

# HIV Viremia and the Development of AIDS-Related Lymphoma in Patients Treated with Highly Active Antiretroviral Therapy

Caroline A. Sabin

Research Department of Infection and Population Health, Division of Population Health, University College London Medical School, London, United Kingdom

(See the article by Zoufaly et al., on pages 79–87.)

The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s for the treatment of human immunodeficiency virus (HIV) infection was associated with a rapid reduction in the incidence of most AIDS-defining events. Although early studies suggested that HAART appeared to have a less dramatic effect on the incidence of AIDS-related lymphomas, particularly non-Hodgkin lymphoma (NHL), than on the incidence of other AIDS-related events [1, 2], subsequent studies confirmed that the incidence of these events had also decreased [3–6]. In the CASCADE (Concerted Action of SeroConversion to AIDS and Death in Europe) Collaboration, the incidence of NHL decreased by 75% from the period before 1997 to 1999–2002 [3]. Among participants in the Swiss HIV Cohort Study [4], the incidence of NHL decreased from 13.6 cases/1000 person-years

during the period from 1993 to 1995 to only 1.8 cases/1000 person-years during the period from 2002 to 2006. However, AIDS-defining lymphoma remains a major cause of death among those infected with HIV. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [7], 82 (27%) of 305 deaths due to AIDS-related malignancy were caused by NHL. Recent data from the French Mortalité 2005 Survey [8] demonstrated similar results, with NHL contributing to 30% of AIDS-related deaths and 10% of all deaths among HIV-infected individuals in France in 2005.

The association between NHL and an immunocompromised status has long been recognized. In a recent meta-analysis [9], Grulich and colleagues reported that individuals infected with HIV were >76 times more likely to develop NHL than were individuals in the general population, and several studies noted an association between a lower CD4 cell count and the incidence of NHL in those infected with HIV [3, 5]. Confirming an association with immunosuppression, Grulich et al. [9] also found that organ transplant recipients treated with immunosuppressive drugs were >8 times as likely to develop NHL as were their counterparts in the general population [9]. Not surprisingly, therefore, the focus of many early studies

was the association between the CD4 cell count (and other immunologic markers) and the development of AIDS-related malignancies. In particular, early studies [1, 10] reported that the nadir CD4 cell count (i.e., the lowest count attained during infection) was a particularly strong risk factor for NHL, even among successfully treated patients. Such an association would be consistent with a long-term, nonreversible association with an immunocompromised status, providing justification for earlier initiation of HAART to prevent this from occurring. Subsequent studies [3, 7, 11], however, found no evidence that either the nadir CD4 cell count or other measurements of an individual's total "exposure" to immunosuppression (e.g., the time-weighted mean CD4 cell count or the proportion of time spent when the CD4 cell count was <100 cells/mm<sup>3</sup>) were better predictors of the risk of NHL than was the latest CD4 cell count, arguing that the most important determinant of risk is the current immune status of an individual. Such an association is arguably more consistent with the decrease in the incidence of NHL seen since the introduction of HAART.

Noting that several studies have suggested that HIV replication may induce immune activation and B cell stimulation, Zoufaly and colleagues have considered,

Received 16 March 2009; accepted 16 March 2009; electronically published 28 May 2009.

Potential conflicts of interest: none reported.

Financial support: none reported.

Reprints or correspondence: Caroline A. Sabin, Research Dept. of Infection and Population Health, Div. of Population Health, UCL Medical School, Royal Free Campus, Rowland Hill St., London NW3 2PF (c.sabin@pcps.ucl.ac.uk).

**The Journal of Infectious Diseases** 2009;200:8–10

© 2009 by the Infectious Diseases Society of America. All rights reserved.

0022-1899/2009/20001-0003\$15.00

DOI: 10.1093/infdis/jin114

in an article appearing in this issue of the *Journal* [12], whether HIV replication itself contributes to the risk of AIDS-related lymphomas. Using data from the German ClinSurv cohort study of 18,451 HIV-infected patients, the authors identified all patients who initiated HAART and had a follow-up length that was sufficient for analysis. Among the 6022 eligible patients, 66 cases of AIDS-related lymphoma (11 cases of Burkitt-type NHL, 32 cases of non-Burkitt high-grade B cell NHL, 8 cases of primary central nervous system [CNS] lymphoma, and 15 cases of lymphoma of unknown subtype) were diagnosed at least 30 days after the initiation of HAART (with the 30-day cutoff being used to exclude existing lymphomas that had simply been unmasked by the use of HAART). Exposure to HIV viremia was categorized in several ways: (1) through the baseline, maximum, and latest HIV load and (2) by the proportion of viral load measurements that were >500 HIV RNA copies/mL after initiation of HAART. In addition, a measurement of cumulative exposure to HIV viremia, calculated as the area under the curve of the log viral load and expressed as the number of viral load “days,” was determined for each individual. High levels of this variable can be attained both by individuals exposed to high levels of viremia for short periods and by individuals exposed to lower levels of viremia for longer periods.

The investigators found a strong association between cumulative HIV viremia and the risk of lymphoma, with each 2000 days  $\times$  log HIV RNA copies/mL associated with a 67% increase in risk. These findings were independent of an association with a lower latest CD4 cell count, which was also significant. The association with cumulative HIV viremia was seen for both Burkitt-type and non-Burkitt high-grade lymphomas, whereas no association was noted with primary CNS lymphomas. (However, because only 8 cases of primary CNS lymphoma occurred, the power to detect significant associations was low.)

Although the hazard ratio was slightly higher for Burkitt-type lymphomas (3.45) than for non-Burkitt type lymphomas (2.02), Zoufaly et al. did not formally test whether these associations were different, and this difference may reflect chance variation. Of note, when the calculation of cumulative viremia was based only on viral loads measured in the most recent 3 years, a similar association was found, leading the authors to conclude that recent exposure to viremia might be a more important determinant of the risk of lymphoma than lifetime exposure.

Few other studies have considered the role of viremia in determining the risk of lymphoma. Although Bonnet et al. [13] reported that patients who had achieved a viral load of <500 copies/mL while receiving treatment had a reduced risk of NHL, compared with untreated patients and patients whose viral load did not decrease to this level, the association did not remain significant in multivariable analyses. In the United Kingdom Collaborative HIV Cohort study [11], each log<sub>10</sub> copy/mL increment to the latest viral load was associated with a 17% increase in the risk of NHL, after adjustment for the various measurements of an immunocompromised status.

The results of Zoufaly et al. are interesting and raise many questions about the optimal care of HIV-infected patients. Currently, most HIV treatment paradigms aim to ensure that CD4 cell counts remain relatively high, with suppression of the viral load mainly perceived as a tool with which to achieve this outcome. However, current findings suggest that viral suppression may be important in the prevention of AIDS-related lymphomas in its own right, independent of the CD4 cell count; these findings are consistent with findings from the Strategies for Management of Antiretroviral Therapy (SMART) trial [14], which showed that ongoing HIV replication at any given CD4 cell count places patients at higher risk for opportunistic infection or death. Furthermore, the finding in the study by Zoufaly et al.

[12], as well as the finding of another study [11], that a substantial proportion (15%–22%) of lymphomas occurred in patients with CD4 cell counts of >350 cells/mm<sup>3</sup> confirms the need to identify additional risk factors for lymphoma.

The study by Zoufaly et al. did not consider the association between HIV viremia and the development of lymphoma in patients who were not receiving HAART. One immediate question that arises is why, if exposure to HIV viremia is an important risk factor for lymphoma development, the rate of lymphoma is not much higher in untreated patients, many of whom may be exposed to high levels of viremia for many years. It may be that a low CD4 cell count is a prerequisite to lymphoma development, and it is only after a low CD4 cell count has occurred that exposure to viremia plays a role. Unfortunately, few studies include viral load measurements from the pre-HAART era, and it may be difficult for study investigators to answer this question for untreated patients with a wide range of CD4 cell counts. The other main limitation of the study was its small size, which meant that the authors were restricted in their ability to consider associations with specific lymphoma types. Larger cohorts and cohort collaborations with information on well-characterized lymphomas may provide an opportunity to study this issue further.

So what of the future, given that the efficacy of antiretroviral agents has improved over time, most antiretroviral-naïve individuals starting HAART should now achieve rapid viral suppression, and the strategy of treatment interruptions (which leaves patients exposed to periods of uncontrolled viral replication) is no longer recommended? We would expect these changing circumstances to result in a continued decrease in the incidence of lymphoma over the coming years, as exposure to HIV viremia occurs less frequently. However, a minority of patients will experience virologic failure while receiving HAART, and some continue to take breaks in therapy. Coupled with the

fact that a high proportion of patients do not receive a diagnosis of HIV infection until their CD4 cell count has already fallen to very low levels, it is possible that further reductions in incidence may not be possible. Furthermore, findings of an association between NHL and both diabetes mellitus [15] and hepatitis C virus [16] suggest that the decline may even start to be reversed if these etiologies increase in frequency. Thus, in addition to continued education on the importance of maintaining good adherence to therapy and the development of new antiretroviral drugs that are forgiving to lapses in adherence and/or are active in those with existing resistance, continued attempts to encourage earlier diagnosis of HIV infection may at least permit individuals to start receiving HAART before their CD4 cell count decreases to levels that place them at risk for lymphoma.

## References

1. Matthews GV, Bower M, Mandalia S, Powles T, Nelson MR, Gazzard BG. Changes in acquired immunodeficiency syndrome-related lymphoma since the introduction of highly active antiretroviral therapy. *Blood* **2000**;96:2730–4.
2. CASCADE Collaboration. Changes over calendar time in the risk of specific first AIDS-defining events following HIV seroconversion, adjusting for competing risks. *Int J Epidemiol* **2002**;31:951–8.
3. CASCADE Collaboration. Systemic non-Hodgkin lymphoma in individuals with known dates of HIV seroconversion: incidence and predictors. *AIDS* **2004**;18:673–81.
4. Diamond C, Taylor TH, Aboumradi T, Anton-Culver H. Changes in acquired immunodeficiency syndrome-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: incidence, presentation, treatment, and survival. *Cancer* **2006**;106:128–35.
5. Polesel J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS* **2008**;22:301–6.
6. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS* **2006**;20:1645–54.
7. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* **2008**;22:2143–53.
8. Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: The Mortalité 2005 Survey. *Clin Infect Dis* **2009**;48:633–9.
9. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **2007**;370:59–67.
10. Stebbing J, Gazzard B, Mandalia S, et al. Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol* **2004**;22:2177–83.
11. Bower M, Fisher M, Hill T, et al. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. *Haematologica* 31 March **2009** (electronic publication ahead of print).
12. Zoufaly A, Stellbrink H-J, an der Heiden M, et al. Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor for AIDS-related lymphoma. *J Infect Dis* **2009**;200:79–87 (in this issue).
13. Bonnet F, Balestre E, Thiébaud R, et al. Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France. *Clin Infect Dis* **2006**;42:411–7.
14. Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Inferior clinical outcome of the CD4<sup>+</sup> cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4<sup>+</sup> cell counts and HIV RNA levels during follow-up. *J Infect Dis* **2008**;197:1145–55.
15. Chao C, Page JH. Type 2 diabetes mellitus and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis. *Am J Epidemiol* **2008**;168:471–80.
16. Engels EA. Infectious agents as causes of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* **2007**;16:401–4.