Poster no 343

# The frequency and clinical implications of a discordant CD4 count and CD4 percentage

Mark Gompels[1], Caroline A Sabin[2], Andrew N Phillips[2] and David Dunn[3] for the United Kingdom Collaborative HIV Cohort (CHIC)

[1]North Bristol NHS Trust, Bristol, [2]Royal Free and UC Medical School, London, [3]MRC Clinical Trials Unit, London, UK

*Correspondence:*
*Professor Caroline Sabin*
*Royal Free and UC Medical School*
*Rowland Hill Street*
*London NW3 2PF, UK*
*c.sabin@pcps.ucl.ac.uk*

## BACKGROUND

- There is a perception that a proportion of individuals infected with HIV exhibit a discordance between their absolute CD4 count and their CD4%, with some patients having a low CD4 count but relatively normal CD4% or vice versa. It is unclear whether CD4/CD4% discordancy has any clinical implications, i.e. do individuals with a discordant CD4/CD4% value have a different risk of clinical progression to their counterparts with concordant values?
- We wished to identify factors associated with discordant CD4/CD4% values among untreated HIV-infected individuals, and to describe the relationship between discordant CD4/CD4% values prior to starting highly active antiretroviral therapy (HAART) and subsequent virological, immunological and clinical outcomes on HAART

## METHODS

*Determination of a discordant CD4/CD4% value*

- We used data from untreated participants in UK CHIC to describe the distribution of CD4% values for individuals with absolute CD4 counts (where these were measured on the same sample) within specific ranges (<50, 50-99, 100-149,…, 700-749, ≥750 cells/mm$^3$).
- A linear regression model, using generalised estimating equations to take account of the multiple measurements contributed by participants, was used to identify factors associated with a higher/lower CD4% for any given CD4 count; these analyses were repeated in the subgroup of patients with HIV RNA levels measured on the same day as the CD4/CD4% values
- Each CD4/CD4% 'pair' was classified as discordant if the CD4% was <10$^{th}$ percentile (low discordancy; LD) or >90$^{th}$ percentile (high discordancy; HD) of values in that stratum. All other CD4/CD4% 'pairs' were classified as concordant. Using this definition, approximately 10% of 'pairs' will be classified as LD, 10% as HD and the remaining 80% as concordant.

*Relationship between CD4/CD4% discordancy pre-HAART and response to HAART*

- Using Cox proportional hazard regression models, we assessed whether CD4/CD4% discordancy prior to starting HAART was associated with the following outcomes on HAART:
  - Initial virological response – time to the first viral load <50 copies/ml;
  - Viral rebound – time to confirmed viral load >500 copies/ml in those with an initial response;
  - Immunological response – change in CD4 count at 6 months;
  - Clinical response – the development of a new AIDS event or death.
- Eligible patients were ARV-naïve at the time of starting HAART (any regimen including at least one protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or abacavir, regardless of the number of drugs in the regimen); had a CD4/CD4% measurement in the 6 month period prior to starting HAART; and had at least one post-HAART CD4 count and viral load. Discordancy was defined using the cut-off values determined above.
- Regression models also controlled for the pre-HAART CD4 count and the following potential confounding factors: age at start of HAART, sex, risk group, ethnicity, type of HAART regimen and calendar year.

## RESULTS

*Determination of CD4/CD4% discordancy*

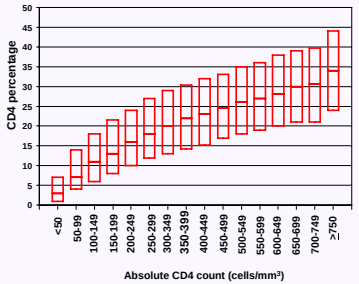
- 99,351 CD4/CD4% 'pairs' (measured from 1980-2005) were included from 15,543 untreated patients (Table 1). A summary of the CD4% measurements in each CD4 strata, along with the 10$^{th}$ and 90$^{th}$ percentiles of the distributions, is shown in Figure 1.
- Results from the model that included all CD4/CD4% 'pairs'(left-hand side of Table 2) showed that for any given CD4 count, the CD4% was 2.5% higher in females, 1.3% higher in injection drug users (compared to homosexual men) and was higher in more recent calendar years, whereas the CD4% decreased with age, was 1% lower in those who were heterosexual or had an 'other' risk for infection and around 0.7% lower in those of non-white or unknown ethnicity
- When the model was repeated among 'pairs' where a viral load was also available (right-hand side of Table 2), associations were similar although the relationship with injection drug use became non-significant after adjustment for the viral load. Individuals with higher viral loads tended to have lower CD4% values on average.
- 9.2% of 'pairs' met our definition of LD and 10.7% met our definition of HD

## RESULTS

### TABLE 1: DEMOGRAPHIC BREAKDOWN OF EACH CD4/CD4% 'PAIR' IN UNTREATED PATIENTS, AND OF ARV-NAÏVE PATIENTS STARTING HAART

| | | CD4/CD4% 'pairs' | | Patients starting HAART | |
|---|---|---|---|---|---|
| | | n | % | n | % |
| Total number included in analysis | | 99351 | 100.0 | 5879 | 100.0 |
| Sex | Male | 83869 | 84.4 | 4332 | 73.7 |
| | Female | 15480 | 15.6 | 1547 | 26.3 |
| Age (years) | <30 | 24448 | 24.6 | 1064 | 18.1 |
| | 30-39 | 48757 | 49.1 | 2911 | 49.5 |
| | 40-49 | 19841 | 20.0 | 1380 | 23.5 |
| | ≥50 | 6305 | 6.4 | 524 | 8.9 |
| Risk group | Homosexual | 72118 | 72.6 | 3203 | 54.5 |
| | IDU | 5795 | 5.8 | 213 | 3.6 |
| | Heterosexual | 19505 | 19.6 | 2252 | 38.3 |
| | Other/not known | 1933 | 2.0 | 211 | 3.6 |
| Ethnicity | White | 68615 | 69.1 | 3224 | 54.8 |
| | Black | 14181 | 14.3 | 1774 | 30.2 |
| | Other | 10343 | 10.4 | 654 | 11.1 |
| | Not known | 6212 | 6.3 | 227 | 3.9 |
| Viral load (copies/ml) (n=42109) | <1000 | 4083 | 9.7 | n/a | |
| | -9,999 | 9352 | 22.2 | | |
| | -99,999 | 19567 | 46.5 | | |
| | ≥100,000 | 9107 | 21.6 | | |
| Pre-HAART CD4 | (cells/mm$^3$) | | | 180 | 90, 274 |
| Pre-HAART CD4% | | | | 13 | 8, 19 |
| Pre-HAART viral load (n=5459) | (copies/ml) | | | 4.9 | 4.3, 5.4 |

### FIGURE 1: DISTRIBUTION OF CD4% VALUES IN UNTREATED INDIVIDUALS WITH ABSOLUTE CD4 COUNTS IN SPECIFIED RANGES; VALUES SHOWN ARE MEDIAN, 10TH AND 90TH PERCENTILES




### TABLE 2: ESTIMATES FROM MULTIVARIABLE LINEAR REGRESSION MODELS OF THE FACTORS ASSOCIATED WITH CD4%

| | | Model excluding viral load (99351 observations, 15543 patients) | | Model including viral load (42109 observations, 10272 patients) | |
|---|---|---|---|---|---|
| Factor | | Estimate (SE) | P-value | Estimate (SE) | P-value |
| Intercept* | | 19.93 (0.54) | 0.0001 | 17.92 (0.17) | 0.0001 |
| CD4 count* | (per 50 cells/mm$^3$ higher) | 0.70 (0.10) | 0.0001 | 0.95 (0.05) | 0.0001 |
| Age* | (per 5 years older) | -0.70 (0.05) | 0.0001 | -0.52 (0.05) | 0.0001 |
| Sex | Female | 2.53 (0.28) | 0.0001 | 1.81 (0.27) | 0.0001 |
| Risk group | Heterosexual | -0.89 (0.29) | 0.003 | -0.98 (0.28) | 0.0005 |
| | IDU | 1.30 (0.38) | 0.0006 | 0.31 (0.45) | 0.49 |
| | Other/not known | -1.03 (0.40) | 0.01 | -0.74 (0.40) | 0.06 |
| Ethnicity | Black | -3.12 (0.29) | 0.0001 | -2.99 (0.27) | 0.0001 |
| | Other | -0.72 (0.23) | 0.002 | -1.03 (0.23) | 0.0001 |
| | Not known | -0.79 (0.31) | 0.01 | -0.92 (0.36) | 0.01 |
| Year* | (per later year) | 0.07 (0.02) | 0.0001 | 0.07 (0.02) | 0.004 |
| Viral load* | (per $\log_{10}$ higher) | n/a | | -1.81 (0.08) | 0.0001 |

* Estimates have been centred so that the intercept relates to the expected CD4% for a white homosexual man of 30 years of age with a CD4 count of 200 cells/mm$^3$ measured in 2000 and, for the model including viral load, a viral load of 5 $\log_{10}$ copies/ml

## RESULTS (continued)

*Outcomes on HAART*

- 5879 patients starting HAART met the criteria for inclusion in this analysis (Table 1); 10.7% and 10.1% of these patients exhibited LD and HD, respectively, prior to starting HAART
- By six months after starting HAART, the median (IQR) CD4 count had risen to 300 (190, 439) cells/mm$^3$ (median increase of 111 (44, 192) cells/mm$^3$) and the median CD4% was 19 (13, 25.6). Median increases in CD4 count were 90 (19, 161), 110 (48, 190) and 140 (64, 250) cells/mm$^3$, respectively, in those with LD, no discordancy and HD (p=0.001). After adjustment for the pre-HAART CD4 count in a linear regression model, CD4 increases remained lower (by 31 cells/mm$^3$, p=0.0001) in those with LD, and higher (by 38 cells/mm$^3$, p=0.0001) in those with HD, even after adjustment for potential confounding factors (Table 3).
- 5235 (89.1%) of patients experienced an initial virological response to HAART, a median of 120 days (95% confidence interval [CI] 117, 124) after starting HAART. There was no evidence that discordancy was associated with the likelihood of an initial virological response either before or after adjusting for other potential confounders (Table 3).
- 904 (17.3%) of individuals with an initial response to HAART experienced viral rebound (10.8% by 1 year). Whilst univariable analyses suggested that there may be an increased risk of viral rebound in those exhibiting LD, this effect became non-significant after controlling for the pre-HAART CD4 count and other potential confounders (Table 3)
- Over follow-up, 411 patients developed a new AIDS event (542 events in total) and 236 patients died (412 patients either developed a new AIDS event or died). There was no suggestion that discordancy status was associated with clinical progression (Table 3).

### TABLE 3: SUMMARY OF RESULTS FROM MULTIVARIABLE REGRESSION ANALYSES ASSESSING THE RELATIONSHI PBETWEEN PRE-HAART DISCORDANCY STATUS AND RESPONSE TO HAART

| | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | Estimate* (95% CI) | P-value | Estimate* (95% CI) | P-value |
| **Immunological response** | | | | |
| LD | -33.1 (-45.1, 21.1) | 0.0001 | -31.7 (-43.5, 19.8) | 0.0001 |
| Concordant | 0 | - | 0 | - |
| HD | 32.6 (20.3, 44.9) | 0.0001 | 38.4 (26.1, 50.7) | 0.0001 |
| **Initial virological response** | | | | |
| LD | 0.97 (0.89, 1.06) | 0.51 | 1.02 (0.93, 1.11) | 0.70 |
| Concordant | 1 | - | 1 | - |
| HD | 0.96 (0.88, 1.06) | 0.43 | 0.98 (0.89, 1.08) | 0.66 |
| **Viral rebound** | | | | |
| LD | 1.25 (1.03, 1.52) | 0.03 | 1.17 (0.95, 1.44) | 0.13 |
| Concordant | 1 | - | 1 | - |
| HD | 1.07 (0.86, 1.33) | 0.55 | 1.02 (0.82, 1.28) | 0.83 |
| **Clinical outcome** | | | | |
| LD | 0.88 (0.63, 1.22) | 0.43 | 0.95 (0.68, 1.33) | 0.77 |
| Concordant | 1 | - | 1 | - |
| HD | 1.18 (0.88, 1.60) | 0.28 | 1.09 (0.79, 1.50) | 0.60 |

* Estimate obtained from a linear regression model for immunological response (impact on overall mean) and from a logistic regression model (odds ratio) for other outcomes

## CONCLUSIONS

- Absolute CD4 count increases on HAART were lower in those with LD compared to other patients.
- One potential explanation for our findings is that LD may be an indication that the CD4 count is on a temporary or random high at that time point, and so we would expect less of an increase from this value in those with LD, with the reverse argument true for HD (i.e. a 'regression to the mean' effect)
- Despite this, the clinical implications of a discordant CD4/CD4% may be limited and, as long as CD4 counts are being monitored, it appears that there is little added cause for concern if the CD4% is lower than expected

**United Kingdom Collaborative HIV Cohort (UK CHIC)**

***Medical Research Council Clinical Trials Unit, London:*** Abdel Babiker, David Dunn, Esther Fearnhill, Kholoud Porter; ***HIV Epidemiology and Biostatistics Unit, Department of Primary Care & Population Sciences, Royal Free and University College Medical School (RFUCMS):*** Caroline Sabin, Teresa Hill, Colette Smith, Loveleen Bansi, Andrew Phillips; ***Brighton and Sussex University Hospitals NHS Trust*** : Martin Fisher, Duncan Churchill, Wendy Harris, Nicky Perry, Anthony Pullin; ***Chelsea and Westminster NHS Trust, London:*** Brian Gazzard, Steve Bulbeck, Jemima Clarke, Sundhiya Mandalia; ***King's College Hospital, London:*** Philippa Easterbrook, Stephen Duffell, Eghosa Bazunaye, Emma Macfarlane; ***Mortimer Market Centre, RFUCMS:*** Richard Gilson, Julie Dodds, Andy Rider, Ian Williams; ***Royal Free NHS Trust & RF&UCMS:*** Margaret Johnson, Clinton Chaloner, Helen Gumley, Fiona Lampe, Dewi Ismajani Puradiredja, Mike Youle; ***St. Mary's Hospital, London:*** John Walsh, Christian Kemble, Jonathan Weber; ***St Bartholomew's/Royal London:*** Chloe Orkin, Kevin Jones, Rachel Thomas, James Hand; ***Homerton:*** Jane Anderson, Selina Gann, Kevin Jones; ***Edinburgh:*** Clifford Leen, Alan Wilson; ***North Middlesex Hospital, London:*** Achim Schwenk, Jonathan Ainsworth; ***Health Protection Agency – Centre for Infections, London:*** Valerie Delpech