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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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.