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HEATHER

CHERUB

Collaborative HIV Eradication of Reservoirs: UK BRC

(www.cherub.uk.net)

The effect of time to viral suppression at primary HIV infection on long term immunological recovery

BHIVA Spring Conference 2019

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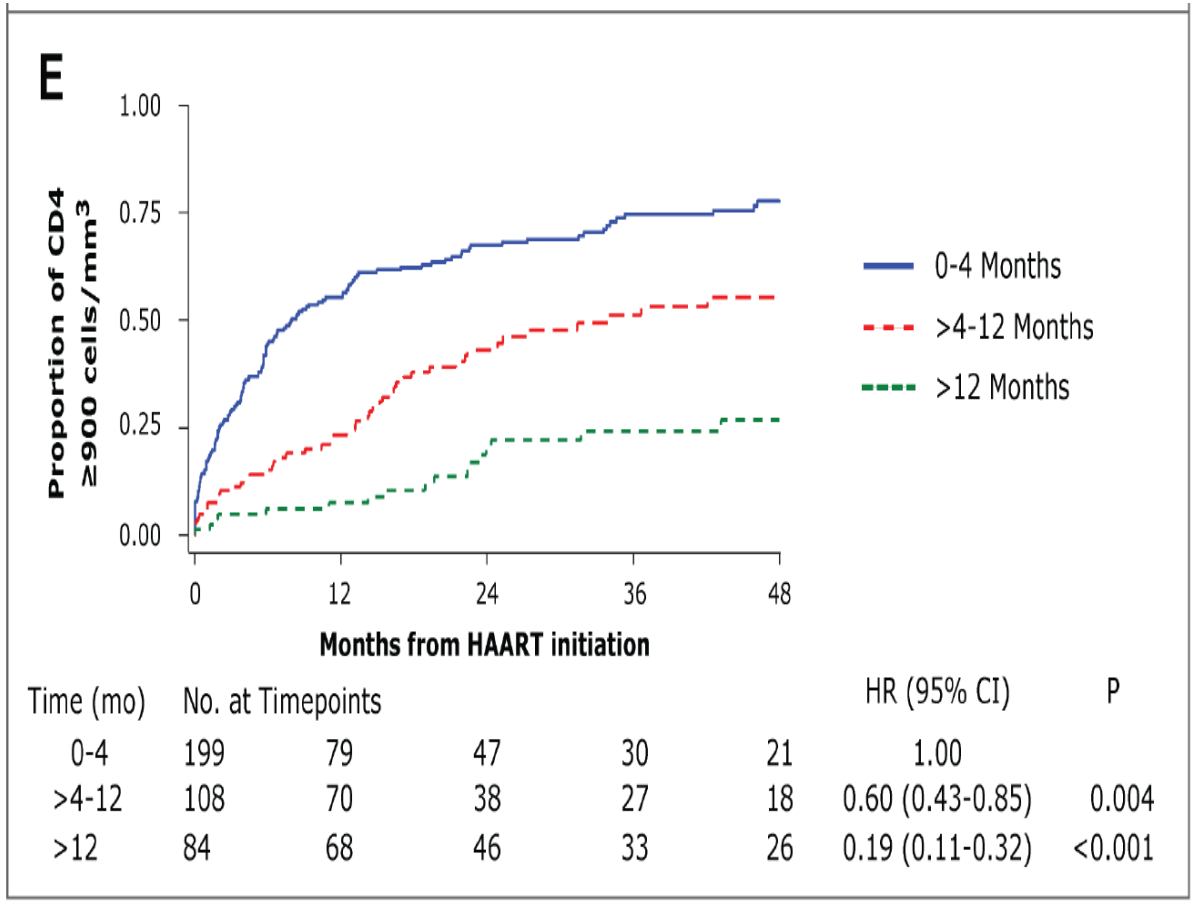
Background

- The HIV-1 reservoir is currently the main barrier to a cure for HIV and may act as a source of viral recrudescence on cessation of ART[1]
- Initiation of ART during primary HIV infection (PHI) limits the seeding of the HIV-1 reservoir[2,3]
- Normalization of the CD4/CD8 ratio compared with later initiation of therapy[4,5]
- Integrase inhibitors increasingly used as first-line agents

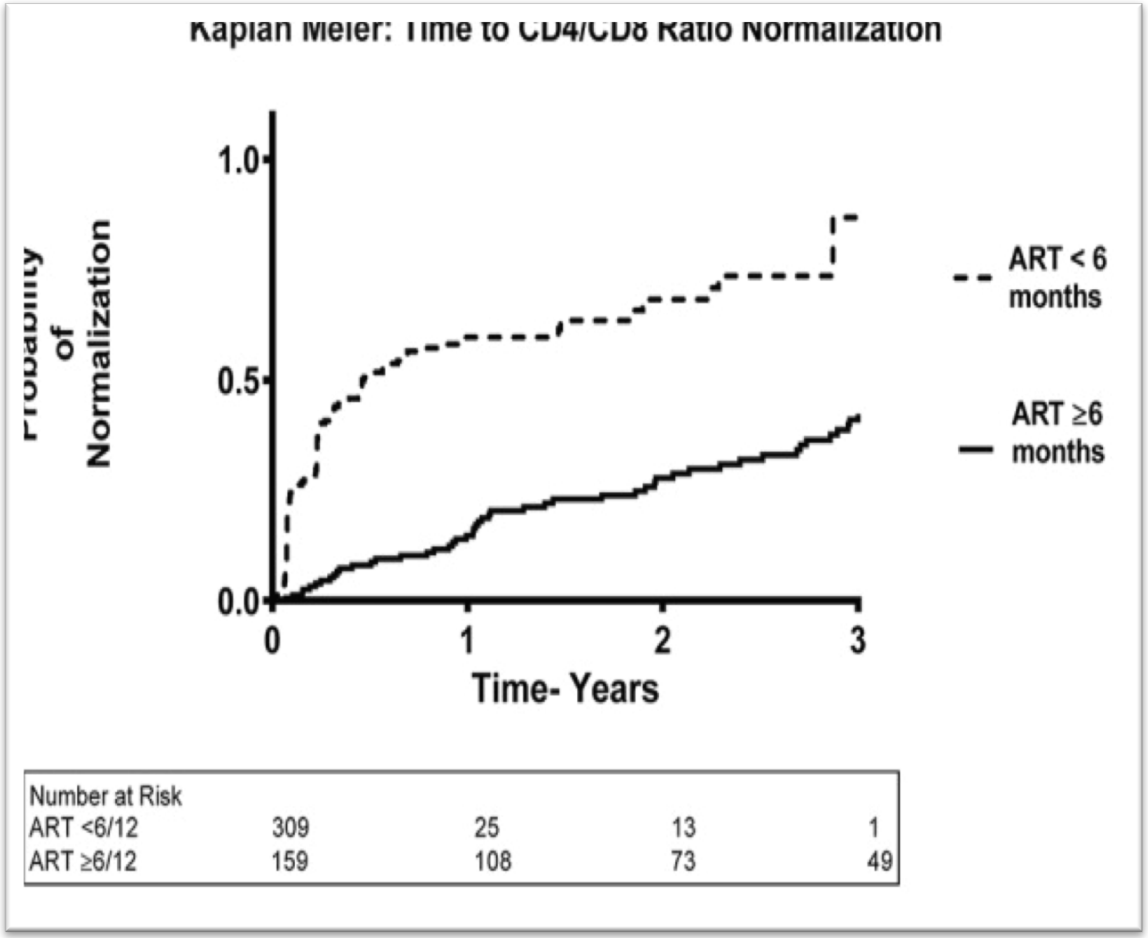
1. Joos, B., *et al. Proc Natl Acad Sci U S A* (2008); **2**. Ananworanich, J., *et al. EBioMedicine* (2016); **3**. Yukl, S.A., *et al. The Journal of infectious diseases* (2013); **4**. Le T, et al. N Engl J Med 2013**5**. Thornhill J, *et al. J Acquir Immune Defic Syndr*. 2016

Enhanced CD4+ T-Cell Recovery with Earlier HIV Antiretroviral Therapy



Time (mo)	No. at Timepoints					HR (95% CI)	P
0-4	199	79	47	30	21	1.00	
>4-12	108	70	38	27	18	0.60 (0.43-0.85)	0.004
>12	84	68	46	33	26	0.19 (0.11-0.32)	<0.001

Le NEJM 2013



Thornhill Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3)

Aims

Through our CHERUB group we aimed to determine:

1. Whether a rapid reduction in HIV viral load at PHI led to enhanced immunological outcomes (defined as CD4 > 900 or CD4:CD8 ratio ≥ 1)[1]

2. What are the factors that are associated with immune recovery at 2 years?

1. Torti C, Prosperi M, Motta D, et al. Factors influencing the normalization of CD4+ T-cell count, percentage and CD4+/CD8+ T-cell ratio in HIV-infected patients on long-term suppressive antiretroviral therapy. Clin Microbiol Infect. 2012;18:449–458

Methods

- Retrospective analysis of the HEATHER cohort. This is the largest treated seroconverter cohort in Europe.

‘HIV Reservoir targeting with Early Antiretroviral Therapy’

  - Eligibility
    - Starting ART within 3 months of documented HIV seroconversion
    - Defined as: p24 +ve, Ab negative, HIV positive within 6 months of HIV negative test or PHE recent incident assay test

- Followed up longitudinally according to clinic visits

Analysis

- Using time-to-event methods and Cox models we examined factors associated with VL <50 copies/ml at 12 weeks
- Correlation between time to undetectable and time to immune recovery
  - Immune recovery defined as CD4 > 900 or CD4:CD8 ratio ≥ 1
- Factors examined were age, risk group, ART regimen, baseline CD4, VL, CD4/CD8 ratio and resistance genotype.

Results: Demographics

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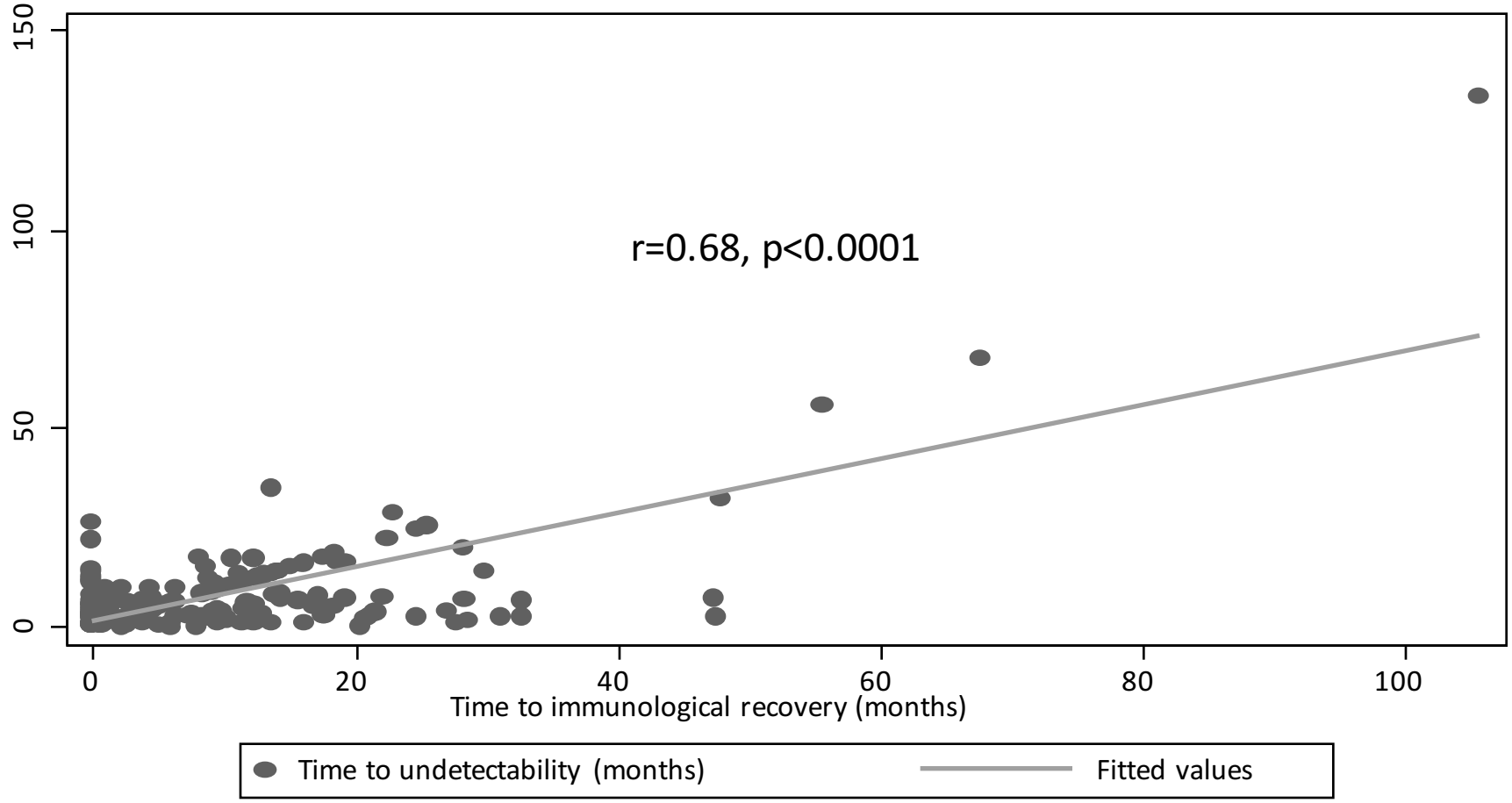
308 individuals

- 99% were male
- Predominantly white (85.4%)
- MSM (96.6%)
- Mean age 36 years

Time to undetectable viral load correlated with immune recovery



Factors associated with V/L suppression at < 12 weeks

Variable		Unadjusted OR	p-value
Sex	Male	1	
	Female	7.16 (0.42, 123.1)	0.11
Ethnicity	Caucasian	1	
	Black/other	0.61 (0.13, 2.86)	0.53
HIV acquisition risk	MSM	1	
	Other	1.69 (0.18, 16.2)	0.64
Age at seroconversion	Per year increase	0.96 (0.92, 1.01)	0.13
HIV clade	Subtype B	1	
	Recombinant	0.84 (0.10, 7.47)	0.89
	Other	1.13 (0.32, 3.91)	0.85
Baseline HIV viral load	Per log10 increase	1.06 (0.91, 1.23)	0.45
Baseline CD4 cell count	Per 50 cell increase	1.01 (0.91, 1.12)	0.86
Baseline CD4 cell count	<350 cells/mm^3	1	
	350-500 cells/mm^3	4.89 (0.55, 43.5)	0.12
	>500 cells/mm^3	3.92 (0.47, 32.9)	0.17
Baseline CD4:CD8 ratio	Per 0.1 increase	1.05 (0.93, 1.19)	0.45
Time to starting ART	Per week increase	0.95 (0.88, 1.03)	0.22
ART regimen at PHI	**2NRTI+PI**	**1**	
	2NRTI+INI +/- PI	**4.88 (1.54, 15.4)**	**0.0028**
	2NRTI+NNRTI	0.91 (0.17, 4.79)	0.91

Conclusion

Using a large cohort of individuals with confirmed seroconversion, we show that:

- Rapid virological suppression correlates with an enhanced immune recovery

- Rapid virological suppression was associated with INI based regimens.

Limitations

- Highly selected group of predominantly MSM – frequency of testing
- Time to being undetectable not precise – cohort study therefore no visit schedule.
- We did not examine other evidence of immunological recovery – CD4 as per clinical practice

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Acknowledgments

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Author contributions

The HEATHER and RIVER studies were conceived and designed by Sarah Fedler, John Frater and Jule Fox. Experiments were performed by John Thornhill, Genevieve Martin and others, and data analysed by Lisa Hamzah. Recruitment and follow up of the trials was performed by Teresa Solano, Julianne Lwanga, Nneka Nwokolo, Sarah Fidler, and Julie Fox with trial management performed by Jodi Meyerowitz.

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