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Chronic Hepatitis and Non-Hodgkin Lymphoma Among People With HIV: Implications for Screening, Treatment, and Prevention

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People living with HIV (PLWH) have a high risk for lymphoma, particularly non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma. The likelihood of developing NHL with severe immunosuppression is approximately 1% annually, an increase of about 100-fold compared with the general population. Even with a stable, effective antiretroviral therapy (ART) regimen, PLWH have a roughly 10-fold higher NHL risk than the general population. Non-Hodgkin lymphoma is now a leading cause of death for PLWH (1). Thus, identifying NHL-specific risk factors and interventions is a high priority for improving HIV/AIDS clinical care.

A team of investigators from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) analyzed data from more than 50 000 European patients to examine whether NHL risk in PLWH is further increased by co-infection with hepatitis C virus (HCV) or chronic hepatitis B virus (HBV) (2). In their analysis, the hazard ratios for NHL were 0.67 (95% CI, 0.40 to 1.12) with HCV infection and 1.33 (CI, 0.69 to 2.56) with HBV infection before ART initiation versus 1.73 (CI, 1.21 to 2.46) and 1.74 (CI, 1.08 to 2.82), respectively, during ART. Thus, these viral infections seem to be un-associated with NHL risk in the absence of ART but associated with NHL risk similar in magnitude to the estimated risk in the general population during ART (3, 4).

Although this study was large and carefully conducted, there are reasons for caution in its interpretation. First, control of HIV replication with ART apparently had minimal effect on NHL risk. Incidence of NHL in the absence of HCV or HBV infection was 186 cases per 100 000 person-years in ART-naïve patients versus 149 cases per 100 000 person-years in ART-treated patients. Incidence was actually higher in ART-treated patients than ART-naïve patients among those with HCV infection, HBV infection, or dual infection. This finding runs counter to a substantial body of literature showing that HIV treatment consistently decreases risk for NHL. In particular, a previous article from COHERE reported systemic NHL incidence of 463 cases per 100 000 person-years in untreated patients versus 205 cases per 100 000 person-years among those receiving combination ART (rate ratio, 0.44) and

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primary brain lymphoma incidence of 57 versus 24 cases per 100 000 person-years, respectively (rate ratio, 0.43) (5). Speculation on the reasons for this inconsistency is possible, given that the treated and untreated cohorts in the current study largely comprise the same persons who were switched after initiation of ART. However, the expected association of ART with NHL is so large that, in its absence, a superimposed effect of HCV or HBV infection becomes suspect.

A second concern is the extrapolation of NHL risk estimates up to 10 years based on data for median follow-up of 13 months for untreated patients and 50 months for treated patients, with many more NHL cases indicated in the spline-based parametric cumulative incidence curves compared with the numbers actually observed among HCV- or HBV-infected patients. Because the association of ART with NHL risk was null, this extrapolation to intervals with sparse information could be problematic.

Third, several previous studies of AIDS-related NHL have failed to detect increased hazard ratios for hepatitis virus co-infection. As cited by the authors, HCV infection was associated with decreased NHL risk in the Aquitaine cohort after adjustment for treatment (6). Also, HCV or HBV co-infection did not increase NHL risk in the Swiss HIV Cohort, although treatment status was not reported (7). Moreover, there was no association between HCV infection and NHL in the Chelsea and Westminster HIV cohort during the ART era (8). Finally, co-infection with HCV and HBV was not associated with hematologic cancer in patients in the Montefiore HIV cohort, 55% of whom were receiving ART (9). Although these new findings are potentially more specific for ART-treated patients, additional research is needed for confirmation.

If HCV and HBV infection are actually associated with increased risk, several mechanisms could be responsible. These infections or their antiviral treatment could be immune stimulators, which contribute directly to lymphomagenesis. In patients with a low CD4 cell count, NHL arising soon after ART initiation could represent unmasking in the phenomenon known as immune reconstitution inflammatory syndrome. On the other hand, chronic HCV or HBV infection could hamper immune recovery or attenuate ART effectiveness. Hypothetically, anti-HCV or anti-HBV therapies could themselves be lymphomagenic. However, none of these potential carcinogenic effects would be important if HCV and HBV infection could be prevented or effectively treated. In fact, the main reasons to prevent and treat HCV and HBV infection are to reduce hepatic failure and hepatocellular carcinoma, which are more common sequelae of these viral infections than NHL.

The ART-treated patients without HCV and HBV infection had a median CD4 count of 0.256×10^9 cells/L at NHL diagnosis, and the counts in co-infected patients were even lower, which speaks to the need for earlier initiation of ART. Given that NHL among PLWH too often presents at a late stage, we have recently suggested that simple screening methods (physical examination, chest radiography, and serum lactate dehydrogenase measurement) might afford earlier detection of and lower mortality from lymphoma (10). In research studies of ART-naïve PLWH, circulating levels of chemokines, other cytokines, micro-RNAs, and markers of microbial translocation have been predictive of AIDS lymphoma, but these parameters have not been evaluated in patients receiving effective ART or with regard

to their performance in the presence of HCV or chronic HBV co-infection. The finding that NHL risk during ART is elevated 1.7-fold with HCV or HBV co-infection may partially explain the persistent excess of NHL in patients with well-controlled HIV infection. More important, this study highlights the urgent need to prevent HCV and HBV infection in PLWH and to treat those who are co-infected.

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