Two recent studies provide new clues to why people infected with human immunodeficiency virus (HIV) are at high risk—sometimes very high risk—for lymphoma.

One of the studies adds new data linking macrophages in HIV patients with the development of AIDS-related lymphoma (ARL). The other suggests that AIDS patients who develop lymphoma have higher levels of certain cytokines as early as 2 years before their diagnosis. The findings could lead to new prevention and treatment strategies not only for ARL but also for other types of lymphoma, according to the researchers, who presented their findings in April at the annual meeting of the American Association for Cancer Research (AACR).

“Because of the homogeneity of ARL, we can use its pathogenesis as a window into other types of lymphoma, which is a very heterogeneous disease,” said Charles Rabkin, M.D., senior investigator at the National Cancer Institute and author of the cytokine study.

Unlike most other lymphomas, ARL is usually high grade and metastatic at diagnosis; patients commonly die within weeks of diagnosis. It’s a common cancer in AIDS patients but did not become an AIDS-defining disease until 1985, which suggested that it develops more slowly than other AIDS-related cancers such as Kaposi sarcoma. The simple explanation for its late appearance is that the more time that passes after HIV infection, the more likely one is to develop lymphoma, said Michael McGrath, M.D., Ph.D., a professor at the University of California, San Francisco, and senior author of the macrophage study. “The more complex explanation may involve the evolution of HIV in macrophages that harbor mutations.”

**Macrophages**

Last year, a study by McGrath and Leanne Huysentruyt, Ph.D., assistant research scientist at UCSF, suggested that macrophages in ARL patients could be a haven for HIV, allowing the virus to develop resistance to standard antiviral treatments. In the study presented at AACR, their aim was to determine the prevalence of these HIV-infected macrophages in a larger sample population. Examining 150 ARL biopsy samples taken from 1984 to 2007, they found that after 1996, when highly active antiretroviral therapy (HAART) was introduced, approximately half of ARLs contained HIV-infected macrophages, compared with 26% in the pre-HAART era.

“This [finding] was surprising, as HAART targets HIV replication,” Huysentruyt said. “But apparently HAART has little or no effect on the virus in macrophages.”

Macrophages in general, and specifically HIV-infected macrophages in ARL patients, are long lived. That longevity made McGrath suspect that they could play a role in ARL, which typically doesn’t appear until 4 or 5 years after an AIDS diagnosis. To test that hypothesis, he injected human lymphoma-associated macrophages into immunodeficient mice. In findings reported in *Cancer Research* in 2002, those animals eventually developed aggressive lymphoma, but others receiving normal macrophages produced no tumors.

“We knew then that there was something unique about macrophages in lymphoma that made this cancer grow,” he said. “This experiment suggested that lymphoma-related macrophages are somehow programmed to set up a lymphomagenic environment.”

Then, last year, McGrath and colleagues discovered that different forms of HIV exist within the macrophages of individuals who develop ARL. The researchers analyzed 780 HIV genetic sequences extracted from 53 tissues from seven patients who had various HIV-related pathologies: two with dementia, three with ARL, and two with systemic HIV–AIDS infection. About half of the HIV in cancerous tissue was recombinant virus, hybrid strains of HIV with genetic material from different parent viruses, according to findings published in *PLOS One* in March 2009. The researchers also found that HIV in tumors had a different genetic sequence from that of HIV in nontumor sites, suggesting that the strains evolved separately in the same patient. That work was published in *PLOS One* last December.

“This suggests that HIV undergoes genetic changes in macrophages and that they serve as reservoirs for HIV,” McGrath said. He hypothesizes that the macrophages, which resist antiretroviral drugs, enable the virus to mutate within them and drive ARL development.

If as many as half of ARL patients have tumor-specific HIV within infected macrophages, as the AACR study suggests, then macrophage-targeted drug therapy might be beneficial, Huysentruyt said. “From our findings, we believe that new drugs to target HIV-infected macrophages could be effective in treating ARLs and may also be necessary to wipe out HIV infection itself,” she said.

McGrath is now working with a grant from the National Institute of Mental Health,
part of the National Institutes of Health, to develop such drugs, specifically, drugs targeted at HIV-infected macrophages in the brains of patients with AIDS dementia.

**Cytokines**

Whereas McGrath’s goal is to directly target macrophages, another anticancer strategy is to disrupt macrophage products—cytokines, such as interleukin 10 (IL-10) and IL-6—and growth factors, such as vascular endothelial growth factor. Not only do these cytokines help cancer grow, but some also hyperstimulate B cells, driving B-cell proliferation and development of both lymphoma and HIV.

In the other ARL study presented at AACR, NCI’s Rabkin and colleagues examined blood levels of 30 cytokines in 66 ARL patients from three prospective cohort studies. They found cytokines that were elevated as early as 2 years before ARL diagnosis. That means, Rabkin said, that to try to prevent ARL in the short term, “scientists could monitor cytokine levels of patients on HAART, along with CD4 and other biomarkers, and modify HAART drug combinations to see if that can alter cytokine levels.”

In related research, Otoniel Martinez-Maza, Ph.D., at the University of California, Los Angeles, investigated cytokine levels at 1, 3, and 5 years before a lymphoma diagnosis in AIDS patients. The findings, not yet published, showed elevated levels “a long time” before diagnosis, he said. They also showed several elevated biomarkers for B-cell stimulation.
Rabkin, Martinez-Maza, and others are also investigating polymorphisms in cytokine genes as an ARL risk factor. In a newly published study in *AIDS* with 160 ARL patients, Rabkin and Martinez-Maza examined variations in the gene for IL-10, an anti-inflammatory cytokine that also stimulates B cells. Patients with two copies of a “low response” IL-10 gene variation, which predisposes them to have lower IL-10 levels, had a reduced risk of lymphoma. One possible explanation is that the B cells were not hyperstimulated by the low-response IL-10 variant, he said.

Researchers are also beginning to find similarities between ARL and lymphoma in patients without HIV–AIDS. In a prospective study published last year in *Blood*, Martinez-Maza found elevated levels of some of the same cytokines found in ARL patients, as well as elevated IL-6 and IL-10, before diagnosis of non-Hodgkin lymphoma in healthy adults. In an ongoing study, using the Department of Defense’s large serum repository, he and Lynn Levin, Ph.D., a geneticist at the Walter Reed Army Hospital in Washington, D.C., have identified 600 individuals diagnosed with NHL in the general population. The researchers are now matching them with control subjects reaching back a decade before diagnosis and will analyze samples to see whether certain cytokines are elevated years before diagnosis in this population, as they are in ARL patients.

“We are beginning to find some similarities between ARL and NHL profiles, and I think we will see more,” Martinez-Maza said.