Enhanced immune reconstitution with initiation of ART at HIV-1 seroconversion (PHI)

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and the Royal Free HIV Research Database

Background

- Suggestion of benefits of early ART intervention in terms of smaller viral reservoirs and preservation of HIV specific T cell immunity[1]
- Additionally to CD4 count, CD4:CD8 ratio is now increasingly recognised as an important marker for chronic immune activation, which in turn has been shown to be associated with premature aging and non-AIDS-related morbidity

- It is unclear whether long-term immune reconstitution, and the CD4:CD8 ratio in particular, is enhanced with intervention at primary HIV infection (PHI)[2]

[1]Cohen BMC; [2] Thornhill, HIV Glasgow 2014

Study aims

- Assess the long-term immunological outcomes in a PHI cohort who started ART at time of seroconversion and remained on continuous successful ART for >5 years
- Compare these immune responses to a cohort of immuno-competent individuals who started ART during the chronic phase of infection (CHI) and remained on continuous successful ART for >5 years

Methods - Study population

- Included individuals were attendees at the Ian Charleson Clinic, Royal Free Hospital, London
- PHI Cohort
  - Laboratory-confirmed diagnosis of PHI*
  - Rapid initiation of ART within 12 weeks of diagnosis
  - Received continuous ART for ≥5 years
- CHI cohort
  - Started ART ≥1 year after HIV diagnosis
  - Pre-ART CD4 count ≥ 300 cells/mm^3
  - Received continuous ART for ≥5 years

*Negative or indeterminate HIV-1 antibody test and VL>5000 copies/ml; or positive HIV-1 antibody test with incomplete Western Blot; or positive HIV-1 antibody test with detuned assay ≤0.6 for clade B viruses

Statistical methods

- On treatment analyses performed and follow-up censored at time of ART discontinuation*
- Follow-up available until June 2014
- Immunological outcomes after 1, 5 and 10 years of ART compared between groups (χ^2 and Mann-Whitney U test)
  - CD4 count and percentage
  - CD8 count
  - CD4:CD8 ratio
  - Optimal Immunological Response (CD4 count ≥ 800 cells/mm^3, CD4% ≥ 40%, or CD4/CD8 ratio ≥ 1.00)
- Time to achieving CD4:CD8 ratio ≥ 1.00 assessed using Kaplan-Meier plot

*Interruption of all ART for >28 days

Characteristics at start of ART 1

		PHI (n=37)	CHI (n=115)
Age (years)	Median (range)	34 (19-69)	36 (32-59)
Gender	Male	35 (95%)	100 (87%)
Ethnicity	White	34 (92%)	81 (70%)
Risk for HIV acquisition	MSM	32 (86%)	84 (73%)
Year of HIV diagnosis	Before 1997 1997-2001 2002-2005 2006-2009	0 (0%) 6 (16%) 26 (70%) 5 (14%)	33 (29%) 40 (35%) 39 (34%) 3 (3%)
Time since diagnosis (months)	Median (range)	0.7 (0.2-2.8)	36 (12-172)
Regimen type	PI-based NNRTI-based Other	36 (97%) 1 (3%) 0 (0%)	66 (57%) 44 (38%) 5 (4%)
Symptomatic PHI infection	Yes	35 (95%)	-

Characteristics at start of ART 2

	Median (Range)		
	PHI (n=37)	CHI (n=115)	P
VL (log copies/ml)	5.7 (3.5->5.9)	5.4 (3.4->5.9)	-
CD4 count (cells/mm^3)	430 (67-893)	364 (302-2126)	0.11
CD4%	19 (4-40)	18 (8-14)	0.18
CD8 count (cells/mm^3)	1252 (205-6957)	1320 (344-4780)	0.34
CD4:CD8 ratio	0.30 (0.06-1.13)	0.29 (0.09-1.09)	0.23

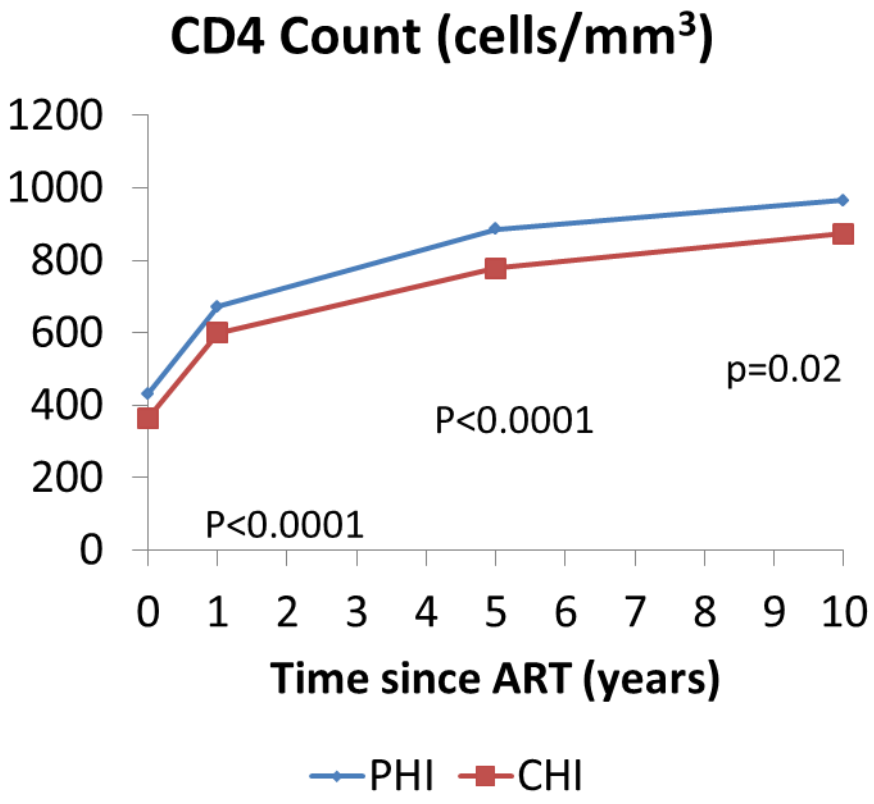
Follow-up and ART discontinuation

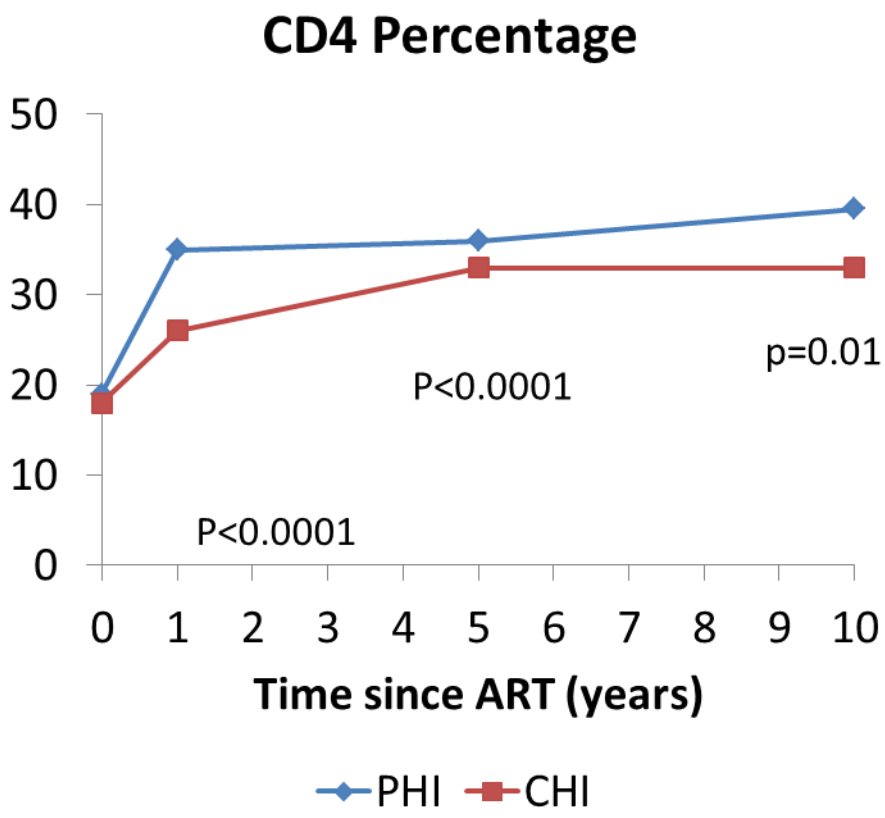
- Median (range) follow up was 10.7 (5.2 - 13.7) years for PHI and 7.6 (5.0 - 16.4) years for CHI
- Follow-up censored in PHI cohort for:
  - Administrative censoring (remained on ART): 33 (90%)
  - ART interruption: 2 (5%)
  - Moved centre: 2 (5%)
- Follow-up censored in CHI cohort for:
  - Administrative censoring (remained on ART): 92 (80%)
  - ART interruption: 6 (5%)
  - Moved centre: 17 (15%)

Viral load levels

- PHI:
  - Viral control achieved at median (range) 12 (1-31) weeks
  - 4 (11%) temporary loss of virological control (median 223 [34-426] weeks after starting ART),
  - 37 (100%) VL<50 cps/ml at last follow-up
- CHI:
  - Viral control achieved at median (range) 8 (1-120) weeks
  - 11 (10%) temporary loss of virological control (median 339 [214-500] weeks after starting ART)
  - 109 (95%) VL<50 cps/ml at last follow-up

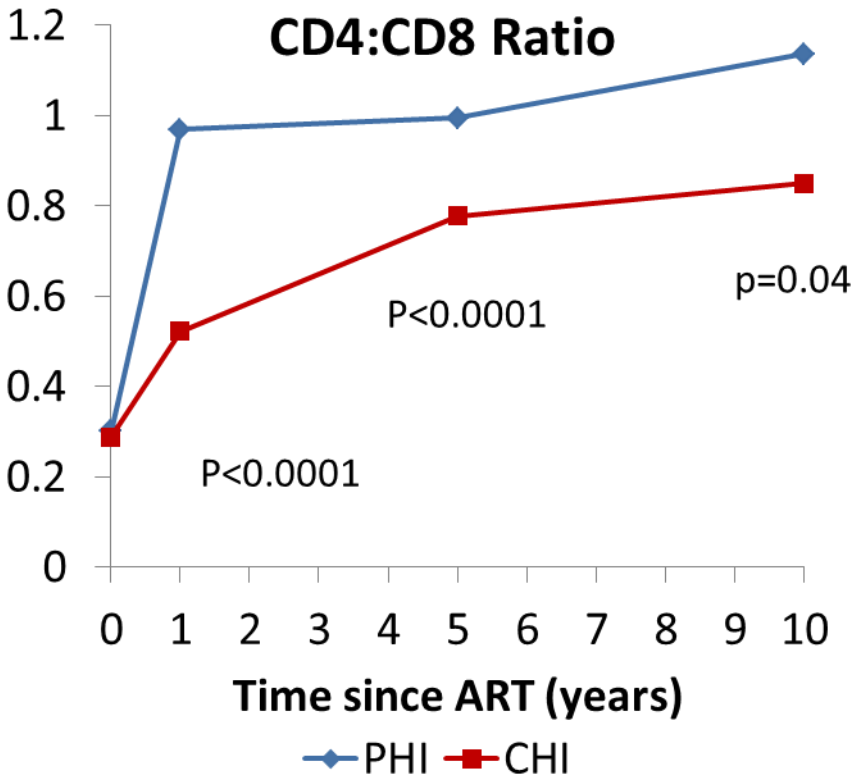
Long-term immune response to ART

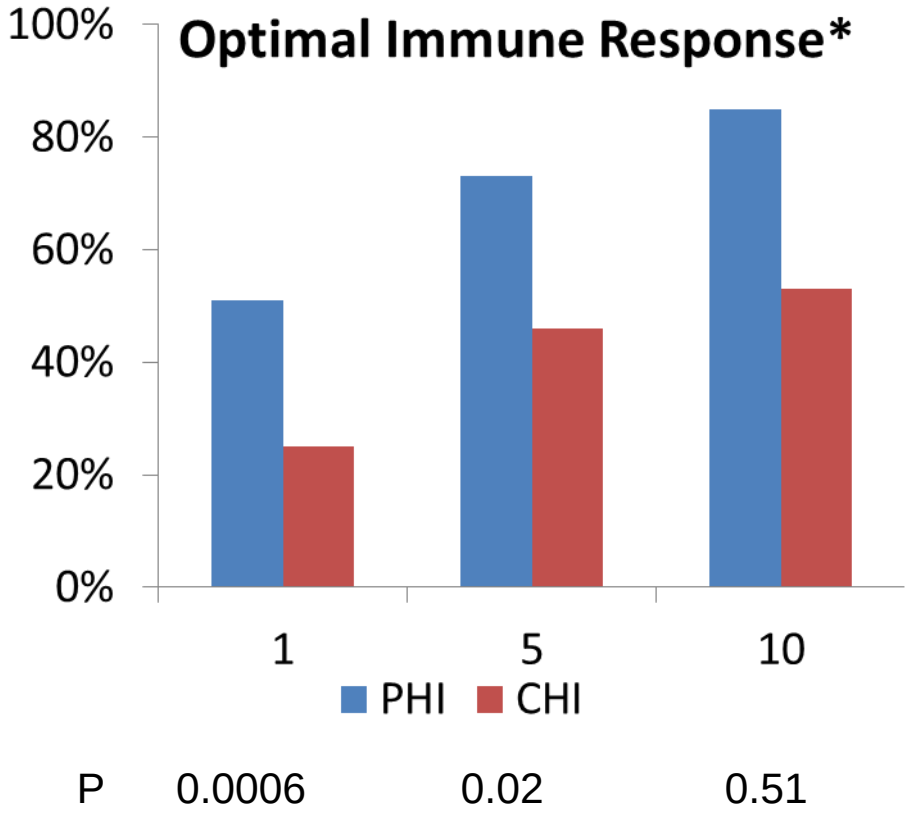




Data shown are median values

Long-term immune response to ART

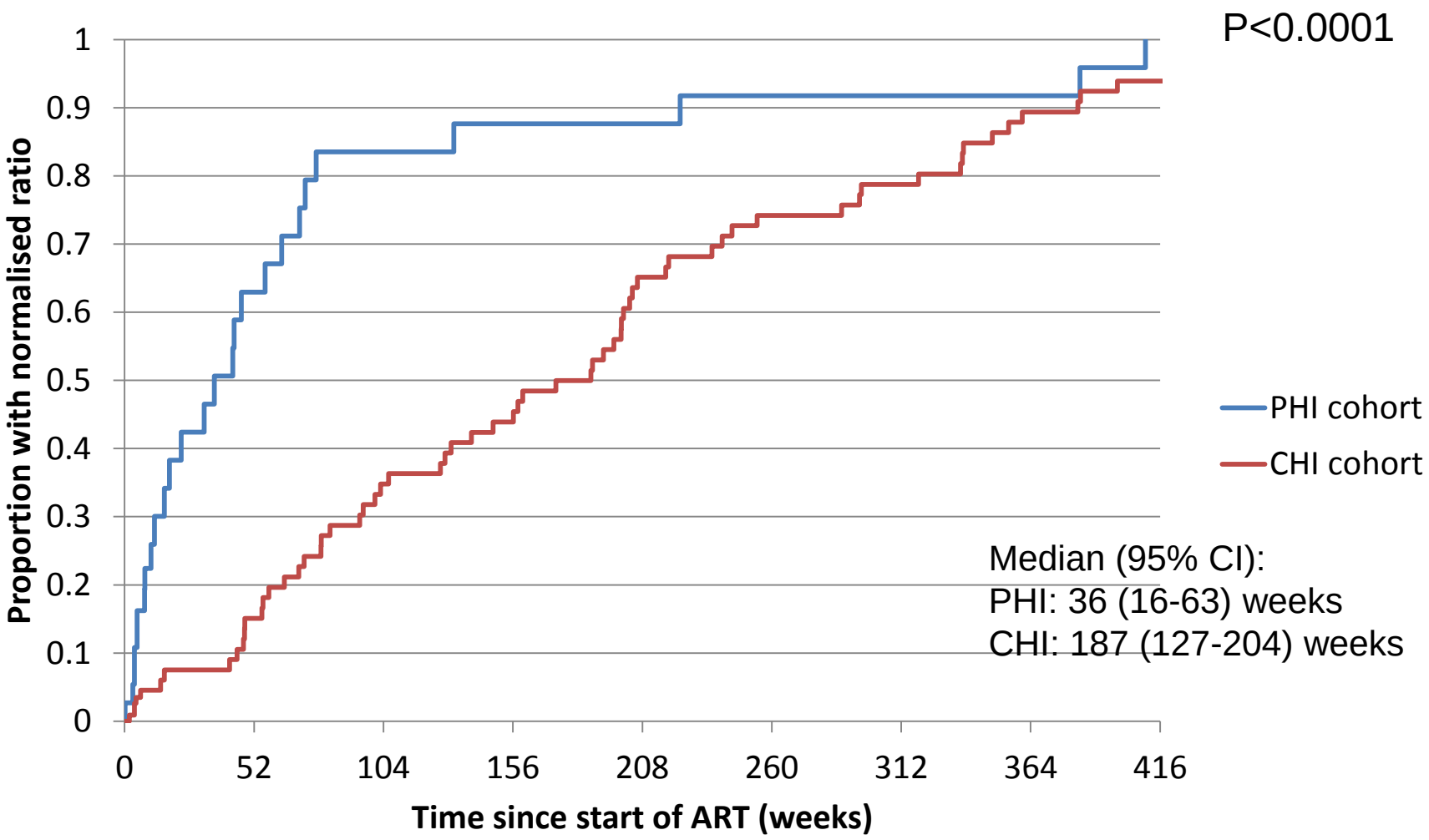




*CD4 count ≥ 800 cells/mm^3, CD4% ≥ 40%, or CD4/CD8 ratio ≥ 1.00

Data shown are median values

Time to achieving CD4:CD8 ratio ≥ 1



Conclusions

- Those treated during PHI, as compared to CHI with a good CD4 count, were more likely to achieve enhanced immunological reconstitution, suggesting a greater potential to re-establish a normal immune function
- The ability to achieve a normal CD4:CD8 ratio in a shorter time frame may reduce severe immune activation, and potentially reduce risk of non-AIDS related morbidity
- Further research into clinical non-AIDS outcomes could provide additional information

Conclusions

- Comparison is not randomised study of immediate vs deferred ART in PHI, and so potential confounding cannot be eliminated
- These results provide some support for the benefits of early treatment intervention with respect to CD4 and CD8 immune markers in those diagnosed during primary HIV-1 infection

Royal Free HIV Cohort Database

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