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Prevalence of Post-Treatment Controller Phenotype is Rare in HIV-infected Persons after Stopping Antiretroviral Therapy

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Introduction

Effective antiretroviral therapy (ART) has transformed the care of patients with HIV, however, cure remains elusive. Identification of individuals who achieve control of HIV infection in the absence of ART, with inquiries made into their immunologic, genetic and virologic characteristics, may prove valuable in the quest for an HIV functional cure.

Post-treatment controllers (PTCs) are HIV-infected individuals who after discontinuing ART remain virologically suppressed with stable CD4+ T-lymphocyte counts¹. The presence of PTCs has been examined in both prospective treatment-interruption (TI) and retrospective cohort studies^{2–15}. Reported rates of post treatment control are variable and have ranged from the absence of the phenotype^{2–6} to rates ranging from 4–14%^{7–14}. This variation is partially explained by differences in baseline characteristics of the populations and the definitions of post treatment control in these studies.

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We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document, and the approval of the submission of this version.

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The majority of identified PTCs started ART during early or acute HIV infection^{1, 7–11}. The SPARTAC (Short Pulse Antiretroviral Therapy at Acute Seroconversion) trial examined PTC in the context of early treated individuals⁸. In this large study (n=165), 14% of individuals who were treated with >12 weeks of ART prior to treatment interruption maintained virologic suppression for 52 weeks and 5% remained suppressed at 104 weeks⁸. In another analysis of SPARTAC data, Martin, et al. compared rates of transient viral control in untreated individuals to those who had undergone treatment interruption, finding no statistically significant difference between the two groups⁹. Interestingly, the PTCs tended to have higher pre-ART baseline HIV RNA levels compared to those who controlled spontaneously suggesting that PTCs may be exhibiting a unique phenomenon⁹. Retrospective cohort studies have reported incidence rates of PTCs ranging from 0–15% among individuals started on ART in early HIV^{6, 10, 11}.

PTCs have also been reported among individuals who started ART during chronic infection^{12–15}. In a TI study of individuals initiating ART during chronic HIV infection (CHI) rates of post-treatment control of 7.4% at 12 months and 4.2% at 36 months were reported¹³. Conversely, a TI study comparing initiation of ART during early infection versus CHI found an 8.3% rate of post treatment control at 48 weeks among those who started ART during early infection and no post-treatment control among those who started ART during CHI⁷. Even in a highly preselected group of individuals (based on low cell-associated DNA) who initiated therapy in chronic infection and underwent a TI the rates of PTC were 10%¹⁴. In a retrospective cohort study of individuals started on ART during CHI, 1.6% of individuals were reported to be PTCs¹⁵.

Prior studies into the incidence and characteristics of PTCs have been limited by small study size and limited follow-up time among TI studies. Limitations among retrospective cohort studies include an often poor characterization of seroconversion date and, as with TI studies, a focus on individuals who started on ART during early or acute HIV infection. Given the typically long duration of follow up and relatively accurate characterization of seroconversion date among HIV-infected individuals in the U.S. Military HIV Natural History Study (NHS) cohort, it is well-designed to characterize the incidence and demographic and immunogenetic features of PTCs^{16, 17}. We examined this cohort for the presence and features of PTCs.

Methods

Study Population

NHS visits are conducted about every six months at one of six military treatment facilities (MTFs). As service members are HIV seronegative on entry into the military and undergo mandatory HIV testing every 1–5 years the cohort is enriched in dated seroconverters, making it ideal to study this phenomenon.

During their structured interviews and through the abstraction of electronic medical records, research personnel collect clinical information (to include ART history, reasons for ART switch, CD4 counts, and viral load). HIV-1 viral RNA determinations on EDTA plasma specimens received from Army and Navy sites were performed in a College of American

Pathology accredited laboratory at Walter Reed Army Institute of Research using all generations of the Roche HIV-1 Viral Load tests from 1997 to the present. This sub-study included participants followed in the NHS between January 1, 1986 and September 16th, 2016.

Definitions and Data Analysis

We retrospectively identified HIV-1 infected individuals who met the following criteria: (1) treated with ART for a period of ≥ 2 years, (2) achieved virologic suppression (VS) to <400 copies/mL between 6 months and 2 years after ART initiation, (3) discontinued ART for ≥ 30 days and, (4) had one or more viral load determination ≥ 30 days after ART discontinuation. Elite controllers and long-term nonprogressors, identified as HIV controllers (HICs), had been previously identified in our cohort and were excluded¹⁸. To avoid viral heterogeneity, we also excluded patients with known non-clade B virus infection. As the assay characteristics have varied with time, VS was defined as a viral load (VL) <400 copies/mL, and to avoid including subjects who had temporarily discontinued ART during a regimen switch, we required subjects to be off ART at-least for 30 days.

For this study, PTCs were defined as individuals who had sustained VS to <400copies/mL for ≥ 6 months after discontinuation of ART. We further defined those with VS for ≥ 6 months but <2 years off of ART as “transient controllers” (TCs), and those with VS for ≥ 2 years off of ART as durable controllers (DCs). Descriptive statistics were used to describe the population, and are presented as numbers (percentages) for categorical variables and medians (interquartile ranges [IQRs]) for continuous variables.

Results

Of the 6070 participants enrolled in the NHS, 4882 received ART at some point during their follow-up. Those infected with non-clade B virus (n=73) and HICs (n=21) were excluded. Figure 1, provides details of the subjects included in this study. In brief, 1903 subjects who lacked documentation of at a viral load after initiating ART and 322 with at-least one blip (>400 copies/ml) after starting ART were excluded. After initiating ART, 2563 subjects had documented virologic suppression (i.e. to a viral load <400 copies/ml). Of those who achieved virologic suppression, 976 discontinued ART for 30 or more days. Of these, 881 lacked assessments of viral load 30 or more days after discontinuation of ART (the majority of these likely started on a new ART regimen shortly after discontinuation of the prior regimen). In total, 95 patients met our criteria, i.e. achieved virologic suppression between 6 months and 2 years after initiating ART and had two or more VL determinations 30 or more days after ART discontinuation.

From this group of 95, we identified 4 PTCs (4.2%). Two met our definition of TCs with suppression of viremia for 267 and 575 days off of ART and two met our definition of durable control with suppression of viremia for 794 days and 1058 days off of ART. Three of our PTCs were men and all were African American, their age at HIV diagnosis ranged from 21 to 38 years and time from their documented positive HIV test to ART initiation ranged from 25 to 1031 days. The number of viral load determinations obtained during the period of suppression of viremia ranged from 1 to 12 (median 5, IQR 3.25, 7.5).

Demographic and clinical characteristics of the four PTCs are described in table 1. ART history along with viral loads and CD4 counts are displayed graphically in figure 2. Two subjects (patients #2 and #3) initiated ART relatively early after diagnosis (i.e. within 25 and 56 days of being diagnosed with HIV, respectively), albeit, both individuals were in Fiebig stage V infection with fully matured Western blots at the time of their HIV diagnosis¹⁹. Estimating the approximate seroconversion dates in these individuals is difficult, as the last negative HIV tests in both occurred approximately 2.5 years before starting ART and records of symptomatic primary HIV infections are lacking. Patient #3 was classified as a transient controller with viral suppression for 559 days off of ART and patient #2 as a durable controller with viral suppression for 794 days off of ART. The two other individuals (patients #1 and #4) had ART initiated during chronic HIV infection at 1031 and 420 days after their documented seroconversion, respectively.

Both of the durable controllers (patients #2 and #4) had low baseline pre-ART viral loads of 2011 and 1008 copies/mL respectively. Among the 4 PTCs, CD4 count nadirs prior to ART initiation ranged from 293 to 566 cells/ μ L, and a majority (3 of 4) had preserved CD4+ cell counts during the period of viral suppression of off ART with counts ranging from 670 to 1155 cells/ μ L at the time of viral rebound. Three of the four PTCs were treated with a boosted protease inhibitor regimen and one was treated with a non-nucleoside reverse transcriptase inhibitor.

One of the four (patient #3) discontinued ART while being treated for Hodgkins lymphoma with ABVD chemotherapy (doxorubicin, bleomycin, vinblastine and dacarbazine) and another discontinued ART in order to pursue alternative therapies for HIV (patient #1). It is unclear why the other two patients discontinued ART. Patient #2 had viral suppression for 794 days off of ART, restarted ART without ever having rebound viremia to 400 copies/mL.

Demographic and clinical characteristics of the four PTCs were similar to the 91 who lacked virologic control described in a supplementary table.

Discussion

The phenomenon of post-treatment control has rarely been described in patients who were started on ART during CHI^{12–15}. We describe four PTCs (4.2%) from a large military cohort who initiated ART during chronic infection. Our rate (4.2%) was near the range reported in prior cohorts however in most comparator studies ART was initiated in early HIV infection^{1, 7–11}.

It is thought that early initiation of ART may limit the size of the viral reservoir and allow for a more optimal immune reconstitution resulting in a stable equilibrium between a small viral reservoir and HIV-specific immune responses leading to post-treatment control²¹. The circumstances leading to a similar phenomenon among those started on ART during CHI are unclear. Immunologic studies of previously identified PTCs who started ART during CHI have reported low levels of HIV unspliced RNA in peripheral blood mononuclear cells compared to other ART-treated patients²⁰. Further study of PTCs who started ART during CHI is needed to better delineate their underlying genetic, immunologic, and virologic

characteristics. Peripheral blood mononuclear cell-associated HIV RNA and HIV DNA levels for reservoir quantification, HLA genotypes, expression of exhaustion and activation markers on CD4+ and CD8+ T cells and CD8+ T cell responses to HIV peptides for genetic and immunologic characterization is planned.

Limitations of our study include the fact that therapeutic drug monitoring was not performed to confirm that the PTCs were off ART. However, we believe that surreptitious use was unlikely as our data captures use of ART paid for by the Department of Defense. Our inclusion criteria, requiring two years of treatment with ART with sustained viral suppression without any viral load blips > 400 copies/ml, were somewhat stringent and additional PTCs may have been identified if they were relaxed. While we used strict criteria to eliminate HICs, cases may have been misclassified as PTCs when in fact they were HICs. For example, two of our four PTCs (subjects 2 and 3) initiated ART when a set point may not have been established (i.e. about 3 and 8 weeks after their western blot had matured). This seems unlikely given that recent studies characterizing acute HIV infection indicate that the set-point viral load occurs within 4–6 weeks of infection²². A majority of patients identified with HIV, are identified in chronic infection. For any functional cure strategy to be successful, it is imperative that it be applicable to those who started ART during chronic infection. Hence, examining other cohorts and pooling data to examine the determinants of PTC in chronically HIV infected patients is essential. With the identification of individuals started on ART during chronic HIV-1 infection who went on to exhibit varying degrees of post-treatment control, our cohort study is a significant contribution to the post-treatment control literature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Identification of PTCs in the NHS cohort

Figure 2.
Graphical representation of serial viral loads and CD4+ counts from baseline (prior to ART initiation) to resumption of ART after the period of treatment interruption

TABLE 1

Demographic and clinical characteristics of post-treatment controllers

Patient	1	2	3	4
Last negativeHIV test	2/1990	6/2001	11/1996	10/1995
First positiveHIV test	5/3/1995	12/17/2003	2/16/1999	6/6/1996
Age at HIV diagnosis	29	21	30	38
Sex	M	M	M	F
ART regimen	Boosted PI + 2 NRTIs	NNRTI + 2 NRTIs	Boosted PI + 2 NRTIs	Boosted PI + 2 NRTIs
ART start date	2/27/1998	1/12/2004	4/14/1999	7/31/1997
ART stop date	3/20/2007	3/27/2007	11/13/2002	4/15/2001
Time from HIVdiagnosis to ARTInitiation (days)	1031	25	56	420
CD4+ cell countnadir (cells/mm ³)	566	293	486	438
CD4+ cell countat ART stop date(cells/mm ³)	866	575	353	995
CD4+ cell countat time of new viremia (cells/mm ³)	1155	697 *	730	670
Baseline viral load (copies/ml)	35454	2011	46773	1008
Date of last confirmed viral suppression	12/12/2007	5/29/2009	5/25/2004	3/8/2004
Number of viral load determinations during period of suppression	1	4	6	12
Duration of suppression of viral load to <400copies/ml off of ART (days)	267	794	559	1058

PI: protease inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor.

* Patient #2 never redeveloped a viremia >400 copies/ml prior to restarting on ART

TABLE 2

Comparison of demographic and clinical characteristics of post-treatment controllers versus patients who rapidly redeveloped viremia after cessation of ART

	Post-treatment Controllers (n=4)	Rapidly Viremic (n=91)
<u>Sex</u>		
Male	3	84
Female	1	7
<u>Race</u>		
Black	4	32
White	0	46
Hispanic	0	5
Asian	0	4
Other	0	4
Age at HIV diagnosis (years) (Median, [IQR])	29.5, [27, 32]	29.6, [26.6, 34.4]
Time from HIV diagnosis to initiation of first ART (days) (Median, [IQR])	238, [48.3, 573]	346, [65, 1476]
CD4+ T-cell Nadir (cells/mm³) (Median, [IQR])	462, [401.8, 506]	320, [248.5, 427]
Baseline viral load prior to initiation of first ART regimen (copies/mL) (Median, [IQR])	18732.5, [1760.3, 38283.8]	22366 [10520, 66165] [*]

* For 20 individuals who did not have documented viral loads prior to their first ART regimen the viral load prior to initiation of the last ART regimen before period of time off of ART was used as baseline viral load.