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Absolute Level of Epstein-Barr Virus DNA in Human Immunodeficiency Virus Type 1 Infection Is Not Predictive of AIDS-Related Non-Hodgkin Lymphoma

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To study whether Epstein-Barr virus (EBV) load can be used to predict the occurrence of acquired immunodeficiency syndrome-related non-Hodgkin lymphoma (AIDS-NHL), we determined EBV load longitudinally for individuals infected with human immunodeficiency virus type 1. EBV load in peripheral blood mononuclear cells (PBMC) was high and displayed considerable fluctuations over time, indicating that absolute EBV load in PBMC is not predictive of the development of AIDS-NHL. EBV DNA was also detectable in serum at some time points but at a lower level.

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Results

Longitudinal analysis of EBV load in PBMC of HIV-1–infected individuals. To investigate the kinetics of EBV load during HIV-1 infection, we determined EBV load in 9 AIDS-NHL patients with DLCLs, 5 LTA individuals, and 7 progressors. Figure 1 shows the results for 6 representative AIDS-NHL patients, 3 LTA individuals, and 3 progressors. Over time, most AIDS-NHL patients displayed bursts in EBV load (figure 1A) that could reach levels of >1 × 10^6 copies/10^6 PBMC (figure 1A, patient NHL8199). However, in most of these AIDS-NHL patients, EBV load did not reach levels >2 × 10^4 copies/10^6 PBMC (figure 1A, patients NHL0292, NHL0068, and NHL0118). EBV load at the time that AIDS-NHL was diagnosed was 1.4 × 10^3–3.1 × 10^6 copies/10^6 PBMC (figure 1A). This absolute amount of EBV DNA was not related to CD4^+ T cell numbers or HIV RNA load at the time of diagnosis or to HIV-positive follow-up (data not shown).

Although in the LTA group, EBV load could be undetectable early in the course of HIV-1 infection (figure 1B, patient LTA1160), bursts of EBV load also were observed that reached levels of 7 × 10^4 copies/10^6 PBMC (figure 1B). Similarly, bursts of EBV load were observed in the group of progressors (figure 1C). EBV load peaks varied from 1 × 10^3 to 1.6 × 10^5 copies/10^6 PBMC but decreased again to baseline values in most LTA individuals and progressors. Bursts of EBV load were not caused by increases in the number of B cells in the blood (data not shown).

We calculated the mean EBV load for each individual both early (approximately the first 4 years of follow-up) and late (approximately the last 4 years of follow-up) in infection. As shown in figure 2, there was no difference in absolute EBV load (mean) between AIDS-NHL and LTA individuals, either early or late in infection (P = .44 and P = .7, respectively; Mann-Whitney U test). The mean EBV load for AIDS-NHL patients and that for the group of progressors also did not differ (P = .41 early in infection and P = .1 late in infection; Mann-Whitney U test). In addition, no difference was found among the 3 groups when we compared the highest peaks in EBV load observed for each individual during the entire follow-up period (data not shown). Interestingly, whereas LTA individuals and progressors had a stable EBV load or a significant decrease (P = .35 for the LTA group and P = .018 for the progressor group; Wilcoxon test), 7 of 9 AIDS-NHL patients had an increase in EBV load during the course of HIV-1 infection (P = .05; Wilcoxon test). The change in EBV load for AIDS-NHL patients was significantly different from that for progressors (P < .008; Mann-Whitney U test).

EBV load in PBMC versus EBV load in serum. We subsequently compared the EBV load in PBMC with that in serum for 7 AIDS-NHL patients, 3 LTA individuals, and 1 progressor from whom serum samples were available at the same time points. Figure 1A and 1B shows the results for 4 AIDS-NHL patients (patients NHL0068, NHL0118, NHL0308, and NHL6006) and 2 LTA individuals (patients LTA0750 and LTA0036). In most individuals at some time points EBV could be detected in serum. Levels were much lower, however, than levels in PBMC, and the kinetics often were different. One AIDS-NHL patient had detectable levels of EBV in serum only at the last time point studied (figure 1A, patient NHL0068). Interestingly, a high peak in the serum load occurred when the load in PBMC was decreasing after initiation of highly active antiretroviral therapy (figure 1A, patient NHL0068) and following the initiation of successful chemotherapy after a diagnosis of lymphoma was made (figure 1A, patient NHL6006).

Overall, no correlation between EBV load in PBMC and EBV load in serum was found (data not shown).

Discussion

In the present study, we investigated the kinetics of EBV load in PBMC and serum in different groups of HIV-1–infected individuals, using a real-time quantitative PCR assay. We observed bursts in the EBV load in PBMC in all subgroups of HIV-infected patients that we studied and found that the absolute EBV load is not predictive of whether AIDS-NHL will develop. Furthermore, there is no clear correlation between EBV load in PBMC and EBV load in serum.
Figure 1. Epstein-Barr virus (EBV) load in peripheral blood mononuclear cells (PBMC; solid lines) and in serum (dashed lines) for 12 individuals with human immunodeficiency virus infection, measured by a real-time quantitative polymerase chain reaction assay. Measurements were made beginning a few years after seroconversion or on study entry and continued until (A) the diagnosis of AIDS-related non-Hodgkin lymphoma (NHL), for those who developed lymphoma ($n = 6$); (B) late in infection, for long-term asymptomatic (LTA) individuals ($n = 3$); or (C) the diagnosis of AIDS, for those who progressed to AIDS but did not develop a lymphoma (PROG; $n = 3$). Black arrows indicate diagnosis of NHL or AIDS-related opportunistic infection (AIDS-OI). White arrows indicate initiation of chemotherapy (CHOP) or highly active antiretroviral therapy (HAART).

The EBV load found in HIV-1 infected individuals in the present study was comparable with that reported elsewhere for pediatric bone marrow transplant recipients with lymphoproliferative disorders [6–8, 16] and for patients with AIDS-NHL [9]. The latter study did show a relationship between high EBV load and the development of a lymphoma, but no other groups of HIV-infected individuals were investigated. Although EBV load measurements seemed to be useful for predicting the development of a lymphoma in transplant recipients, this did not appear to be the case for HIV-infected individuals. Of course, the first study group was more homogeneous; all patients received similar immunosuppressive treatment regimens (e.g., similar dosages) [6–8, 16], whereas, in the present study, the HIV-infected individuals all had different virologic and immunologic status. Because, on
In conclusion, among HIV-1 infected individuals, absolute EBV load is high and is not predictive of the development of AIDS-NHL, although an overall increase in EBV load seems to parallel the occurrence of AIDS-NHL. This suggests that the risk for AIDS-NHL is not solely determined by EBV load.

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References

12. Van Essew JWJ, Van der Holt B, Meijer E, et al. Epstein-Barr virus (EBV) reactivation is a frequent event after allogeneic stem cell transplantation.
(SCT) and quantitatively predicts EBV-lymphoproliferative disease following T cell-depleted SCT. Blood 2001;98:972–8.


16. Riddler SA, Breinig MC, McKnight JLC. Increased levels of circulating Epstein-Barr virus (EBV)-infected lymphocytes and decreased EBV nuclear antigen antibody responses are associated with the development of post-transplant lymphoproliferative disease in solid-organ transplant recipients. Blood 1994;84:972–84.