# CD4/CD8 ratio at ART initiation, HIV Viral Load and Duration of ART predict time to viral rebound after ART interruption for individuals initiating ART in Primary HIV Infection

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## Introduction

Virological Post-treatment control has been described in cohorts commencing Antiretroviral Therapy (ART) in Primary HIV Infection (PHI). Biomarkers to predict likelihood of viral control after stopping ART are needed to inform treatment interruption (TI) studies. Preserved immunological function plays a key role in viral control amongst Elite controllers. We investigate the association of CD4/CD8 with time to viral rebound using data from two cohorts initiating transient short-term ART during PHI.

## Methods

Time to event analyses and Cox proportional hazards models were used to investigate time from ART interruption to virological rebound (single HIV Viral Load >400c/mL), censoring at ART re-initiation. Data from two cohorts of treated HIV-seroconverters; the UK Register of HIV Seroconverters and the SPARTAC Randomised Control Trial, were used. Factors of interest were: Sex, Age, Exposure Category, Enrolment site, CD4/CD8 at time of seroconversion, ART Initiation and TI, HIV Viral Load (VL), Time from seroconversion to ART initiation and ART Duration.

## Results

206 individuals contributed data, 142 were male, median age was 34 years. Median time from seroconversion to ART initiation was 84 (IQR 57-106) days; median ART duration was 3.37 months. Baseline characteristics are summarised in Table 1. 202 individuals reached the endpoint (VL> 400 copies/ml) at a median time (95% CI) of 32 (29, 35) days, 4/206 did not experience virological rebound after a maximum of 3.1 years. In unadjusted analyses, higher CD4/CD8 ratios (as a continuous variable) at HIV seroconversion (p=0.021) and ART initiation (p=0.01), in addition to lower HIV viral load and longer duration on ART were associated with longer time to viral rebound (see table 2). Furthermore CD4/CD8 ≥ 1.2 was significantly associated with longer time to endpoint as compared with ratio <1.2 (p= 0.001) (see figure 1).

Figure 1. Kaplan Meier - ART Initiation CD4/CD8 ratio ≥1.2 compared to <1.2, and time to endpoint (VL>400 copies/ml)

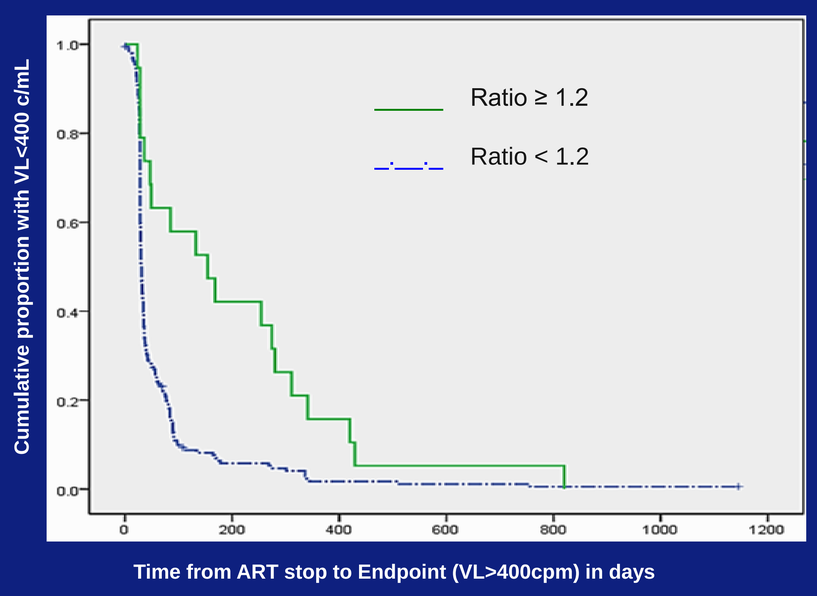


Table 1. Baseline Characteristics (n=206)

| Characteristic | N (IQR) |
|---|---|
| Female | 64 |
| Male | 142 |
| Median Age / years | 34 (27-40) |
| Median Days from seroconversion to ART initiation | 84 (57-106) |
| Median Time on ART / months | 3.37 (2.7-11.0) |
| Median CD4/CD8 value at seroconversion | 0.56 (0.4-0.9) |
| Median CD4/CD8 at date of ART start | 0.59 (0.4-0.9) |
| Median CD4/CD8 at time of ART stop | 0.96 (0.7-1.3) |
| ART Start VL/Log copies per ml | 4.39 (3.5-5.0) |
| Median Year of seroconversion | 2006 (2005-2006) |

Table 2. Univariable Analysis

| Variable | Hazard Ratio [95% Confidence Interval] | | P value |
|---|---|---|---|
| Sex (Female) | 0.76 | [0.56-1.04] | 0.09 |
| Age Category (Quartiles) | | | 0.58 |
| Exposure Category (compared to MSM) | | | 0.12 |
| Heterosexual | 0.78 | [0.59-1.06] | |
| Exposure unknown | 0.36 | [0.09-1.47] | |
| Enrolment from an African site | 1.42 | [1.01-1.98] | 0.04 |
| Seroconversion VL (per Log copy/ml increase) | 1.23 | [1.07-1.42] | <0.01 |
| ART Initiation HIV VL (per Log copy/ml increase) | 1.27 | [1.11-1.46] | <0.01 |
| Days from seroconversion to ART Initiation | 0.999 | [0.998-1.000] | 0.19 |
| CD4/CD8 ratio at seroconversion (per unit increase) | 0.67 | [0.47-0.94] | 0.02 |
| CD4/CD8 at ART initiation (per unit increase) | 0.64 | [0.44-0.91] | 0.02 |
| CD4/CD8 at Time of Treatment Interruption (per unit increase) | 0.76 | [0.58-1.01] | 0.06 |
| Duration on ART (per month increase) | 0.97 | [0.93-1.00] | 0.03 |
| ART initiation CD4/CD8 ≥ 1.2 versus <1.2 | 0.43 | [0.27-.070] | <0.01 |
| CD4/CD8 at TI ≥ 1.2 compared to <1.2 | 0.72 | [0.53-0.98] | 0.03 |
| Year of HIV seroconversion | 0.97 | [0.90-1.04] | 0.35 |

In multivariable analyses (see table 3), CD4/CD8 as a continuous variable at ART start (p=0.39) and all other time-points was no longer significant, however a borderline significantly decreased risk of viral rebound remained when the ratio at time of ART start was ≥ 1.2 (p=0.049), as compared with <1.2. Lower VL at time of starting ART (p=0.017), and longer duration on ART (p=0.045) were associated with decreased risk of rebound.

Table 3. Multivariable Analysis

| Variable | Hazard Ratio [95% Confidence Interval | | P Value |
|---|---|---|---|
| Sex (Female) | 0.72 | [0.27-1.96] | 0.52 |
| Enrolment from an African site | 1.63 | [0.80-3.29] | 0.18 |
| Days from seroconversion to ART Initiation | 1.000 | [0.999-1.001] | 0.60 |
| **ART Initiation HIV Viral Load (per Log copy/ml increase)** | **1.22** | **[1.04-1.44]** | **0.02** |
| **Duration on ART (months)** | **0.96** | **[0.93-0.99]** | **0.05** |
| **ART initiation CD4/CD8 ≥ 1.2 compared to <1.2*** | **0.586** | **[0.345-0.997]** | **0.049** |

*Multivariable model adjusted for sex, age category (quartiles), exposure category, enrolment from an African site, time from seroconversion to ART Initiation, HIV Viral Load (Log), Duration on ART, and Time from both viral load and CD4/CD8 measurement to ART Initiation*

**Model for CD4/CD8 ratio as a continuous variable was not significant, a poorer model fit (as measured by AIC) and is not shown*

## Conclusion

Higher HIV VL, longer duration on ART and immune status as measured by CD4/CD8 ratio of ≥ 1.2 at the time of initiating ART were the strongest predictors of viral rebound, while we found no evidence of an association with Total CD4 count or CD4/CD8 ratio prior to TI. Initiation of ART before disruption of immune homeostasis below a threshold may be important in controlling viraemia on TI and CD4/CD8 ratio warrants further evaluation in cohorts with longer duration of treatment where PTC would be anticipated.

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