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Reference curves for CD4 response to antiretroviral treatment in HIV-1 infected naïve patients

Rodolphe Thiébaut[1] on behalf of the Standard Reference distribution of CD4 response to HAART Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord
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Background & Objective

- The primary virological goal of combination antiretroviral treatment (cART) is the attainment of an undetectable viral load as soon as possible after cART initiation, usually in the first 6 months
- A good immunological response, however, is less clearly defined
- The risk of clinical progression is more strongly associated with the absolute CD4 count at a given time than the rate of increase in the CD4+ T cell count
- Reference curves may help in the management of patients

Objective: To provide 'reference curves' for CD4+ T cell responses during the first 12 months of cART for patients with virological suppression and according to different characteristics at cART initiation.

Methods

Population

- Cohorts participating in the COHERE Collaboration, a collaboration of 39 European observational cohorts of HIV-infected individuals
- Age ≥ 18 years
- First cART started from 1/1/2005 to 1/1/2010
- At 6 (+/- 3) months after cART initiation
  - at least one available CD4 count (in cells/µL)
  - HIV-1 RNA ≤ 50 copies/mL
- cART regimen containing at least three drugs, including a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), an entry inhibitor or an integrase inhibitor, or containing abacavir + 2 nucleoside reverse-transcriptase inhibitors.

Statistical analysis

- A priori stratification factors: baseline CD4+ T cell count, AIDS clinical stage, age, HIV transmission group, gender, HCV co-infection, HIV-1 RNA level, year of cART initiation and type of cART
- Quantile regression on repeated measurements of CD4+ T cell count available for each individual until 9 months and then until 15 months
- Models adjusted for time with squared and cubic effects to fit a nonlinear evolution of CD4 over time
- Models fitted after including adjustment for the covariates listed above; this set of models can be used to make predictions for individual responses taking into account individual characteristics.
- Models fitted using SAS v9.3 PROC QUANTREG. Robustness analyses with median regression including a random intercept to take into account correlation of repeated measurements (1) in patients yielded similar results as well as when using a non-parametric approach (2).

Results

Population characteristics: N=28,992 individuals

- Median (interquartile range (IQR)) age at cART initiation : 39 (33-46) years
- HIV transmission risk group: 43% Men having Sex with Men (MSM), 40% Heterosexual, 7% Intravenous Drug Use (IDU)
- 21% CDC stage C
- 8% Hepatitis C Virus positive
- Baseline CD4+ T cell count (/µL):
  - 0-199: 36%
  - 200-349: 42%
  - 350-499: 14%
  - ≥ 500: 8%
- cART regimen based on:
  - NNRTI : 51%
  - PI/r : 44%
  - Unboosted PI: 2%
  - Both PI and NNRTI: 1%
  - Free of PI and NNRTI: 2.4% (1.7% abacavir, 0.5% Integrase inhibitor, 0.08% Fusion inhibitor, 0.05% other combination)

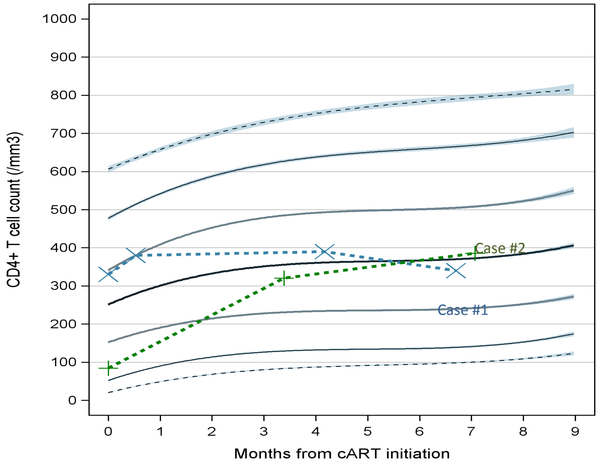

Figure 1. Percentiles (5th, 10th, 25th, 50th, 75th, 90th, 95th) of CD4+ T cell count over time from cART initiation.
Two individual trajectories are added for illustration : Case 1 *and* Case 2 *. Cases are described in boxes.*

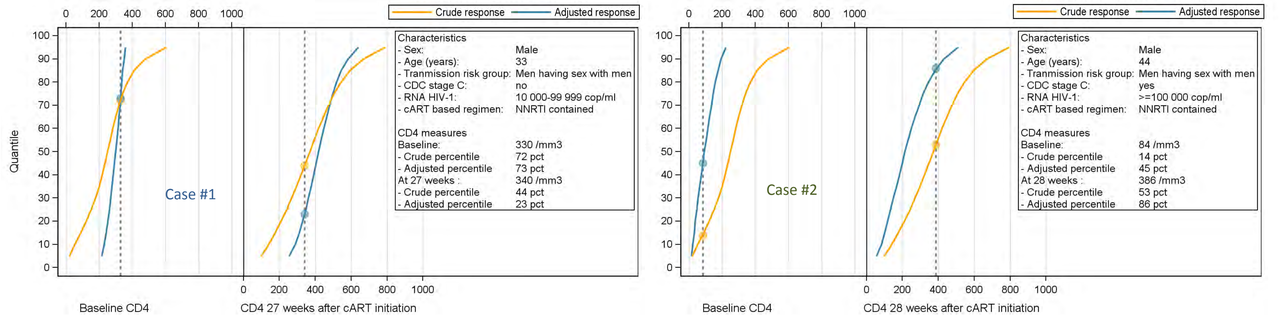

Figure 2. Example of individual CD4 cell count responses (crude and adjusted) for cases 1 and 2. ***Crude (orange) and adjusted (blue) percentile at baseline (left) and during follow-up (right) are provided according to the measured CD4+ T cell count (dashed line).*** *Adjustment on baseline CD4, sex, age, HIV transmission risk group, CDC stage C, cART regimen, HIV-1 RNA.*

Case # 1

- Male, 33 years old, started cART (Nevirapine + Tenofovir/Emtricitabine) with a CD4 count of 330 cells/µL (27% of total CD3+ T cells) **(figure1 and figure 2, left part)**
- He started at the 72th percentile, 73th after adjustment for sex, age, transmission risk group, clinical stage, HIV RNA and cART regimen at baseline.
- After 27 weeks on cART, his CD4+ T cell count did not increase substantially: 44th percentile from crude analysis (340 cells/µL, 27% of total CD3+ T cells).
- Taking the individual's characteristics into account, the patient's attained CD4+ T cell count is found to lie on only the 23th percentile after adjustment.
- This increase of only 10 cells/µL in about 7 months means that, in relative terms, the patient has switched from the 73th percentile to the 23th percentile; this is clearly a poor response.

Case # 2

- Male, 44 years old, started cART (Efavirenz + Zidovudine/Lamivudine/Abacavir) **(figure1 and figure 2, right part)**
- Baseline CD4+ T cell count was just below 100 cells/µL (14th percentile, 45th after adjustment).
- By 7 months, this individual's CD4+ T cell count had reached 386 cells/µL, putting him on the 53th percentile (86th after adjustment).

Conclusion & Perspectives

- Reference curves are easy-to-use tools to monitor CD4+T cell count patients' response to cART
- Individual predictions allow clinicians to compare an individual's CD4 response to cART over the first year to both that which would be expected in the overall population as well as the likely response from a population with similar baseline characteristics
- Large datasets like COHERE are unique opportunities to derive reference curves
- Reference curves need to be adapted in the near future to remain relevant.

References

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(2) Charlier I, Paindaveine D, Saracco J. Conditional quantile estimation through optimal quantization. *J Stat Plan Inference* 2015; **156**:14–30.

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