were classified using either of the following variables: 1) a vzv-specific responder cell frequency (RCF) increase from less than one to any positive measured response, 2) a two-times increase from a baseline RCF of greater than one, 3) an LPA increase from less than three to any number greater than three, or 4) a ten-times increase above a baseline LPA of greater than three. Positive responses were documented in 64.7% patients in the vaccine group, 41.1% in the placebo group, and 81.8% in the healthy control group.

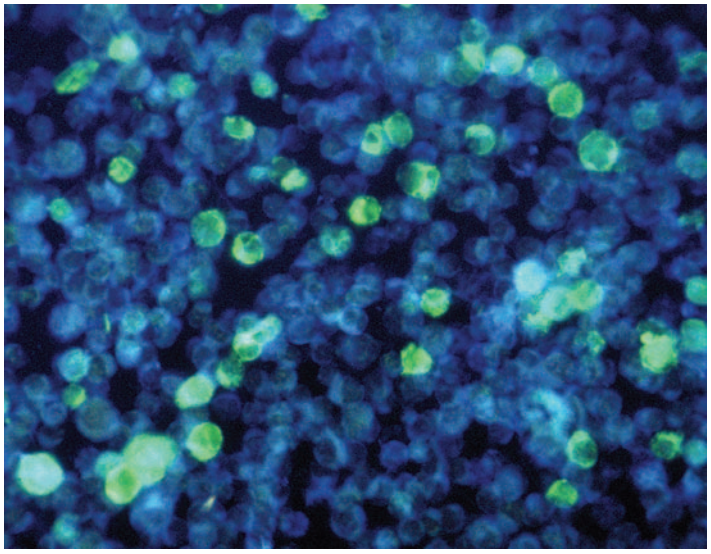
A more recent study set out to determine the effect of antiretroviral therapy on reconstitution of vzv-specific cell-mediated immunity (CMI) in 56 HIV-positive children who had antibodies to vzv (Weinberg, 2004). VZV-CMI did not change over the course of at least three years of observation, despite a reduction in HIV-RNA levels. Improvements in VZV-CMI correlated with lower viral load but not with the CD4+ cell percentage. The incidence of herpes zoster was unaffected by antiretroviral therapy. None of the five children who developed herpes zoster during the study had VZV-CMI before experiencing a zoster outbreak. After developing herpes zoster, only the two children who were adherent to their antiretroviral therapy developed VZV-CMI.

"The bottom line here is that we have studies indicating that the vzv vaccine is safe and effective in less-advanced HIV-infected patients," Dr. Balfour said. "A lot of the vzv disease we see in children, and in adults, may be preventable if we become more proactive in immunizing our patients. vzv vaccination appears to be safe for HIV-positive patients with asymptomatic disease, most notably patients with an absolute CD4+ count above 200 cells/mm^3 and a CD4% greater than 25%. As for patients with more profound immune suppression, studies are needed."

CMV: Does Viral Load Predict Outcome?

IN HIV-POSITIVE PATIENTS WITH COMPROMISED IMMUNE SYSTEMS, THE loss of CMV-specific CMI can lead to active CMV replication, dissemination of the infection and, ultimately, to end-organ disease. New data also seem to suggest that active CMV replication may be indicative of advancing HIV disease, regardless of whether or not a recognized CMV-related complication occurs.

In one study conducted at the University College Medical School in London, investigators set out to determine if CMV viremia remains a significant risk factor for progression of HIV disease and death in the setting of antiretroviral therapy (Deayton, 2004). Three-hundred seventy-four



Photomicrograph of EBV in Leukemia Cells Using FA Staining Technique

Epstein-Barr virus (EBV) is one of the most common human viruses. When infection with EBV occurs during adolescence or young adulthood, it causes infectious mononucleosis 35% to 50% of the time. EBV is also associated with non-Hodgkin's lymphoma (NHL) and oral hairy leukoplakia (OHL) in patients with HIV disease and has been documented in patients with lymphoproliferative disease, nasopharyngeal carcnimoa, T-cell lymphomas, CNS lymphoma, and Hodgkin's disease.

Source: CDC Public Health Image Library

patients who had a history of at least one CD4+ count nadir below 100 cells/mm^3 were enrolled in the prospective study. Serial blood samples were tested for CMV by PCR. After stratification according to baseline and most recent CMV-PCR staus, rates of new CMV disease, new AIDS-defining disorders, and death were calculated over a median follow-up of 37 months, after stratification according to baseline and most recent CMV-PCR status at any point during the follow-up period.

Of 2,969 PCR assays, 375 (12.6%) were positive for CMV-DNA. Two-hundred fifty-nine (69.3%) patients were persistently negative for CMV by PCR; 15 were persistently positive; and 100 were intermittently positive. In multivariate models, CMV-PCR-positive status as a time-updated covariate was significantly associated with increased relative rates of progression to a new AIDS-defining disorder (2.22)—not necessarily CMV-related end-organ disease—and death (4.14).

"It didn't really matter if these patients had consistent or intermittent CMV viremia," Dr. Balfour added. "Even among patients who had transient viremia, the relative rate of experiencing an AIDS-defining event was increased over those without evidence of viremia. The most important finding was that mortality, even in the absence of a clinical event, was increased in the patients with viremia, which implies that CMV may be harming these patients, not with classic tissue invasive disease, but by contributing to immune destabilization."

There are a number of possible explanations for these findings. Dr. Balfour explained that there are data supporting the notion that, as with HSV-2, CMV increases HIV replication. Data also indicate that CMV itself has been shown to be immunosuppressive and could possibly damage CD4+ cells. "The explanation that I favor is that CMV may be directly pathogenic without producing focal tissue invasive disease, and is contributing to death," he offered. "This would explain a number of studies that have shown anti-herpes drugs having a positive impact on survival, without necessarily showing that they had an impact on CMV disease."

To explore this further, the AIDS Clinical Trials Group is conducting a randomized, double-blind study (ACTG 5030) evaluating valganciclovir as pre-emptive therapy for CMV viremia. "The study is now closed to enrollment, with 338 patients accrued," Dr. Balfour said. "We're primarily looking at the role of valganciclovir in preventing CMV disease. However, there may be a need for other studies, looking at the effect of ganciclovir in viremic patients, primarily looking at survival."

Quantititative EBV

EBV WAS DISCOVERED IN 1964 IN CELLS CULTURED FROM BURKITT'S lymphoma. Four years later, EBV was shown to be the etiologic agent responsible for infectious mononucleosis. In 1970, EBV DNA was detected in tissues from patients with nasopharyngeal carcinoma. In the 1980s, EBV was found to be associated with non-Hodgkin's lymphoma (NHL) and oral hairy leukoplakia (OHL) in patients with HIV disease and has also been documented in patients with lymphoproliferative disease, T-cell lymphomas, CNS lymphoma, and Hodgkin's disease.

At the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Dr. Balfour and his colleagues presented data from a study evaluating the quantity of EBV DNA in blood and oral washings among University of Minnesota students with primary infectious mononucleosis (Balfour, 2003). "We collected samples, every other day from these students, beginning approximately seven days after the onset of illness," he recalled. "Approximately three weeks after the onset of symptoms, the students usually started feeling better."

Using PCR, Dr. Balfour's group noted a lack of detectable EBV DNA in plasma. However, in whole blood and PBMCs, there was a noticeable decline in EBV DNA levels, beginning approximately seven days after the onset of symptoms. In whole blood, EBV levels appeared to peak at nine days after the onset of symptoms, at approximately 4 $\log_{10}$ copies/mL, and declined steadily after that point. "When we looked at the PBMCs, we saw a nice decay, with a half-life of approximately three days," he said. "In the oral wash cells and oral wash supernatant, we saw consistently elevated levels of EBV-DNA, between 4 and 5 $\log_{10}$ copies/mL for up to 45 days past the onset of symptoms."

Prolonged periods of EBV replication are cause for concern given that infectious mononucleosis-related EBV infection has been associated with an increased risk of Hodgkin's lymphoma in young adults. To take a closer look at this association, a team of researchers at the Statens Serum Institut in Copenhagen compared the incidence rates of Hodgkin's lymphoma in two population-based Danish cohorts of patients who were tested for infectious mononucleosis: 17,045 with serologic evidence of having had acute EBV infection, and 24,614 without evidence of infection (Hjalgrim, 2003). They also combined the cohort of patients who had serologically verified infectious mononucleosis with a cohort of 21,510 Swedish patients with infectious mononucleosis, for a total of 38,555 patients. Biopsy specimens of Hodgkin's lymphomas diagnosed during follow-up of this combined cohort were tested serologically for the presence of EBV. The study team then modeled the relative risk of EBV-negative and EBV-positive Hodgkin's lymphoma in different periods after the diagnosis of infectious mononucleosis and estimated the median incubation time for mononucleosis-related EBV-positive Hodgkin's lymphoma.

Only serologically confirmed infectious mononucleosis was associated with a persistently increased risk of Hodgkin's lymphoma. Sixteen of 29 (55%) tumors, obtained from patients with infectious mononucleosis, had evidence of EBV. There was no evidence of an increased risk of EBV-negative Hodgkin's lymphoma after infectious mononucleosis. In contrast, the risk of EBV-positive Hodgkin's lymphoma was significantly increased (relative risk: 4.0). The estimated median incubation time from mononucleosis to EBV-positive Hodgkin's lymphoma was 4.1 years.

"Obviously, there's something else going on in these patients," Dr. Balfour commented. "But these are still important data to consider. When you consider the thousands of cases of mono that we see every year, I think this should give us pause and think about whether we should be trying to reduce EBV viral load in some way, or thinking about a vaccine."

OHL has been a significant problem for a number of HIV-positive patients. "However," Dr. Balfour said, "OHL has afforded us the opportunity to look at therapies. This is a disease where the oral epithelial cells are actively producing EBV at a rate where an antiviral, such as acyclovir, doesn't appear to have a heck of a lot of activity against viral replication. But in the clinic we do see it as being effective, given that the cells are replicating so rapidly that we can get at it as if it were an alpha herpesvirus, like HSV-1 and HSV-2. We've seen some remarkable responses to acyclovir therapy in our patients with OHL."

There are some clinical data supporting the use of acyclovir (Zovirax) and valacyclovir (Valtrex) as therapies for symptomatic EBV infection. Ganciclovir (Cytovene), best known for its activity against CMV, has also been shown in uncontrolled studies to have anti-EBV activity. "Acyclovir looks to be the safest of all the options," Dr. Balfour commented. "We need to study the effect of these therapies on EBV viral load to see if they reduce the risk of tumor development."

Persistent, active EBV replication is evident in many HIV-infected patients. Dr. Balfour reviewed data from a study conducted by a team at Baylor College of Medicine in Houston (Ling, 2003). Compared to HIV-

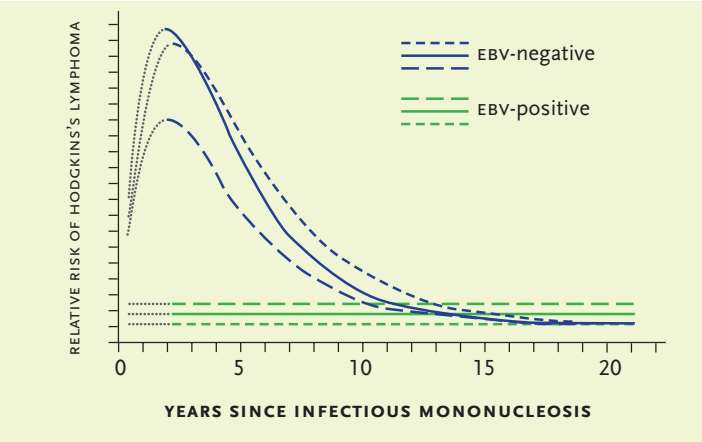


FIGURE 2. Relative Risk of Epstein-Barr Virus (EBV)—Positive and EBV-Negative Hodgkin's Lymphoma After Infectious Mononucleosis

A team of researchers at the Statens Serum Institut in Copenhagen compared the incidence rates of Hodgkin's lymphoma in two population-based Danish cohorts of patients who were tested for infectious mononucleosis: 17,045 with serologic evidence of having had acute EBV infection, and 24,614 without evidence of infection. They also combined the cohort of patients who had serologically verified infectious mononucleosis with a cohort of 21,510 Swedish patients with infectious mononucleosis, for a total of 38,555 patients. Biopsy specimens of Hodgkin's lymphomas diagnosed during follow-up of this combined cohort were tested serologically for the presence of EBV. Solid lines represent the relative risks of EBV-positive (blue) and EBV-negative (green) Hodgkin's lymphoma, given that EBV status was determined in an unbiased way and that the missing data on viral status in 11 tumors were uninformative with respect to their true EBV status. Short-dashed lines represent the relative risks of EBV-positive and EBV-negative Hodgkin's lymphoma given that all tumors whose EBV status was unknown were EBV-positive. Long-dashed lines represent the relative risks given that all tumors whose EBV status was unknown were EBV-negative. The analyses were restricted to the period two years or more after infectious mononucleosis.

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negative volunteers, HIV-infected patients on antiretroviral therapy have significantly higher rates of EBV-DNA detected in blood by real-time PCR: 11/68 (16%) vs. 57/70 (81%) respectively. The mean EBV-DNA levels in blood and saliva samples were also higher in the HIV-infected patients than in HIV-negative volunteers. EBV detection in blood was associated with lower CD4+ cell counts among the HIV-infected individuals.

"We've stumbled upon similar findings," Dr. Balfour said in highlighting data from his group at the University of Minnesota. "In our HIV/AIDS patients, active EBV replication has been documented in approximately 30% of those with fairly normal CD4+ cell counts. But when we look at individuals with CD4+ counts below 100 cells/mm^3, active replication can be seen in up to 70%, with persistently positive EBV DNA in whole blood. This is not a good thing. This might be one reason why the risk of lymphoma in our more advanced HIV-positive patients is so much higher."

Conclusion

"IN RECENT YEARS," DR. BALFOUR SAID, "WE'VE IDENTIFIED A NUMBER of possibilities in the context of herpes infections, all of which will need to be evaluated in future studies. With HSV-2, we really may see reduced HIV transmission rates with the treatment and suppression of HSV-2 infection, even in patients without symptoms of disease. As for VZV, maybe we really should be stepping up efforts to immunize our VZV-seronegative patients, including HIV-positive patients with decent immunity, using the chickenpox vaccine. And I would like to add here that the Oka strain vaccine is susceptible to acyclovir. So, should we see disseminated chickenpox as a result of giving this live vaccine, even in someone with compromised immune function, we do have a therapy we can call upon. For CMV, given the not-so-obvious ways in which it might contribute to HIV disease progression, there's probably a need for additional data looking at the effects of pre-emptive therapy on mortality rates in HIV. Finally, with EBV—an infection that I still think is being overlooked—we really do need to study the effect of therapy on reducing EBV viral load and the benefit it may have in terms of reducing the risk of certain malignancies." *prn*

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