HIV-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence, outcome, and evolution of CD4+ T cell lymphocytes

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Clinical background
HIV-infected patients are at increased risk to develop Hodgkin lymphoma (HL). We examined the incidence and risk factors for HL, the evolution of CD4 cell counts before HL diagnosis and prognosis of patients with HIV-related HL and in the era of combined antiretroviral therapy (cART) in the Collaboration of Observational HIV Epidemiological Research Europe (COHERE).

Patients and methods
40,168 adult HIV-1 infected patients who started cART in one of 16 prospective cohort studies in Europe were included. Incidence rates per 100,000 person-years, Kaplan-Meier estimates of cumulative incidence and survival, and adjusted hazard ratios from Weibull random-effects models, with 95% confidence intervals (CIs), were calculated. CD4 counts over time were compared between patients who were free of AIDS, on cART and developed HL (cases), and control patients. Cases and controls were matched 1:5 for cohort, age, sex, risk group, CD4 cell count at start of cART, and HIV-1 RNA at reference date, defined as HL diagnosis (cases), or at identical length of followup since start of cART (controls). We used multilevel linear regression to model changes in CD4 cell counts after start of cART and during the year before reference date and tested for differences between slopes in cases and controls. The analysis was repeated for patients with non-Hodgkin lymphoma (NHL).

Results
During 159,133 person-years of followup, 78 patients were diagnosed with HL. The crude incidence rate of HL was 50.4 per 100,000 person-years for patients who developed HL before starting cART (17 cases) and 48.7 per 100,000 person-years in patients who were already on cART (61 cases). Age, gender, CDC clinical stage, CD4 cell count, and HIV-1 RNA viral load at baseline (start of observation) were not significantly associated with the risk of HL. During a median followup of 18 months (IQR 4.8-34.8 months) 12 of 78 patients with HL died. Survival was 88% (95% CI 77-94) at 1 year and 81% (95% CI 68-89) at 2 years. A total of 18 HL patients were matched to 79 controls. At HL diagnosis, 16 of 18 cases (89%) had undetectable viral loads (<500 copies/ml). The evolution of CD4 cell counts before reference date differed: in HL patients the CD4 cell count increased after start of cART (+126 cells per year) but declined during the year before the HL diagnosis (-99 cells per year). In controls the CD4 cell counts increased throughout (+57 cells per year). Slopes differed significantly during the year before the HL diagnosis (p=0.003), but not after start of cART (p=0.944); see Figure 1. In NHL patients, the CD4 cell count increased after start of cART (+131 cells per year) and remained stable during the year before the NHL diagnosis (-16 cells per year). In controls CD4 cell counts increased throughout (+38 cells per year).

Conclusions
HL incidence rates were similar in cART treated and untreated patients. CD4 cells declined before HL
diagnosis in patients on cART, despite undetectable viral load. In contrast, in NHL patients CD4 cell counts did not sharply decrease in the year before NHL diagnosis. Patients on successful cART who experience a sudden decline of CD4 counts should be investigated for HL.

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