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## **HAART significantly lowers risk of non-Hodgkin's lymphoma for up to ten years, regardless of nadir CD4 count**

**Edwin J. Bernard**, Tuesday, January 15, 2008

Antiretroviral therapy greatly reduces the incidence of non-Hodgkin's lymphoma and its beneficial effect remains after ten years of treatment, according to the results of the largest, and longest, study into the effects of highly active antiretroviral therapy (HAART) on the incidence of this AIDS-defining cancer. The results were published in the January 11<sup>th</sup> edition of the journal, *AIDS*.

Following the advent and widespread use of HAART in wealthier nations more than a decade ago, a decrease in the incidence of AIDS-related illnesses was observed, including that of non-Hodgkin's lymphoma. However, previous studies of non-Hodgkin's lymphoma incidence in the post-HAART era included relatively small numbers of people diagnosed with non-Hodgkin's lymphoma following HAART initiation. Consequently, there are few data on the incidence of non-Hodgkin's lymphoma in the HAART era and the effects of long-term HAART on incidence over time.

Investigators for the Swiss HIV Cohort Study – which includes half of all people with HIV, and 68% of people with AIDS in Switzerland – analysed their database (which began in 1984 and included data until March 31<sup>st</sup> 2006) of 12,959 individuals, contributing a total of 75,222 person-years, of which 36,787 were spent on HAART.

They identified a total of 429 non-Hodgkin's lymphoma cases between 1984 and 2006 (365 from the Swiss HIV Cohort Study dataset and a further 64 from the Swiss Cantonal Cancer Registries).

Of the approximately 3,870 cohort participants who developed AIDS during follow-up, non-Hodgkin's lymphoma was the AIDS-defining illness for 201 (5.2%).

They found that the highest incidence of non-Hodgkin's lymphoma (13.6 per 1000) took place in the pre-HAART era (1993-1995). During the period, 2002-2006, the incidence declined to a low of 1.8 per 1000.

The investigators found that individuals on HAART had a reduced risk (hazard ratio, HR) of non-Hodgkin's lymphoma of 0.26 (95% CI, 0.20-0.33) compared with individuals not on HAART.

Significant factors that increased the risk of non-Hodgkin's lymphoma for individuals not on HAART included being male (HR versus women = 1.94; 95% CI, 1.43-2.61); being over 45 years of age (HR  $\geq$  45 versus < 35 years = 2.71; 95% CI, 2.04-3.60), and acquiring HIV through sex between men (HR versus intravenous drug users = 1.81; 95% CI, 1.36-2.42).

A particularly important finding was that HAART use lowered the risk of non-Hodgkin's lymphoma regardless of the individual's CD4 count at enrolment. In other words, they found no association between CD4 cell count and non-Hodgkin's lymphoma risk in people on HAART.

In contrast, as previous pre-HAART studies have found, non-Hodgkin's lymphoma rates increased steeply as CD4 cell counts decreased for people not on HAART. This study found that individuals not on HAART with a CD4 count at enrolment of fewer than 50 CD4 cells/mm<sup>3</sup> were more than twelve times more likely to be diagnosed with non-Hodgkin's lymphoma than individuals enrolling with more than 350 cells/mm<sup>3</sup>.

The investigators also found that use of HAART reduced the risk of non-Hodgkin's lymphoma by half within the

first five months of use, and the risk continued to decline so that the hazard ratio after 36-59 months on HAART was 0.10 (95% CI, 0.06-0.17). Importantly, the risk remained extremely low after ten years of HAART: hazard ratio = 0.12 (95% CI, 0.05-0.25).

Although histological confirmation was available in the majority of cases, the histological subtype was often not available, and therefore this study only distinguished primary brain lymphoma from other types of non-Hodgkin's lymphoma. When the investigators examined the incidence of primary brain lymphoma, they found that there was a stronger decline in incidence after 1995 than for other non-Hodgkin's lymphomas. Specifically, primary brain lymphoma represented 31.6% of non-Hodgkin's lymphomas before 1996, but only 13.3% in 1999-2006.

The investigators point out that although this is the largest, and longest, study on the incidence of non-Hodgkin's lymphoma before and after HAART, there were several limitations to their study. These include a lack of information on the year of seroconversion; a lack of non-Hodgkin's lymphoma histology; and no information on adherence to HAART.

The latter means that the investigators may have underestimated treatment efficacy since they included people who interrupted treatment as people on HAART. "Indeed," they write, "we found that 22% of non-Hodgkin's lymphoma in HAART users arose in persons who were no longer on HAART at cancer diagnosis."

The investigators note that "the near complete disappearance of the association between CD4 cell count at enrolment or at initiation of antiretroviral treatment and [non-Hodgkin's lymphoma] risk supports the strong efficacy of HAART regardless of the degree of immune impairment when follow-up or treatment begins.

"Thus," they conclude, "although it was already clear that HAART prevents [non-Hodgkin's lymphoma] through improvement of immune status, this study shows that HAART avoids the majority of [non-Hodgkin's lymphoma], even among the most severely immunosuppressed individuals."

## Reference

Polesel, J et al. *Non-Hodgkin's lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy*. AIDS 22(2), 301-306, 2008.

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