

Antiretroviral Therapy Reduces T-cell Activation and Immune Exhaustion Markers in Human Immunodeficiency Virus Controllers

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Background. Despite low plasma human immunodeficiency virus (HIV) RNA, HIV controllers have evidence of viral replication and elevated inflammation. We assessed the effect of antiretroviral therapy (ART) on HIV suppression, immune activation, and quality of life (QoL).

Methods. A5308 was a prospective, open-label study of rilpivirine/emtricitabine/tenofovir disoproxil fumarate in ART-naïve HIV controllers (N = 35), defined as having HIV RNA <500 copies/mL for ≥12 months. The primary outcome measured change in %CD38+HLA-DR+ CD8+ T cells. Residual plasma viremia was measured using the integrase single-copy assay. QoL was measured using the EQ-5D questionnaire. Outcomes were evaluated using repeated measures general estimating equations models.

Results. Before ART, HIV controllers with undetectable residual viremia <0.6 HIV-1 RNA copies/mL had higher CD4+ counts and lower levels of T-cell activation than those with detectable residual viremia. ART use was effective in further increasing the proportion of individuals with undetectable residual viremia (pre-ART vs after 24–48 weeks of ART: 19% vs 94%, $P < .001$). Significant declines were observed in the %CD38+HLA-DR+CD8+ T cells at 24–48 (−4.0%, $P = .001$) and 72–96 (−7.2%, $P < .001$) weeks after ART initiation. ART use resulted in decreases of several cellular markers of immune exhaustion and in a modest but significant improvement in self-reported QoL. There were no significant changes in CD4+ counts or HIV DNA.

Conclusions. ART in HIV controllers reduces T-cell activation and improves markers of immune exhaustion. These results support the possible clinical benefits of ART in this population.

Keywords. HIV controllers; antiretroviral therapy; inflammation; immune activation; immune exhaustion.

A small proportion of people living with human immunodeficiency virus (HIV) maintain low or even undetectable levels of HIV RNA without antiretroviral therapy (ART). These individuals are referred to as “HIV controllers”; those without detectable virus are referred to as “nonviremic” or “elite” controllers. Generally asymptomatic from the HIV perspective, HIV controllers usually have high CD4+ T-cell counts and are not at risk for AIDS-related opportunistic infections. Because few HIV controllers were enrolled in the pivotal START study of early vs deferred ART in patients with high CD4+ cell counts, the

benefits of ART in HIV controllers remain uncertain [1], with this uncertainty also reflected in treatment guidelines [2].

Although these HIV controllers have low or even undetectable viremia by conventional assays, they harbor replication-competent virus and have evidence of viral evolution secondary to immune selection pressure [3–6]. The ongoing viral replication in HIV controllers may be associated with adverse consequences, including the progressive loss of CD4+ cells, increased T-cell activation, and inflammation [7–10]. Chronic immune activation and systemic inflammation have been associated with poor clinical outcomes in noncontrollers [11–14] but also in HIV controllers who are reported to have an increased risk of cardiovascular disease [15] and hospitalizations [16].

While ART is likely to be effective in suppressing HIV replication in HIV controllers [17], the effect that ART may have on immune activation and inflammation has not been confirmed. In HIV noncontrollers with high viral loads, the decline in viral load after ART initiation has been found to occur in at least 3 phases [18]. The evaluation of such viral decay rates has also

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not been performed in HIV controllers and can provide insights on the composition and half-life of HIV-infected cellular reservoirs.

We performed a prospective, open-label trial to assess the effect of ART on HIV suppression, levels of cellular immune activation and exhaustion, CD4+ cell dynamics, ART tolerability, and quality of life (QoL) in treatment-naive HIV controllers. We also evaluated the effect of ART on soluble markers of inflammation and the HIV reservoir. Finally, we compared the rates of ART-induced viral decay in HIV controllers vs noncontrollers.

METHODS

Study Design and Participants

A5308 was a prospective, open-label study of fixed-dose combination rilpivirine/emtricitabine/tenofovir disoproxil fumarate (RPV/FTC/TDF) in ART-naive HIV controllers conducted at 19 clinical research sites within the AIDS Clinical Trials Group (ACTG). Participants were aged ≥ 18 years diagnosed with HIV infection based on a positive screening antibody test and confirmed by a Western blot or a second antibody test. They were ART-naive (received ≤ 7 days of ART) with documented HIV-1 viral loads < 500 copies/mL for 12 months or longer. Viral loads ≥ 500 HIV-1 copies/mL were permitted provided they represented fewer than half of the total measurements over the prior 12 months and the screening HIV-1 RNA was < 500 copies/mL. Any measurement ≥ 1000 HIV-1 RNA copies/mL over the prior 12 months was exclusionary.

Procedures

After study entry, there was a 12-week lead-in period during which participants remained off ART. All participants then initiated open-labeled ART with RPV/FTC/TDF for 48 weeks with on-ART evaluations at 4, 12, 24, 36, and 48 weeks after ART initiation (step 1). After 48 weeks, participants could be followed for an additional 48 weeks (weeks 60, 72, and 96 after initial ART initiation) either on or off ART, based on individual preference (step 2).

Study Endpoints

The primary endpoint was the change in CD8+ T-cell activation as measured by the %CD38+HLA-DR+ CD8+ cells after 24–48 weeks of ART. Secondary endpoints included changes after 24–48 and 72–96 weeks of ART in CD4+ counts, markers of immune activation/exhaustion, systemic inflammation, HIV viremia, reservoir levels, QoL, and safety. Safety was defined as grade ≥ 3 symptoms, diagnoses, or laboratory abnormalities.

Viral and Immune Characterization

Plasma viremia was quantified using the Abbott RealTime HIV-1 viral load assay. Levels of residual viremia were measured using the ultrasensitive integrase single-copy assay (iSCA) as previously described [19]. Levels of total cell-associated HIV-1 DNA

in CD4+ cells were quantified by droplet digital polymerase chain reaction [20]. Immune phenotyping was performed with flow cytometry using an LSRFortessa (BD Biosciences) and analyzed using FlowJo software (Treestar, version 9.9.3). Levels of CD4+ and CD8+ cell activation were assessed by the percentage of cells expressing both CD38+ and HLA-DR+. Immune exhaustion was quantified by the percentage of CD4+ and CD8+ cells expressing PD-1+, TIGIT+, LAG-3+, Tim-3+, CD73+, and CD160+ (BD Biosciences). Levels of 6 soluble inflammatory markers were measured using enzyme-linked immunosorbent assay according to the manufacturer's instructions: D-dimer (Diagnostica Stago), hs-CRP, hsIL-6, IP-10, sCD14, and sCD163 (R&D Systems). Additional details of the HIV DNA quantification and viral decay analysis are outlined in the [Supplementary Methods](#).

QoL Measurements

QoL was measured using the EQ-5D questionnaire [21]. The QoL index at each time point was obtained by averaging the 5 responses from the questionnaire (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Statistical Analyses

Analyses of change from baseline after 24–48 weeks and after 72–96 weeks of ART were based on the estimated treatment effect from a repeated measures analysis using general estimating equations. In assessing the effects of ART, analyses excluded time points after ART discontinuation. Pre-ART values were generally an average of 2 measurements prior to ART initiation, study entry, and study week 12. Rank-based (Spearman) correlations for continuous outcomes and exact Wilcoxon rank sum and Fisher tests for categorical outcomes were used to assess cross-sectional associations. No adjustments were made for multiple comparisons.

RESULTS

A total of 59 candidates from 19 ACTG clinical sites were screened for this study, and 38 were enrolled. Twenty-one were screen failures, primarily due to individuals who declined to participate or who had out-of-range HIV-1 RNA or other lab values ([Figure 1](#)). Thirty-six participants initiated ART, and 35 reached the first primary endpoint of 24 weeks on ART and were included in the analysis. Twenty-nine individuals elected to be followed for an additional 48 weeks in step 2. One individual died in a motor vehicle accident and the remaining 28 completed 96 total weeks of follow-up after ART initiation.

For the 35 HIV controllers included in the analysis, 43% were female, with a median pre-ART CD4+ cell count of 682 cells/mm³ ([Table 1](#)). Eleven HIV controllers (31%) had pre-ART viral loads consistently below the limit of quantification (< 40 HIV-1 RNA copies/mL; [Figure 1](#)). Longitudinal viral load results by

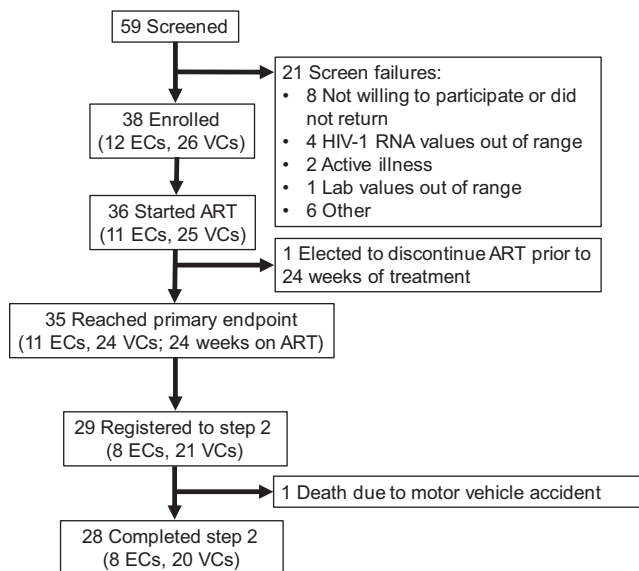


Figure 1. Consort diagram. ECs had pre-ART viral loads consistently below 40 HIV-1 RNA copies/mL. Abbreviations: ART, antiretroviral therapy; EC, elite controller; HIV-1, human immunodeficiency virus type 1; VC, viremic controller.

Table 1. Study Participant Demographics

Characteristic	% or Median (Q1, Q3) (N = 35)
Female, %	43
Age, y	47 (32, 54)
Race/ethnicity, %	
White, non-Hispanic	17
Black, non-Hispanic	74
Hispanic	9
Pre-ART CD4+ count, cells/mm ³	682 (564, 1003)
Pre-ART human immunodeficiency virus type 1 RNA <40 copies/mL, % ^a	31
HLA* B27/57, %	57

Abbreviations: ART, antiretroviral therapy.

^aAt both pre-ART time points.

the iSCA were available for 31 participants, 19% of whom had pre-ART residual viremia below the limit of quantification (<0.6 HIV-1 RNA copies/mL). Before ART, participants with viral load <0.6 copies/mL by iSCA had higher CD4+ counts and CD4/CD8 ratios than those with detectable viral load (median CD4+ count, 1128 vs 659 cells/mm³, $P = .03$; CD4/CD8 ratio, 1.38 vs 0.82, $P = .08$). In addition, those with iSCA <0.6 copies/mL had lower levels of both CD8+ (median, 19.4% vs 26.5%; $P = .04$) and CD4+ cell activation (2.3% vs 2.9%; $P = .04$). There were no significant differences in levels of soluble inflammatory markers or HIV DNA categorized by iSCA viral load detectability.

ART was effective in further reducing low-level viremia as measured by both commercial and iSCA viral load assays. The percentage of measurements with HIV-1 RNA <40 copies/mL increased from 37% at ART initiation to $\geq 96\%$ starting at week 4 after ART initiation. Before ART, 19% of HIV controllers had an iSCA viral load <0.6 HIV-1 RNA copies/mL compared to 94% of measurements after 24–48 weeks of ART (Figure 2; $P < .001$). There was no significant change in HIV DNA levels with ART (Supplementary Figure 1).

ART resulted in a significant decline in CD8+ cell activation by the %CD38+HLA-DR+ CD8+ cells at 24–48 (−4.0%; 95% confidence interval [CI], −6.4%, −1.6%; $P = .001$) and 72–96 (−7.2%; 95% CI, −11.1%, −3.2%; $P < .001$) weeks after ART initiation (Figure 3). This represented a 15% and 26% relative reduction compared to pre-ART levels at 24–48 and 72–96 weeks after ART initiation, respectively. Although not statistically significant, a modest decline in CD4+ cell activation was also observed, representing an 8% and 21% relative reduction compared to pre-ART levels at 24–48 and 72–96 weeks after ART initiation, respectively. ART initiation did not significantly increase CD4+ cell counts (Figure 4) but was associated with significant increases in the CD4/CD8 ratio at both 24–48 (increase of 0.18, $P < .001$) and 72–96 weeks of ART (increase of 0.29, $P < .001$).

Several T-cell markers of immune exhaustion declined with ART. After 24–48 weeks of therapy, significant decreases were observed in the absolute percentages of CD8+ cells expressing PD1 (−1.8%; 95% CI, −3.2%, −0.4%; $P = .02$), TIGIT (−3.6%; 95% CI, −6.5%, −0.6%; $P = .02$), and CD160 (−4.2%; 95% CI, −6.7%, −1.7%; $P = .001$). There were no significant changes in CD4+ cell markers of immune exhaustion after 24–48 weeks of ART. After 72–96 weeks of ART, there were significant decreases in the absolute percentages of both CD8+ and CD4+ cells expressing CD160 (Supplementary Figure 2). Among the soluble inflammatory markers, ART use was associated with decreased IP-10 levels but increased levels of sCD163 (Supplementary Figure 3).

The effects of ART were also categorized by levels of viremia and age. At 24–48 weeks after ART initiation, the reduction in levels of both CD8+ and CD4+ cell activation observed in participants with pre-ART viral loads <40 HIV-1 RNA copies/mL (CD8+, −1.9%; $P = .03$ and CD4+, −0.4%; $P = .02$) did not significantly differ from those observed in HIV controllers with ≥ 40 HIV-1 RNA copies/mL (CD8+, −4.9%; $P = .003$ and CD4+, −0.2%; $P = .45$; Supplementary Figure 4). However, HIV controllers with ≥ 40 HIV-1 RNA copies/mL did show greater declines in markers of CD8+ cell exhaustion at 24–48 weeks compared to participants with pre-ART viral load <40 copies/mL (%PD-1 by pre-ART viral loads <40 vs ≥ 40 HIV-1 RNA copies/mL: −0.3% vs −2.4%, $P = .05$; %TIGIT: −0.2% vs −5.0%, $P = .04$; %CD160: 0.8% vs −6.3%, $P = .003$). No significant differences in levels of T-cell activation decline were detected

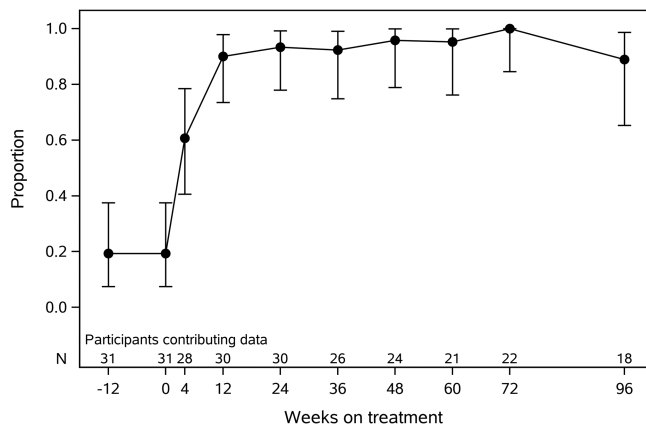


Figure 2. Proportion of human immunodeficiency virus (HIV) controllers with HIV-1 RNA <0.6 copies/mL by the ultrasensitive integrase single-copy assay. Error bars denote 95% confidence intervals.

between individuals aged <50 or ≥50 years. Among the immune exhaustion markers, individuals aged ≥50 years had significantly greater declines only in the %LAG-3+ CD8+ cells (<50 vs ≥50 years: 1.9% vs -1.8%, $P = .005$) and CD4+ cells (1.0% vs -0.5%, $P = .02$) after 24–48 weeks of ART.

RPV/FTC/TDF was well tolerated, with 2 adverse events categorized as possibly related to the treatment. One individual had a transient low phosphorus value of 1.4 mg/dL 4 weeks after initiating ART that resolved at week 8 of ART. A second participant experienced grade 2 nausea 5 days after initiating ART that resolved after RPV/FTC/TDF was withheld for 2 days. After 48 weeks of ART, participants had the option of continuing to be followed in the study for an additional 48 weeks either on or off ART. Of the 29 individuals who agreed, 97% decided to continue ART. In addition, ART resulted in a modest but significant improvement in self-reported QoL (absolute change from pre-ART to 24–48 weeks of ART was -0.07 (95% CI, -0.12, -0.02; $P < .05$).

Eighteen HIV controllers agreed to the additional viral decay visits. Fourteen (78%) had entry iSCA values above the limit of quantification and were included in estimation of phase 1 viral decay (Supplementary Figure 5). Seven (39%) had sufficient detectable iSCA results for estimation of phase 2 viral decay. The median pre-ART viral load by iSCA was 81 HIV-1 RNA copies/mL for the HIV controllers and 56 550 copies/mL for the historical comparator group of noncontrollers. Phase 1 viral decay did not differ between HIV controllers and noncontrollers (median 0.58 vs 0.66 log₁₀ HIV-1 RNA copies/day, $P = .81$). Phase 2 decay rates were significantly shorter in HIV controllers compared to noncontrollers (0.069 vs 0.040 log₁₀ HIV-1 RNA copies/day, $P = .04$), corresponding to a half-life of 10 vs 17 days.

DISCUSSION

Despite the clinical stability of most HIV controllers, there is evidence that this condition is not entirely benign. Some

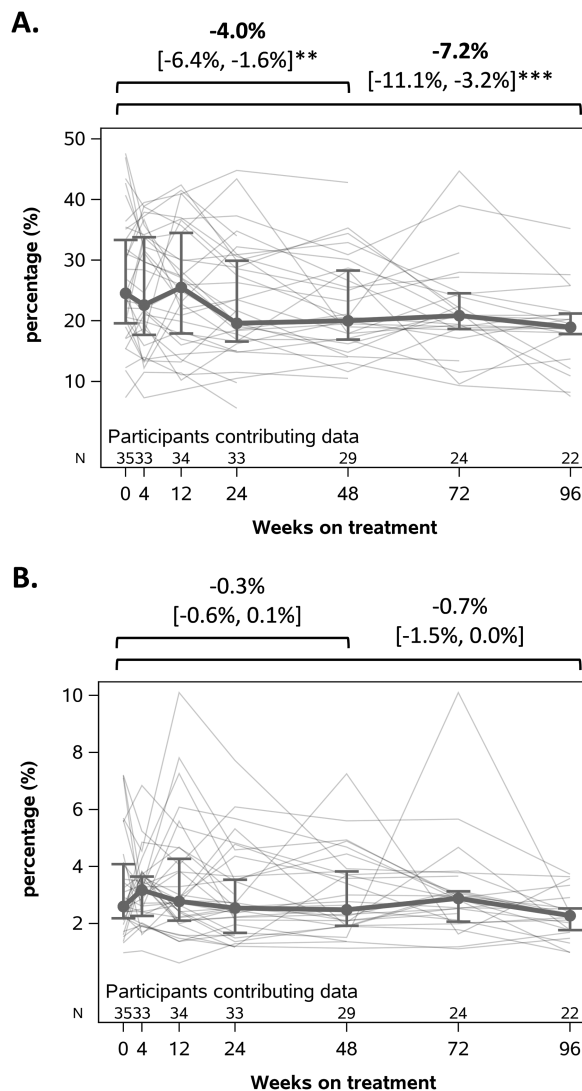


Figure 3. Decline in T-cell activation with antiretroviral therapy as measured by the percentage of (A) CD8+ cells and (B) CD4+ cells coexpressing CD38 and HLA-DR. Mean absolute change in percent-activated T cells with 95% confidence values is shown above each graph. Within each graph, values for each individual are graphed in gray; mean and interquartile ranges are shown in bold. ** $P < .01$; *** $P < .001$.

controllers will experience a loss of viral control, and even among those who maintain low-level viremia, CD4+ cells may decline over time [22]. HIV controllers also have increased levels of immune activation and inflammation compared to both ART-treated and HIV-uninfected individuals [9, 23]. There is evidence that persistent low-level viral replication and inflammation in HIV controllers are associated with disease progression and immune dysfunction [22, 24, 25], as well as increased risk of cardiovascular disease [15] and hospitalizations [16]. Based on these concerning data regarding HIV controllers, we sought to evaluate the potential benefits of ART in this population.

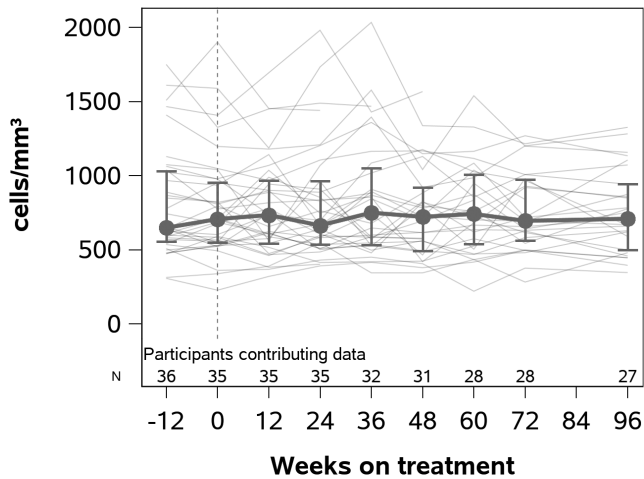


Figure 4. CD4+ counts in human immunodeficiency virus controllers after initiation of antiretroviral therapy (ART). Vertical dotted line represents timing of ART initiation. Median values are shown with the interquartile range.

Prior studies in HIV controllers have reported that ART can further decrease the HIV reservoir and reduce detectable low-level viremia [17, 26], as well as induce modest CD4+ cell gains [27, 28] or immune benefits [29]. However, these studies were limited by small sample sizes and incomplete evaluation of systemic inflammation and lacked an assessment of viral dynamics. The largest of the prospective studies was also limited by a relatively short duration of follow-up [17]. Recruiting from 19 clinical sites within the ACTG, we enrolled the largest study to date of ART for HIV controllers, with longitudinal follow-up for up to 2 years.

Before ART, HIV controllers with lower viral loads were found to have higher CD4+ cell counts and lower levels of T-cell activation, demonstrating important differences between elite and viremic controllers. One year of ART reduced T-cell activation and markers of immune exhaustion, in some cases with further decreases after 2 years of ART; these benefits were seen in both elite and viremic controllers, with the latter group having a greater response. The level of reduction in T-cell activation through 1 year (8% for CD4+ cells and 15% for CD8+ cells) was less dramatic than that reported in the A5321 study of HIV noncontrollers who initiated ART (49% and 57% reduction in CD4+ and CD8+ cell activation, respectively) [30] but not unexpected given the lower baseline pre-ART levels of immune activation in HIV controllers compared to ART-untreated noncontrollers [9]. ART was also effective in further suppressing already low levels of viremia, such that 94% of HIV controllers on ART had viremia <0.6 copies/mL by the ultrasensitive iSCA assay compared to 19% before ART.

In our study, the benefits of ART in HIV controllers did not extend to all viral or immunologic markers. While we detected significant improvements in the CD4/CD8 ratio, there were no significant changes in absolute CD4+ counts. The lack of CD4+ improvement with ART may reflect the relatively preserved

CD4+ cell counts and is consistent with prior studies that demonstrated modest immune recovery after ART initiation in those with very low viral loads [17]. While pre-ART viral load has been associated with HIV DNA levels in noncontrollers [30], we detected no difference in pre-ART HIV DNA levels in HIV controllers with or without detectable residual viremia. After ART initiation, we found no significant decline in levels of total HIV DNA, potentially pointing to the presence of long-lived or clonally expanded populations of HIV-infected cells. Additional characterization of the intact and defective HIV proviral reservoir will be needed to further explore this finding. While ART resulted in significant reductions in levels of T-cell activation and exhaustion, there were no significant improvements in levels of several soluble inflammatory markers (D-dimer, hs-CRP, hsIL-6, and sCD14) and an unexpected increase in levels of sCD163. A study of ART in HIV noncontrollers found that higher baseline viral loads were associated with higher levels of soluble inflammatory factors and that pre-ART levels of soluble inflammatory markers predicted eventual levels while on ART [30]. These findings suggest that the lack of discernible impact of ART on soluble markers of inflammation may potentially be due to their relatively low levels before ART.

We also assessed viral dynamics after starting treatment. In HIV noncontrollers with high pre-ART viral loads, the decline in viral loads after ART initiation occurs initially in 3 phases. The first 2 phases are relatively rapid and occur with a half-life of 1–2 days for the first phase and several weeks for the second phase [31, 32]. However, the third phase of viral decay is much slower (estimated $t_{1/2} = 39$ weeks) and likely reflects the clearance of a latently infected cellular compartment or viral reservoir [18]. In the viral dynamics component of A5308, HIV controllers were found to have similar rates of first-phase viral decay but faster second-phase viral decay. Subsequent viral loads were too low to assess the presence of additional phases of viral decay despite the use of an ultrasensitive assay. These results reveal the extremely low numbers of medium- and long-lived HIV-expressing cells in ART-treated HIV controllers. Furthermore, the second phase decay rates suggest differences between HIV controllers and noncontrollers in the composition or turnover of the cellular populations that support active viral replication. These findings highlight additional potential directions for future HIV reservoir studies.

There are several limitations to our study. Despite being the largest prospective study of treatment in HIV controllers to date, our sample size was still limited and included relatively few elite controllers. Many of the elite controllers at our study sites, even those who had actively participated in research studies for years, were reluctant to begin ART, mostly due to concerns about drug toxicity. We selected RPV/FTC/TDF because of its simplicity and low incidence of side effects and because RPV/FTC/TAF is currently one of the “recommended

initial regimens in certain clinical situations” in the latest guidelines by the US Department of Health and Human Services [2]. We do not know if our results would be similar if a different drug class had been used; previous studies have found a more pronounced effect of integrase strand-transfer inhibitors on soluble inflammatory markers [30, 33]. Finally, the single-arm study design, sample size, and follow-up period do not permit us to make any definitive conclusions about the clinical benefits of ART or improvements in QoL for HIV controllers.

These limitations notwithstanding, the results of the A5308 show that ART given to HIV controllers further reduced viremia and decreased both T-cell activation and markers of immune exhaustion. These virologic and immunologic benefits were observed in both HIV elite and viremic controllers. Treatment was well tolerated and associated with a modest improvement in QoL. Overall, the results of the study suggest possible benefits of initiating ART, even in individuals with very low or undetectable plasma HIV RNA.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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