To the editor:

Degree of immune suppression and risk of HIV-related Hodgkin lymphoma: time points matter

In a recent issue of *Blood*, Clifford and colleagues[1] reported interesting findings from the Swiss HIV Cohort Study pertaining to the debated relationship, in the setting of HIV infection, between occurrence of Hodgkin lymphoma (HL) and degree of immune suppression. In contrast to previous data from the United States,[2] they found that HL risk did tend to increase with lowering $CD4^+$ cell counts, with a statistically significant elevated risk related to a low $CD4^+/CD8^+$ ratio.[1] Lymphocytopenia due to sequestration of lymphocytes at the tumor site is common in immunocompetent people with HL[3,4] and data from Clifford and colleagues[1] provide, for the first time, evidence for a decline in the number of circulating $CD4^+$ cells in the year preceding HL also in the setting of HIV infection. This observation makes timing of $CD4^+$ cell counts with respect to HL diagnosis a key element to help elucidate the still controversial relationship between degree of immune suppression and HL. From this viewpoint, it should be noted that, in the US study, $CD4^+$ cells were counted only once before HL and that only 27% of HL cases had a $CD4^+$ cell count available in the 12 months preceding HL onset.[2] This makes comparison of the findings of the 2 studies difficult.

In our opinion, the data provided by Clifford and colleagues[1] indicate that the meaning of $CD4^+$ cell count should be interpreted with respect to the time period preceding HL diagnosis. According to this view, $CD4^+$ cell count may convey different pathogenic implications for the occurrence of HL when measured at different time points before HL onset. Therefore, in HIV-infected persons, the number of circulating $CD4^+$ T lymphocytes cannot be solely regarded as a surrogate marker of the level of immune competence or immune reconstitution after highly active antiretroviral therapy. In fact, due to the peculiar redistribution of $CD4^+$ T cells that are diverted from periphery to the tumor sites since the early phases of HL pathogenesis,[3,4] the $CD4^+$ T-cell count could also help identify HIV^+ persons at high risk to develop HL. An attractive possibility to be investigated in prospective studies concerns, thus, the potential role of a persistent decline in $CD4^+$ T-cell count as a marker predictive of an impending HL in HIV^+ persons. The regular evaluation of $CD4^+$ T-cell count currently performed in patients treated with highly active antiretroviral therapy makes this type of investigation feasible, while the concomitant evaluation of HIV viral load could help distinguish from progression of HIV disease. In addition, multiparametric evaluation of $CD4^+$ T-cell attributes and their protective functions[5] may help to further refine the predictive value of $CD4^+$ T-cell counts.

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References

1. Clifford GM, Rickenbach M, Lise M, et al. Hodgkin lymphoma in the Swiss HIV Cohort Study. *Blood.* 2009;113:5737-5742.
2. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood.* 2006;108:3786-3791.
3. Romagnani S, Del Prete GF, Maggi E, et al. Displacement of T lymphocytes with the "helper/inducer" phenotype from peripheral blood lymphoid organs in untreated patients with Hodgkin's disease. *Scand J Haematol.* 1983;31:305-314.
4. van den BA, Visser L, Poppema S. High expression of the CC chemokine TARC in Reed-Sternberg cells: a possible explanation for the characteristic T-cell infiltrate in Hodgkin's lymphoma. *Am J Pathol.* 1999;154:1685-1691.
5. Seder RA, Darrah PA, Roederer M. T-cell quality in memory and protection: implications for vaccine design. *Nat Rev Immunol.* 2008;8:247-258.

Response

Lymphocyte counts prior to Hodgkin lymphoma development

We thank Dolcetti and colleagues for their interest in our report and for highlighting our observation of lymphocytopenia close in time to diagnosis of HIV-related Hodgkin lymphoma (HL). We agree that this finding makes the timing of $CD4^+$ assessment critical to elucidating the relationship between degree of immune suppression and HL risk in HIV-infected cohorts and that it complicates comparisons between our findings and those based upon $CD4^+$ counts in the year preceding HL diagnosis.[1]

Dolcetti et al go on to propose that a decline in $CD4^+$ count should be investigated as a marker for HL development. However, it should be noted that the observed decline in cell counts in the proximity of HL diagnosis was not specific to $CD4^+$, but was also seen for $CD8^+$ and total lymphocytes.[2]

To assess the usefulness of declines in lymphocyte counts to predict future HL development, we reanalyzed $CD4^+$, $CD8^+$, and total lymphocyte counts at an additional time point 2 to 3 years prior to HL diagnosis, using the same case:control pairs as in our paper.[2] Complete information across all 3 time points before HL diagnosis, namely 2 to 3 years, 1 to 2 years, and 0 to 1 year, was available for a total of 26 HL cases and 202 matched controls. These data are described in Figure 1. Of note, there was no evidence of a gradual decline in $CD4^+$, $CD8^+$, or total lymphocyte counts across the 3 periods, but only a dramatic drop in cell counts in the year preceding HL diagnosis (Figure 1). As expected, no differences over time were seen in controls. This would suggest that lymphocytopenia does not gradually develop before HL onset, but is rather a consequence of the tumor.

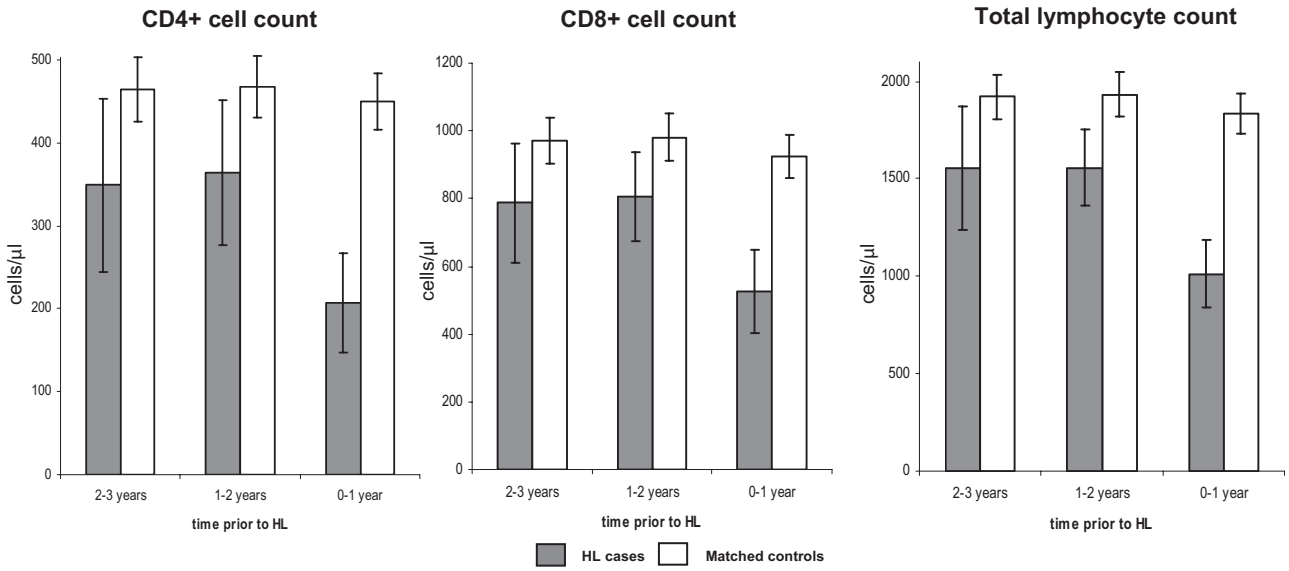

Figure 1. Trends in CD4$^+$ cell, CD8$^+$ cell, total lymphocyte counts and 95% confidence intervals, by time prior to HL diagnosis among 26 HL cases and 202 matched controls.[3]

We agree with Dolcetti et al that other cohorts of closely followed HIV-infected persons, with assessment of CD4$^+$ and CD8$^+$ cell counts at multiple time points with respect to HL diagnosis should be evaluated to clarify these issues. Ideally, EBV-specific CD4$^+$ and CD8$^+$ cell counts might also be assessed.

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The Swiss HIV Cohort Study (SHCS) has been approved by the ethical committees of all the collaborating clinics and the present analysis was additionally approved by the scientific committee of the SHCS and the ethics committee of the International Agency for Research on Cancer (IARC). Written informed consent was obtained from all SHCS participants in accordance with the Declaration of Helsinki.

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References

1. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood.* 2006;108:3786-3791.
2. Clifford GM, Rickenbach M, Lise M, et al. Hodgkin lymphoma in the Swiss HIV Cohort Study. *Blood.* 2009;113:5737-5740.

To the editor:

A monoclonal gammopathy in search of clinical significance: 57 years later

The articles by Landgren et al and Weiss et al published in a recent issue of *Blood* provided incontrovertible evidence that all multiple myelomas are preceded by monoclonal gammopathy of undetermined significance (MGUS).[1,2] While this association is expected, the findings are important and further strengthen the biologic significance of MGUS. What remains unclear and perhaps the most important question at the moment is the clinical significance of MGUS when there is yet no treatment that can prevent its progression to myeloma. Several clinical questions urgently beg answers.

First, do myeloma patients with a preceding diagnosis of MGUS have a better outcome in terms of survival and major complications (fractures and dialysis-dependent renal failure) compared with those who don't? This needs to be addressed due to the high prevalence of MGUS (5.3% among age $\geq$ 50 years) and its low likelihood of progression (0.4%/year).[3,4] There are potential harms or disadvantages of indefinitely following MGUS. While comprehensive quality-of-life studies in MGUS are not available, the psychological burden of cancer anticipation can be disturbing. A preliminary study from our group showed that patients seen at our hematology clinic had similar degrees of psychological distress during follow-up visits regardless of whether the hematologic condition was benign or malignant. The distress level was the same among patients with MGUS and myeloma.[5] Moreover, the health care costs of following MGUS can be considerable. Based on the US Census Bureau, we calculated the number of patients harboring MGUS to be at least 3.6 million.[6] Assuming that only 25% are diagnosed, there would still be almost a million patients to follow annually. This is confounded by the fact that there is a projected shortage of 2550-4080 hematologists-oncologists by 2020.[7]