CD4 cell count response to first-line combination antiretroviral treatment in HIV-2 and HIV-1 positive patients - A Multinational Multicohort Study.

#944

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BACKGROUND

- HIV-2 infection is characterized by a lower plasma viral load (pVL) and a slower clinical progression compared to HIV-1 infection. CD4 cell recovery in HIV-2-infected patients receiving first-line cART has been reported to be 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 are reported 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 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 cART with similar levels of plasma viral load.

METHODS

Data collection

Data were pooled in the COHERE (HIV-1-infected patients) in EuroCoord 2011 and ACHIEV2E (HIV-2-infected patients) 2011 data merger.

- COHERE is a collaboration of 40 cohorts from across Europe and is part of the EuroCoord network.
- The ACHIeV2e network consists of 15 clinical and virological centers caring for HIV-2 infected patients in 10 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 or HIV-1 infected patients
- who started a first-line cART regimen between 1997 and 2011
- had at least one CD4 cell measure before and after start of cART, and no missing data for potential confounders (listed below)
- excluding those HIV-2- and HIV-1-infected patients receiving a NNRTI- or fusion inhibitor containing regimen because of the natural resistance of HIV-2 to these drug classes

Follow-up began at initiation of the first cART regimen (baseline) and was censored when the ART combination was modified, at death or at the last available CD4 cell counts whichever was first.

Virological data and CD4 cell count

We used a cut-off of 500 copies/mL shared by the majority of participating centers in the study to define undetectable pVL ; thus pVL data based on quantification methods with a detection limit above 500 copies/mL were excluded.

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

Statistical analysis

Linear mixed models with a random intercept and a random slope were used for modelling CD4 cell count evolution (cells/mm^3/year). The correlation between individual baseline CD4 value(s) and the subsequent CD4 slope(s) was handled through an unstructured covariance matrix of random effects.

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

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

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

- age, gender, geographic origin (Europe, Africa, Asia, other/unknown),
- HIV transmission route (heterosexual, homosexual, drug use, other/unknown),
- Prior AIDS diagnosis,
- cART regimen (two NRTIs + one ritonavir-boosted PI (other than lopinavir (LPV/r) and darunavir (DRV/r)), two NRTIs + LPV/r or DRV/r, three NRTIs, other ART combinations), period of cART initiation
- pre-treatment CD4 cell count (per 100 cells/mm^3 increase).

RESULTS

Study population

- The ACHIeV2e dataset contained data from 925 HIV-2-mono-infected patients, of whom 243 full-filled inclusion criteria and of these, 159 were included in the analyses (no missing variables).
- The COHERE dataset 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 analyses (no missing variables).

Characteristics	HIV-1 (n=42,457)		HIV-2 (n=159)	
Median age in years (IQR)	37	(32;44)	46	(36;52)
Female, n (%)	12,813	(30)	75	(47)
Region of origin, n (%)				
Europe	14,367	(34)	43	(27)
Africa	5,955	(14)	112	(70)
Asia	459	(1)	2	(1)
Unknown/Other	21,676	(51)	2	(1)
Transmission risk group, n (%)				
Heterosexual	18,220	(43)	136	(85)
Homo/bisexual males	14,702	(35)	6	(4)
Injecting drug users	5,503	(13)	1	(1)
Mother-to-child	71	(0.2)		
Unknown/other	3,961	(9)	16	(10)
Prior AIDS diagnosis n (%)	9,846	(23)	36	(23)
First line cART regimen, n (%)				
2 NRTIs + LPV/rtv or DRV/rtv	14,713	(35)	74	(46)
2 NRTIs + 1 PI/rtv (not LPV or DRV)	9,577	(22)	36	(23)
3 NRTIs	4,149	(10)	18	(11)
Other combinations	14,018	(33)	31	(20)
Period of treatment initiation, n (%)				
1998-1999	8535	(20)	13	(8)
2000-2001	5576	(13)	13	(8)
2002-2003	6169	(15)	27	(17)
2004-2005	6843	(16)	28	(18)
2006-2007	7854	(19)	39	(25)
2008-2009	6589	(15)	29	(18)
2010-2011	891	(2)	10	(6)
Pre-treatment HIV RNA viral load				
<500 copies /ml, n (%)	6,045	(14)	92	(58)
Log$_{10}$ copies/mL median (IQR)*	4.8	(4.0;5.4)	3.2	(2.2;4.6)
Pre-treatment CD4 cell count cells/mm^3 median (IQR)	224	(100;352)	182	(83;285)

Legend: cART, combination antiretroviral therapy; IQR, Interquartile range; NRTI, Nucleoside reverse transcriptase inhibitor; rtv, ritonavir boost; PI, protease inhibitor; LPV, lopinavir; DRV, darunavir. Other combinations: mainly 2 or 3 NRTIs plus unboosted PI and combinations with integrase inhibitors.*Median and IQR are calculated for those with detectable plasma viral load.

CD4 cell count evolution

Median follow-up until treatment modification, death or last available CD4 cell count after first-line cART start was 15 (IQR: 6; 30) in HIV-2-infected patients and 11 months (IQR: 4; 25) in HIV-1-infected patients (P=0.02), respectively. A respective median of 5 (2; 8) and 5 (3; 8) CD4 cell count measurements per HIV-2- and HIV-1-infected patient were availabl (P=0.23).

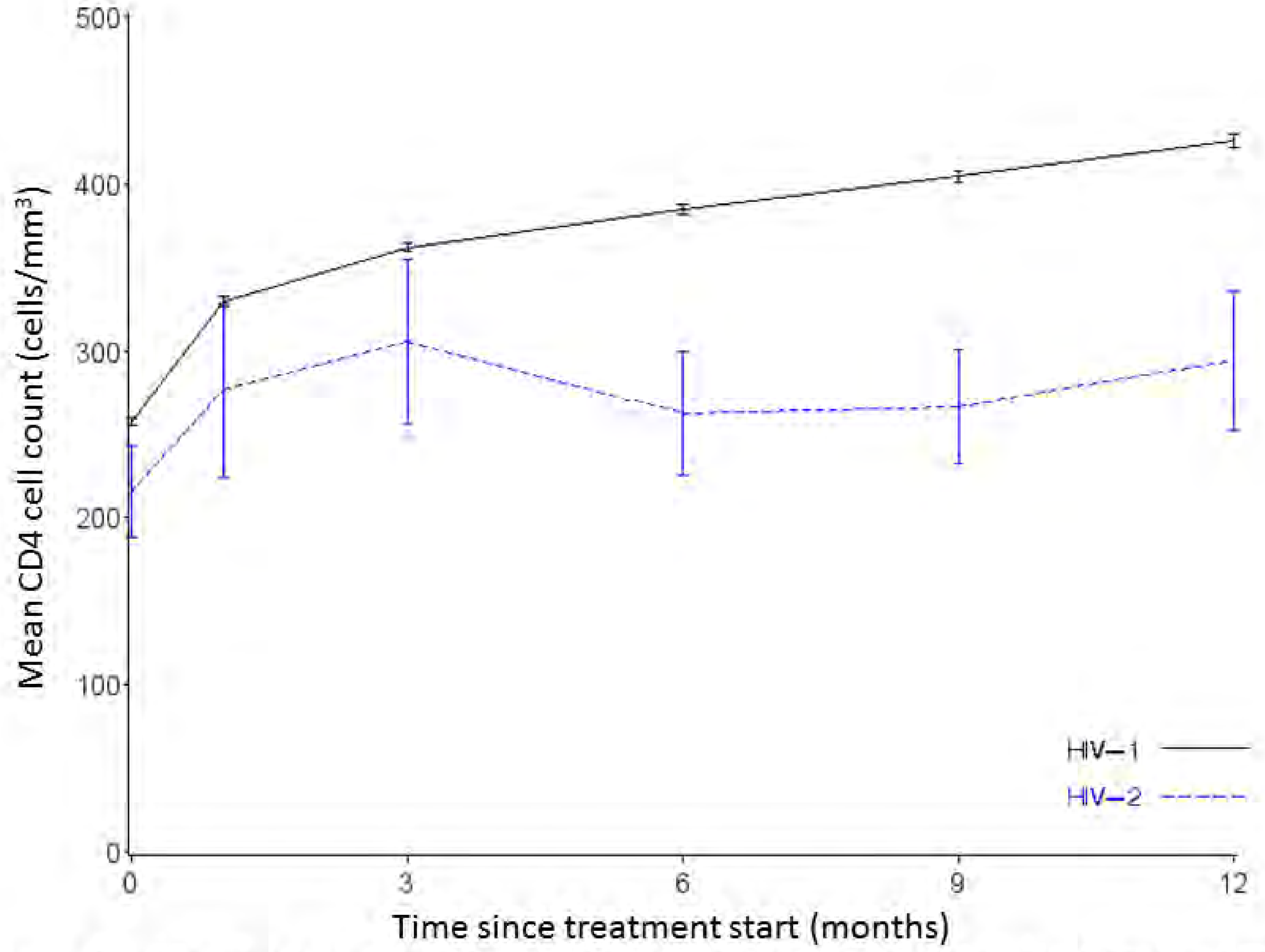

Figure 1: Mean observed CD4 cell count evolution after first line cART initiation in HIV-2 and HIV-1 infected patients. Legend: vertical bars represent 95% confidence intervals. Interpretation of differences observed here should consider that only patients still followed-up are considered for calculation.

In patients still followed-up at 12 months (HIV-1 n=28,596, HIV-2 n=103), the mean observed CD4 cell counts 12 months after cART start was 292 in HIV-2 and 423 cells/mm^3 in HIV-1-infected patients (Figure 1).

After adjusting for pVL, the mean CD4 cell count increase was significantly lower in HIV-2 compared to HIV-1-infected patients (difference of 26 CD4 cells/mm^3/year (95% CI: 7-45); P<0.01). This difference in mean CD4 cell count increase between HIV-2 and HIV-1-infected patients persisted (difference of 31 CD4 cells/mm^3/year (95% CI: 12;50); P<0.01) after adjustment for pre-treatment pVL, age, gender, geographic origin, HIV transmission route, prior AIDS diagnosis period, cART regimen, and pre-treatment CD4 cell counts.

Considering a profile of an european 40 years old female, infected by HIV through heterosexual contacts, initiating lopi or daru/RTV + 2NRTI in 2008-2009, with 200 CD4 cells/µL, a pVL <500 cps/mL and no AIDS diagnosis at treatment initiation, the predicted CD4 cells increase after one year of treatment was 158 cells/µL 95%CI [152;165] and 127 cells/µL 95%C I [107;147] for HIV-1 and HIV-2 infected patients, respectively.

Sensitivity analyses

In sensitivity analyses, when considering only patients with a pVL measured by an assay with a detection limit of 100 copies/mL or lower, CD4 cell increase was lower in HIV-2-infected patients in adjusted analysis (difference of 29 CD4 cells/mm^3/year (95% CI: 4;54); P=0.0223). 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-, or as a continuous covariable (Figure 2).

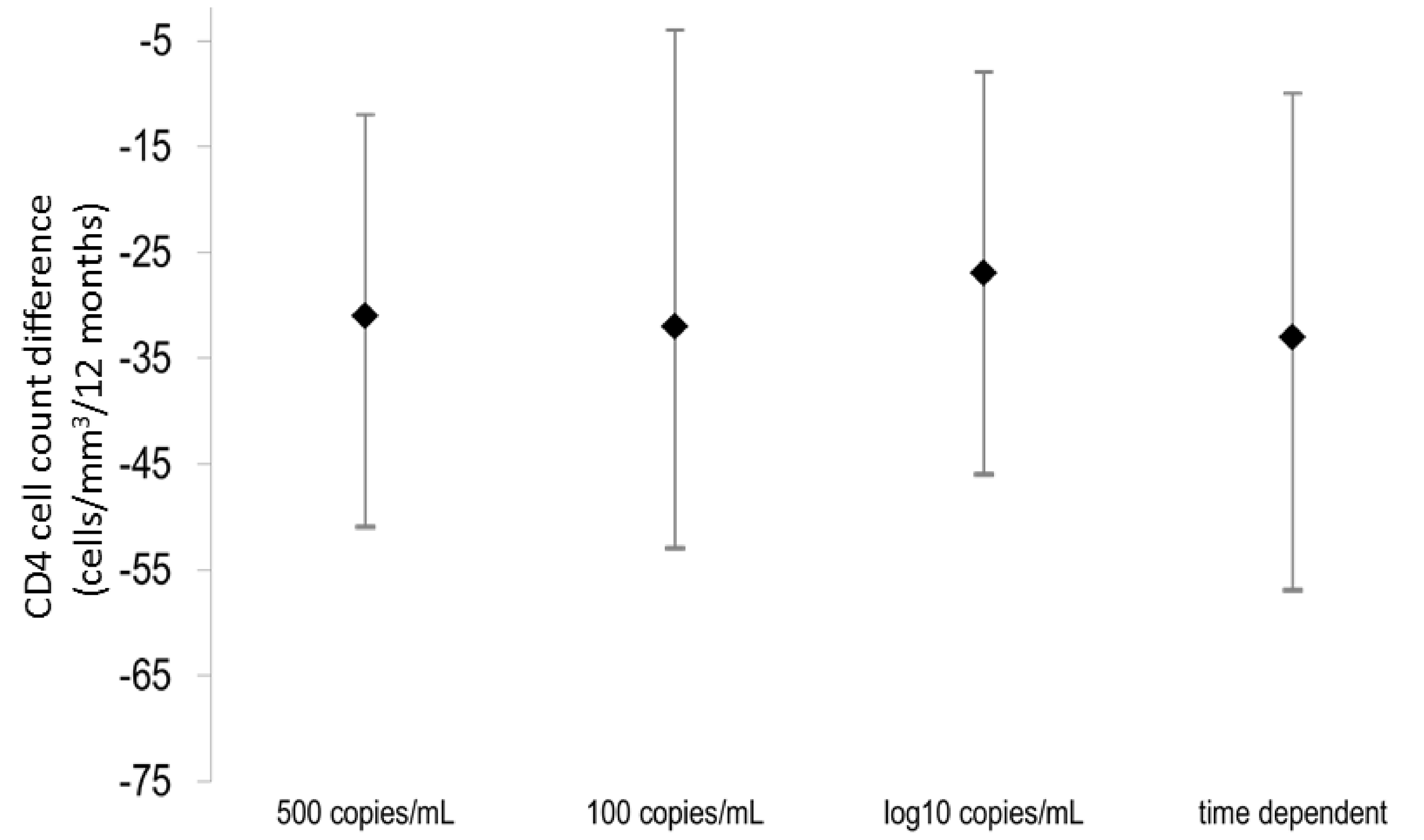

Figure 2: Adjusted estimated mean CD4 cell difference 12 months after cART initiation between HIV-2 versus HIV-1 from adjusted linear mixed models, main and sensitivity analyses. Legend: Vertical bars indicate 95% confidence intervals. The negative difference indicates a slower increase in CD4 cell counts in HIV-2 vs HIV-1 infected patients. PVL was considered in the linear mixed model as a categorical variable with a cut-off of 500 copies/mL (main analyses), 100 copies/mL, as a continuous co-variable (log$_{10}$ copies/mL), and as a time dependent co-variable allowing pVL values to change over time.

In stratified analyses for pre-treatment pVL, the effect of the HIV type on CD4 cell count response was not modified by pVL (P=0.11).

Irrespectively of the HIV type, patients receiving three NRTIs had on average a significantly lower CD4 cell increase when compared to patients receiving a boosted PI based cART regimen with a difference in slope of 33 cells/mm^3/year less (95% CI: 28;38; P<10^{-4}; Table 2). Differences in CD4 cell increases between HIV-2- and HIV-1-infected patients were not modified by the initial cART regimen (interaction test: P=0.94).

SUMMARY AND CONCLUSIONS

- Using data from two large European cohort collaborations, we found a slower CD4 cell increase after starting first-line cART in treatment-naïve HIV-2- compared to HIV-1-infected patients. Differences were not explained by pVL or cART regimen prescribed and remained statistically significant in an analysis restricted to patients receiving LPV/r or DRV/r based regimens.
- The reasons for the poorer immunological response after start of treatment in HIV-2-infected patients are still poorly understood. 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, the replication cycle of HIV-2 is clearly different from that of HIV-1: HIV-2 pVL is generally very low, and sometimes undetectable even at advanced stages of the disease while in HIV-1- and HIV-2-infected patients, adjusting for CD4 cell count, total proviral DNA is very similar. This suggests at least a blockade of HIV-2 replication at the post-integration level and might suggest that HIV-2 could spread by passing from cell to cell at least in aviremic patients. This feature may explain the differences between HIV-1 and HIV-2 with regard to the potency of protease inhibitors. Our results, however, were robust when adjusting for pVL as a time-dependent covariable.
- 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.
- Meanwhile, early treatment of asymptomatic patients with progressive HIV-2 infection, defined by a decrease in CD4 cell slope, may be considered in order to enhance immunological reconstitution.

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