BACKGROUND

• HIV-2 infection is characterized by a lower plasma viral load (pVL) and a slower clinical progression compared to HIV-1. CD4 cell recovery in HIV-2-infected patients receiving first-line ART has been lower than expected and slower than in HIV-1-infected patients.

• These findings are based on studies with small sample sizes and contradictory results regarding CD4 cell recovery when pre-treatment pVL was taken into account.

• In addition, the lower replication rate of HIV-2 has been mentioned as one possible explanation for the lower efficacy of antiretroviral drugs leading to a poorer response to therapy.

Objective

We aimed to compare the immunological outcome in HIV-2- and HIV-1-infected patients starting first-line ART with similar levels of plasma viral load.

METHODS

Data collection

Data were pooled from the COHERE (HIV-2-infected patients) in EuroCord 2011 and ACHEVIE (HIV-2-infected patients) 2011 data merger.

• COHERE is a collaboration of 40 cohorts from across Europe and is part of the EuroCord network.

• The ACHEVIE2 network consists of 15 clinical and virological centers caring for HIV-2-infected patients in 18 European countries.

All participating cohorts have obtained local ethics committee approval. The final data set was merged with strict accordance to quality-assurance guidelines and performing data quality checks.

Study population

• Adult HIV-2 infected patients who started first-line ART regimen between 1997 and 2011.

• With at least 50 CD4 cells/mm³ before and after first line ART and no missing data for potential confounders (listed below)

• With at least 1-year follow-up of HIV-1 infected patients receiving a NRTI- or TLR- inhibitor containing regimen because of the natural resistance of HIV-2 to these drug classes

Follow-up began at initiation of the first ART regimen (base-line) and was censored when the ART combination switch to second-line ART or when the last available CD4 counts were whichever was first.

Virological and CD4 cell data

We used a cut-off of 500 copies/mL shared by the majority of participating centers in the study to define undetectable-viral-load status. CD4 cell counts below 500 copies/mL were excluded.

Pre-treatment and baseline CD4 cell counts were defined as the closest measurement in a window of 6 months before ART start.

Statistical analysis

Linear mixed-effects models and models with a random intercept and a random slope were used modeling CD4 cell count evolution (cells/mm³/year). The correlation between individual baseline CD4 values and the subsequent CD4 slopes was handled through an unstructured covariance matrix of random effects.

In the main analysis, we considered pVL as a binary variable (≥500 vs <500 copies/mL).

In the sensitivity analysis, we adjusted for pVL differently (time-dependent variable, cut-off of 100 copies/mL), and we did stratified analyses to check for interaction with pVL and type HIV.

All models (intercepts and slopes by introducing an interaction term with the slope) were adjusted for:

• age, gender, geographic origin, HIV transmission risk (injection drug use, heterosexual, homosexual, drug use, other/unknown),

• ART regimen (two NRTI vs one non-nucleoside-boosted PI other than lopinavir (LPV/r) and darunavir (DRV/r), two NRTIs + LPV/r or DRV/r, three NRTIs, other ART combinations) prior of ART initiation.

• pre-treatment CD4 cell count (per 100 cells/mm³ increase).

RESULTS

Study population

• The ACHIVE2 database contained data from 525 HIV-2 mono-infected patients, of whom 84% were male, 73% Caucasian, and 27% Black (non-missing variables).

• The ACHIVE2 database contained data from 176.148 HIV-1 mono-infected patients, of whom 66.483 full-filled inclusion criteria and of these, 42.457 were included in the lower efficacy of antiretroviral drug regimens, mainly developed for and validated in HIV-1-infected patients, are likely to be different in HIV-2-infected patients.

• Using data from two large European cohort collaborations, we found a suboptimal CD4 cell increase after starting first-line ART in HIV-2 naïve HIV-2 compared to HIV-1 infected patients. Differences were not statistically significant and not explained by undetectable viral load in HIV-2 patients.

• An HIV-2 transmission rate (infection/100 person-years) of 0.14 (95% CI 0.09–0.22).

• The reasons for the poorer immunological response after start of ART in HIV-2 naïve patients are still unknown. Potency of antiretroviral drug regimens, mainly developed for and validated in HIV-1-infected patients, are likely to be different in HIV-2-infected patients.

• Furthermore, our results underline the need to identify more potent drugs against HIV-2, considering specificity in terms of replication and pathogenicity, in order to improve case management.

• Early treatment, meanwhile systematic assessment of patients with progressive HIV-2 infection, defined by a decline in CD4 cell count, may be considered in order to enhance immunological reconstitution.

• Sensitivity analyses, when considering only patients with a pVL <500 copies/mL, the median CD4 cell increase 12 months after ART initiation was lower in HIV-2-infected patients in adjusted analyses (difference of 77 CD4 cells/mm³/year (95% CI: 53, 101); P=0.001). Furthermore, differences in CD4 cell count evolution between HIV-2- and HIV-1-infected patients were robust when viral load was included as a time-dependent variable, or as a continuous covariate (Figure 2).

• Our results, however, were more robust when adjusting for pVL as a time-dependent covariable.

SUMMARY AND CONCLUSIONS

- CD4 cell count evolution

In sensitivity analyses, when considering only patients with a pVL <500 copies/mL, the median CD4 cell increase 12 months after ART initiation was lower in HIV-2-infected patients in adjusted analyses (difference of 77 CD4 cells/mm³/year (95% CI: 53, 101); P=0.001). Furthermore, differences in CD4 cell count evolution between HIV-2- and HIV-1-infected patients were robust when viral load was included as a time-dependent variable, or as a continuous covariate (Figure 2).