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# No Evidence of Post Treatment Control after Early Initiation of Antiretroviral Therapy in the San Diego Primary Infection Cohort

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## Abstract

As part of a retrospective analysis of 616 individuals followed from incident HIV-infection for up to 18 years as part of the San Diego Primary Infection Cohort we found 16 subjects who started antiretroviral therapy (ART) within the first 4 months of infection and subsequently interrupted ART after being virologically suppressed for a median of 1.75 years. No subject maintained sustained virologic control after interruption of ART, even when treatment was started during the earliest stages of HIV-infection. Median time to HIV RNA rebound after ART interruption was 0.9 months (range: 0.2 – 6 months).

## Introduction

Antiretroviral therapy (ART) suppresses viral replication in most HIV-infected individuals with a substantial impact on morbidity and mortality [1]. However, ART does not eradicate latently infected cells [2], and plasma viremia rebounds after treatment is interrupted [3]. Starting ART during the earliest stages of HIV infection is associated with a smaller HIV reservoir [4], reduced cellular HIV transcription [5], and preserved immune response [6]. A delayed viral rebound has been observed for variable periods of follow-up (generally 6 up to 48 months) in a small proportion of individuals after cessation of ART initiated during the earliest phases of HIV infection [7-9]. However, studies with longer follow-up (18 months up to several years) showed that virus control was not maintained in most individuals after early ART interruption [10-14]. In 2010, the French “Virological and Immunological Studies in Controllers after Treatment Interruption” (VISCONTI) group reported a selected subset of individuals in whom HIV RNA remained below 50 copies/ml for several years after the interruption of prolonged ART that was initiated during primary HIV infection (median duration 75 months) [15]. The same group calculated that the probability of maintaining viral control at 24 months post early treatment interruption could be as high as 15%, which is much higher than observed in persons who exhibit spontaneous control, without ART. This study has revived considerable interest in using early and prolonged

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**Competing Interests**

SG and CA do not have any commercial or other associations that might pose a conflict of interest.

ART to achieve long-term infection control and may have important implications in the search for a functional HIV cure. Similar follow-up studies with larger number of individuals [16-19] confirmed the existence of post treatment controllers at a lower frequency <10%.

Here, we performed a retrospective analysis including clinical and virologic data collected from participants of the San Diego Primary Infection Cohort (SD PIC) over 18 years of follow-up. Our objective was to find post-treatment controllers among those participants who interrupted ART after being virologically suppressed.

## Methods and Results

Since 1996, the SD PIC has enrolled 616 individuals diagnosed during acute and very early HIV infection and followed for several years into chronic infection. The estimated date of HIV infection (EDI) is determined for each individual using established algorithms [20]. Importantly, the duration of HIV infection at the time ART was started was calculated differently for our cohort compared to the VISCONTI group. We calculated the interval between EDI (as described in [20]) and start of ART, while the French group used time from documented primary HIV infection (defined as the date of a negative/incomplete HIV-1 western blot and a positive p24 Ag test, or a positive HIV antibody test with a negative one within the previous 3 months). This corresponds to a difference of 3-5 weeks between our two estimates of ART start. For the purpose of this analysis, we added 4 weeks to our EDI (referred to “adjusted EDI” in the text).

We used the following inclusion criteria for this retrospective analysis of SD PIC participants: (i) ART start within 16 weeks (i.e. 4 months) from the “adjusted EDI” (n=235, 38%), (ii) reached suppressed HIV RNA levels (<50 or <400 copies/ml depending on sensitivity of the assay used) within 36 weeks of ART initiation (n=116, 50%), (iii) maintained suppressed HIV RNA for at least 24 weeks, with one blip <200 copies/ml allowed (n=109, 94%), (iv) documented treatment interruption (for any reason other than virologic failure) (n=16, 15%). If exact information about timing of ART interruption was missing, a manual review of clinical charts was performed and subjects were excluded from this analysis if the ART interruption date could not be documented.

In our cohort, we were able to identify 109 individuals who started ART within 16 weeks from our “adjusted EDI” and subsequently achieved suppressed HIV RNA in blood plasma (median time from ART initiation to HIV RNA suppression was 16 weeks), and remained suppressed for at least 24 weeks. Sixteen had a documented episode of voluntary ART interruption (see figure S1 for selection criteria). Table 1 summarizes the main characteristics of the 16 individuals who did interrupt ART (supplemental table 1 shows individual characteristics). Half of study participants started ART within 8.6 weeks from adjusted EDI and were treated for 1.75 years before ART interruption.

None of the SD PIC participants who met the described criteria for inclusion (0%, 95% CI: 0% – 14.3%) demonstrated sustained control of HIV after interruption of their ART. This

estimate was not statistically different from the VISCONTI estimate (15,6%, CI: 5.3 - 32.8%, Fisher Exact p=0.15).

In fact, 100% of participants who stopped ART had detectable HIV RNA within a median of 50 days from ART interruption (range 6 to 197 days), see figure 1. None of the tested variables (inclusive baseline and peak HIV RNA viral load, baseline and nadir CD4 count, timing of ART initiation and time on ART) was associated with longer time to viral rebound. However, our analysis was limited because of the retrospective study design and the imprecise time to rebound estimates due to sparse sampling.

## Discussion

The recent report of the VISCONTI post-treatment controllers sparked considerable interest among the HIV community. The 15% prevalence of post-treatment controllers in the VISCONTI study is much higher than both previous reports in similar populations and observations of spontaneous viral control in natural history studies. In our cohort of 109 recently HIV-infected individuals who initiated ART within 16 weeks of their EDI and achieved sustained virologic control for a median of 1.75 years, we were able to find 16 individuals who interrupted therapy while their HIV RNA viral load was undetectable in blood plasma (<50-400 copies/ml). All of them rebounded to detectable HIV RNA levels by the following visit, achieving an average of 3.5 $\log_{10}$ HIV RNA copies/ml within 6-197 days from ART interruption. Of note, because of the small sample size we obtained large confidence intervals around our negative result (0% – 14.3%), which are overlapping with the confidence intervals reported by the VISCONTI group (5.3-32.8%) and therefore we were not able to detect a significant difference from the reported VISCONTI group. A similar analysis performed among participants of the Seattle primary infection cohort found 22 subjects who interrupter ART (out of 389) and only one was able to control viral load to levels <500 copies/ml for at least 24 months [21]. Based on our data, we calculated that a sample size of 34 (or 54) individuals interrupting ART would be necessary to detect a statistically significant difference from the VISCONTI cohort with a 76% power (or 90% power respectively), using a Fisher's exact test with $\alpha = 0.05$.

The not significantly different frequency of post-treatment control between the VISCONTI and SD PIC cohort (15% versus 0%) could have several explanations. Most importantly, all of the SD PIC participants started ART later compared to the VISCONTI cohort (median of 8.6 weeks compared to 2.3 and 5.8 weeks for VISCONTI controller and non-controller, respectively) and also had a shorter duration on ART (2.0 years compared to 5 years for the VISCONTI controllers). This resulted in a low ratio of ART duration/time before ART initiation of 0.3, which was much lower that any of the VISCONTI groups (controller, transient controller and non controller). This ratio was the main predictor of post-treatment control in the VISCONTI group. Regarding HLA data, one out of 16 participants interrupting ART (6.7%) carried two protective HLA alleles (HLA-B*27 and HLA-B*57) while four out of 16 (26.7%) carried at least one HLA risk allele (HLA-B*07 and/or HLA-B*35). This relatively high prevalence of risk alleles in our population of early-infected individuals (compared to previous reports [22, 23]) is similar or less compared to the prevalence reported in the VISCONTI cohort (29%) and in the Seattle primary infection

cohort (33%) [21]. This might be a consequence of more severe seroconversion symptoms reported in people carrying HLA risk alleles, making them more likely to be identified during primary infection.

Additionally, VISCONTI post-treatment controllers also had a very small HIV DNA reservoir [19], confirming that the initiation of early ART decreases the pool of latently infected cells [4]. However, a small reservoir alone does not explain why these participants did not experience viral rebound after ART interruption since re-emergence of plasma HIV RNA in HIV-infected individuals treated early and who have small reservoirs has been repeatedly reported [10-14]. One interesting characteristic of the VISCONTI cohort is the relatively small contribution of long-lived central memory T cells to the HIV reservoir compared to previous reports [24]. This suggests that perhaps the distribution of the viral reservoir may play an important role in controlling infection in the absence of ART. Future studies are needed to confirm the VISCONTI findings and further explore the mechanisms of post-treatment control.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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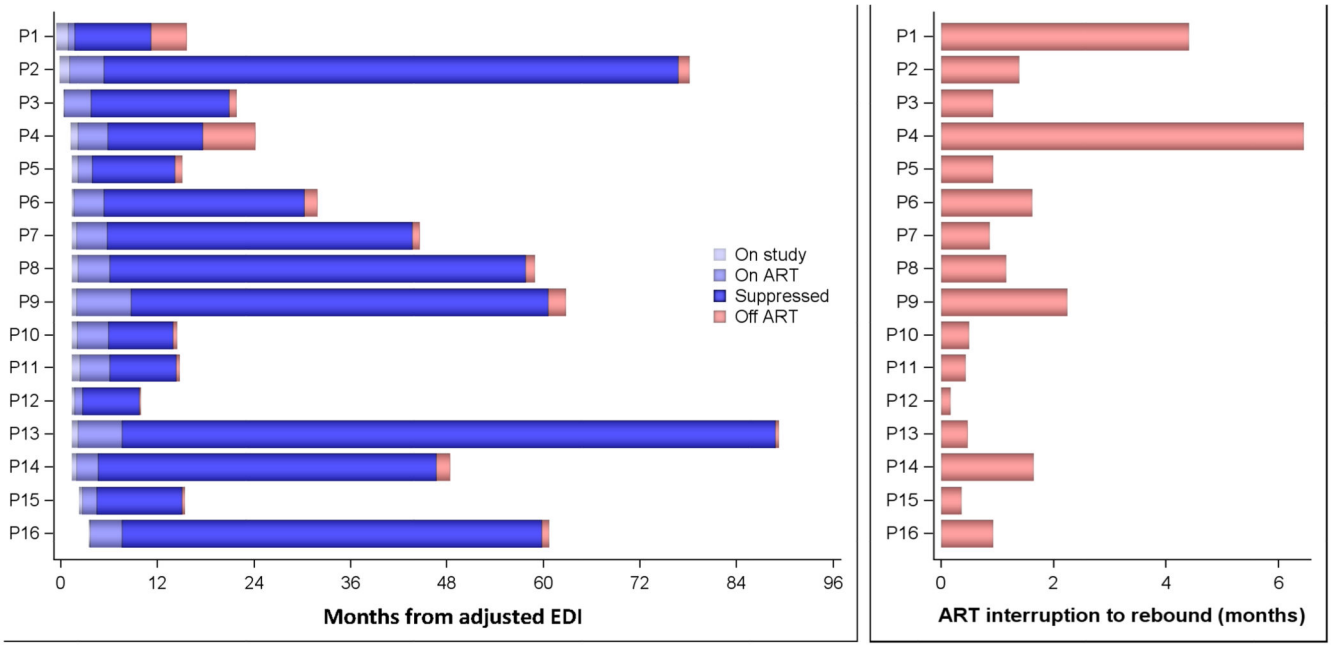


**Figure 1.**

Panel A summarizes ART history (initiation to interruption) for each individual participant; Panel B shows individual times to HIV RNA rebound.

## Table 1

| Overall characteristics | Data | NC (n = 16) |
|---|---|---|
| | Age (years), median (range) | 35 (29.5 – 44.5) |
| | Sex Male, n (%) | 16 (100) |
| | White ethnicity, n (%) | 13 (81.25) |
| | MSM, n (%) | 15 (93.75) |
| | Year (of enrollment), median (range) | 2001 (1997 – 2010) |
| | Symptomatic PHI, n (%) | 11 (64.71) |
| | Protective alleles (HLA-B*27 or HLA-B*57), n (%) | 1 (6.7) |
| | Risk alleles (HLA-B*07 or HLA-B*35), n (%) | 4 (26.7) |
| | CD4/μl at presentation, median (IQR) | 425 (333.5 – 620) |
| | HIV-RNA at presentation, $log_{10}$/ml, median (IQR) | 5.43 (4.77 – 5.84) |
| | Nadir CD4/μl, median (IQR) | 406 (289 – 620) |
| | Peak HIV-RNA, $log_{10}$/ml, median (IQR) | 5.46 (4.84 – 6.10) |
| **Characteristics at the last visit before ART initiation** | | |
| | CD4/μl, median (IQR) | 524.5 (375 – 694.5) |
| | CD4/CD8 ratio, median (IQR) | 0.60 (0.40 – 0.97) |
| | HIV-RNA, $log_{10}$/ml, median (IQR) | 4.75 (4.22 – 5.38) |
| | Adjusted EDI to ART initiation (months), median (IQR) | 1.97 (1.68 – 2.12) |
| **Characteristics at the last visit before ART interruption** | | |
| | ART duration (years), median (IQR) | 2.04 (1.00 – 4.65) |
| | Undetectability duration during ART (years)*, median (IQR) | 1.75 (0.82 – 4.31) |
| | Ratio ART duration (years) / time before ART initiation (weeks), median (IQR) | 0.31 (0.11 – 0.55) |
| | CD4/μl, median (IQR) | 743.5 (572 – 859.5) |
| | CD4/CD8 ratio, median (IQR) | 1.10 (0.77 – 1.55) |
| | PI-based regimen (at the time of ART interruption) | 12 (75%) |
| **Characteristics at the first visit after ART interruption** | | |
| | Time to rebound (months), median (IQR) | 0.9 (0.5 – 1.6) |
| | CD4/μl change per month, median (IQR) | − 14.30 (−44.28 to 5.48) |
| | HIV RNA, $log_{10}$/ml, median (IQR) | 3.52 (2.70 – 4.50) |
| | ART resumption (%) | 7 (43.7) |

NC: Non-controllers (rebound within 6 months), EDI: Estimated date of infection, MSM: men who have sex with men, ART: antiretroviral therapy, PI: protease Inhibitor

*Single blips (VL < 200 copies/ml) allowed