

## Editorial Response: The Need for Investigations of Prophylactic Regimens to Prevent AIDS-Associated Non-Hodgkin's Lymphoma

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Combination antiretroviral therapy is now standard care and received by the majority of HIV-infected patients in this country [1]. Although HIV-infected patients are surviving longer, the long-term consequences of prolonged survival under such therapy remain undefined. Alteration of cancer risk is of particular concern, and HIV-associated cancers have already emerged as a leading cause of death among patients with AIDS [2].

In particular, HIV infection is associated with increased incidence of non-Hodgkin's lymphoma (NHL), exceeding 1% annually in recent data [1, 3]. NHL incidence increases markedly with progression of HIV infection, although the association with level of CD4 lymphopenia is less pronounced than that for many other opportunistic infections [4, 5]. Among the AIDS-defining opportunistic illnesses, NHL has accounted for 3% of clinical AIDS cases in the United States [6].

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See article by Fong et al. on pages 757–61.

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Various genetic lesions are present in many of these tumors, including activation of the *c-myc* (especially in Burkitt's-type lymphomas), *bcl-6*, and *ras* protooncogenes and inactivation of the *p53* tumor suppressor gene [7]. The relationship between acquired somatic mutations and immune dysregulation leading to NHL is incompletely defined, but chronic B cell hyperactivation and disruption of cytokine control may be important factors. Increased levels of the B cell-stimulatory factor sCD23 were predictive of AIDS-associated lymphoma in one study [8], and elevated levels of IL-6 were suggested to be predictive in another study [9], although the latter association was not statistically significant.

The immune restoration of current antiretroviral therapy might be expected to ameliorate NHL risk. However, several studies indicate disproportionate persistence of NHL risk as compared to reductions in opportunistic infections and Kaposi's sarcoma. For example, there was no significant change in NHL hazard during the period July 1997 through June 1998 compared with the period 1992–1994 in the Swiss HIV Cohort Study [10]. NHL incidence was also stable for 1996–1997 in the Multicenter AIDS Cohort Study [3]. Similarly, incidence of

all NHLs combined was stable through June 1997 in the US Centers for Disease Control's Adult Spectrum of Disease Study [1]. These disappointing observations may portend that, as opportunistic infections and Kaposi's sarcoma decrease in frequency, NHL will account for a greater proportion of HIV complications.

Fong et al. [11] now present evidence that long-term anti-herpes therapy with acyclovir, ganciclovir, or foscarnet may substantially decrease risk of NHL. Among patients at 1 hospital and 3 primary-care HIV-specialty medical practices in Toronto, 7% of patients with NHL and 47% of control subjects had completed  $\geq 1$  year of daily acyclovir therapy ( $\geq 800$  mg/d). Similarly, the relative risk of NHL among recipients of this therapy (or at least 1 year of daily ganciclovir or foscarnet) was 0.3 in comparison with the risk for patients who never received antiherpes treatments. If substantiated, decreases of this magnitude would certainly warrant investigation of prophylactic antiherpes regimens to prevent HIV-associated NHL.

How might the findings of Fong et al. [11] be explained? The Epstein-Barr virus (EBV) is suspected to play a role in causing some cases of AIDS-associated NHL, although the specific etiologic mechanisms are uncertain. Monoclonal EBV DNA may be detectable in tumor tissue, especially tumors localized to the CNS, which are almost always EBV-positive [12]. In addition, EBV in CSF is highly predictive of CNS lymphoma [13].

EBV is less frequently detected in AIDS-related systemic lymphoma; its prevalence has ranged from 28% [14] to 66% [15] in various studies. EBV prevalence varies by histologic subtype and is higher in immunoblastic than in small, noncleaved cell tumors. In addition, human herpesvirus 8, associated with Kaposi's sarcoma, is detectable in a subset of AIDS-associated lymphomas, characterized as primary effusion lymphomas [16], for which EBV may be an additional cofactor.

The report by Fong et al. [11] accords with anecdotal evidence that antiherpes therapy may be useful against HIV-associated NHL after clinical presentation. Among 5 patients with primary CNS lymphoma treated with zidovudine, ganciclovir, and IL-2, 4 (80%) had a partial or complete response [17]. Furthermore, 2 patients with EBV-associated high-grade NHL had prolonged remission after combined chemotherapy and acyclovir therapy [18].

There are several reasons for caution in concluding that acyclovir and similar agents prevent HIV-related NHL. The study by Fong et al. was relatively small and requires corroboration with additional, rigorously conducted epidemiological investigations. It will be particularly important to link treatment in-

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formation with testing for EBV in NHL tumors, to determine if EBV-positive tumors are indeed preferentially prevented by antiherpes therapy. Additional epidemiological evidence from existing and readily available data should be examined expeditiously.

If further studies support this initial report, then, as Fong et al. propose, a controlled clinical trial of antiherpes prophylaxis should be seriously considered.

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