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Can ART treatment reduce long-term complications by reducing inflammation?

Netanya G. Sandler^{1,*} and Irini Sereti²

¹ Infectious Diseases Division, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX

² Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda MD.

Abstract

Purpose of review—Serious non-AIDS events or non-infectious complications of HIV infection far outnumber AIDS events in the current combination antiretroviral therapy (ART) era and are attributed to chronic inflammation. Thus, a better understanding of why inflammation persists on ART will assist in developing better therapeutic strategies, including optimal timing of ART initiation.

Recent findings—Markers of inflammation and coagulation, such as D-dimer, IL-6, C-reactive protein, soluble CD14, and soluble CD163, predict end-organ disease and mortality, whereas markers of T cell activation appear more predictive of CD4 T cell decline, AIDS events, or response to therapy. Initiating ART at high CD4 T cell counts can result in less inflammation as supported by studies in acute and early HIV infection, but antiretroviral drugs may differentially affect inflammatory pathways. Decreasing inflammation in HIV-uninfected subjects may decrease morbidity, but long-term outcomes studies in HIV-infected individuals are lacking.

Summary—Circulating biomarkers of inflammation are among the strongest predictors of non-AIDS outcomes in treated HIV infection. With additional investigation, they may serve in the future as specific end-organ disease surrogate endpoints and may help identify those patients at highest risk of non-AIDS events who may benefit from either early ART and/or potential adjuvant anti-inflammatory therapies.

Keywords

biomarkers; T cell activation; monocyte activation; inflammation; morbidity; HIV

Introduction

Since the introduction of combination antiretroviral therapy (ART), significant improvement in mortality has been observed in HIV-infected individuals. However, serious non-AIDS

* Corresponding Author: Netanya G. Sandler University of Texas Medical Branch at Galveston 301 University Boulevard, Route 0435 Galveston, TX 77555-0435 Phone: (409) 747-0240 Fax: (409) 772-6527 neutay@utmb.edu.

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events, including cardiovascular disease, malignancy, bone disorders, and neurocognitive impairment account for most morbidity and mortality in the ART-treated population [1,2]. ART side effects were hypothesized to drive these events, but the SMART study showed that people not receiving continuous ART had a higher frequency of non-AIDS events [3]. The association of HIV infection with non-AIDS events has now been affirmed in some studies. Measurements of soluble biomarkers in SMART and subsequent studies have further highlighted that inflammation is an independent predictor of all-cause mortality, cardiovascular events, and other morbidities in chronic treated HIV infection [4-6*].

Indeed, systemic inflammation has been recognized as a seminal feature of HIV infection. Whether ART alone could normalize the inflammatory state if started early, i.e. during acute infection or at CD4 T cell counts even higher than 500 cells/mm³, remains unclear as most available data are derived from people starting ART in chronic infection with CD4 T cell counts frequently below current World Health Organization treatment guidelines [7]. Randomized controlled studies of conventional treatment strategies compared to early ART, that correlate biomarkers of inflammation and coagulation with clinical events, will address this question.

Inflammation and immune activation in acute and chronic HIV Infection

The terms inflammation and immune activation have been used interchangeably in HIV literature, but they reflect different processes. “Inflammation” refers to the production of cytokines and other mediators primarily by macrophages, in response to a stimulus, resulting in *rubor*, *dolor*, *calor*, and *tumor* (redness, pain, heat, and swelling) and subsequently immune cell recruitment and release of more inflammatory mediators [8]. “Immune activation,” in turn, describes cellular activation indicated by the expression of markers on lymphocytes, monocytes, or antigen presenting cells. T cell activation is often characterized by HLA-DR and/or CD38 expression, Ki67 expression to indicate cycling, and BrdU incorporation and decay to reflect cell turnover [9]. However, numerous other markers of cellular activation exist including molecules that also regulate immune responses (such as PD-1) [10]. Thus, we prefer “immune activation” to describe increases in cellular markers of activation and “inflammation” to describe the systemic response detected by increases in soluble biomarkers of inflammation.

Many inflammatory biomarkers such as IFN α , TNF, and IL-6, reflecting innate immune system activation, increase during acute HIV infection, coincide with peak viremia, and decrease but remain elevated into chronic infection [11,12**]. In acute infection, high IFN γ -induced protein 10 (IP-10) levels predicted disease progression, i.e. CD4 T cell loss [12**], and monocyte activation markers such as neopterin were recognized decades ago as independent predictors of chronic HIV disease progression [13]. Type I interferons (IFN-Is), which stimulate antiviral gene expression, are also thought to drive disease progression based on nonhuman primate studies demonstrating their persistent elevation in progressive but not nonprogressive SIV infection [14,15]. However, blocking IFN-I signaling in rhesus macaques during acute SIV infection resulted in accelerated disease progression, reflecting the importance of early viral control in disease outcomes [16]. In chronic treated HIV infection, elevated levels of soluble markers of inflammation and coagulation, including

IL-6, D-dimer, high-sensitivity C-reactive protein (hsCRP), soluble CD14 (sCD14), and soluble CD163 (sCD163), were shown to predict cardiovascular events, progression to AIDS, and all-cause mortality [4-6, 17-19].

CD4 and CD8 T cell activation also increase during acute infection, correlate with viremia, and remain elevated during chronic infection [20-22]. Increased CD8 T cell activation was recognized early as an independent predictor of disease progression [23], even when measured before seroconversion [24]. Greater CD8 T cell activation predicted a faster rate of CD4 T cell decline without ART [21], slower recovery of CD4 T cells with ART [25, 26*], increased frailty [27*], and increased mortality [28]. T cell activation may not always represent a dysregulated response but rather a response to lymphopenia [29,30] or even to pathogens [31,32]. In addition, other T cell populations (such as CD28⁺ or central memory cells) have been associated with improved vaccine responses and better outcomes [33**,34]. A better understanding of what represents a “healthy” T cell pool may be needed to identify the optimal endpoints for interventional studies.

Monocytes are another cellular population of interest as HIV-infected individuals have been shown to express higher levels of tissue factor, which helps initiate the coagulation cascade [35], and CD16, resembling the monocytes of older individuals [36*,37**]. Soluble markers of monocyte and macrophage activation have been linked to both HIV disease progression and serious non-AIDS events [5,12**,17,18,19,38**,39,40,41*]. More recently, higher CD16 expression was found to be an independent predictor of atherosclerosis progression [42], highlighting the need to assess monocyte phenotypes as potential targets of therapeutic interventions.

Effect of ART on inflammation and T cell activation

ART dramatically decreases most markers of immune activation and inflammation in peripheral blood and tissue [17,18,43-45]. However, many studies have shown persistently increased T cell activation and inflammation in chronically treated patients [5,13,18,22-25,31,35,36*,37**,38**,39,41*,44-46]. The potential causes include residual HIV replication, gut mucosal injury and subsequent microbial translocation, tissue fibrosis, co-infections such as cytomegalovirus and hepatitis C virus, and homeostatic drive [47,48]. The contribution of each of these factors may vary depending when ART is initiated (acute or chronic infection, high or low CD4 T cell counts), degree of CD4 T cell restoration, age, comorbidities, and genetic background [49].

Biomarkers that associate independently with morbidity and mortality in patients on ART reflect predominantly chronic activation of the innate rather than adaptive immune system. Two recent studies demonstrated that only soluble markers of inflammation, not T cell activation, independently predict clinical events [50,51]. A hyperactive innate immune system is more proximal to the vascular and endothelial complications of HIV, but the adaptive system may still contribute: CD8 T cells from HIV-infected individuals express increased protease-activated receptor (PAR)-1, which increases thrombin-enhanced IFN γ secretion and thereby links vascular injury and coagulation with the adaptive T cell response [52**].

ART intensification and differential effects of antiretroviral drugs on inflammation and immune activation

Despite the decrease in inflammation and T cell activation after ART initiation, treatment intensification, i.e. adding another antiretroviral drug to a suppressive ART regimen, has not consistently resulted in further decreases. Although initial reports suggested maraviroc intensification decreased the activated CD8 T cell frequency [53,54*], a randomized controlled study subsequently showed that maraviroc intensification increased peripheral and rectal CD8 T cell activation, perhaps because CCR5 blockade decreased monocyte chemotactic protein-1 (MCP-1) uptake [55**]. Raltegravir intensification studies are also conflicting. CD8 T cell activation decreased in some participants in some studies [56,57*, 58*,59], but more recently, a decrease in D-dimer levels with no effect on T cell activation was observed [60*,61**]. In sum, antiretroviral intensification has not resulted in a profound decrease in inflammation or immune activation.

Switching antiretrovirals, however, may have a more substantial effect. Subjects switched from enfuvirtide to raltegravir had significant decreases in hsCRP, D-dimer, and IL-6 levels [62*]. Similarly, patients switched from a ritonavir-boosted PI or NNRTI regimen to raltegravir experienced decreases in hsCRP, MCP-1, IL-6, D-dimer, TNF α , and sCD14 relative to the control arm [63*,64] but without changes in flow mediated dilation [65*]. In contrast, a randomized controlled trial comparing tenofovir to abacavir, which was controversially implicated in cardiovascular events [66-68], found that hsCRP levels increased and IL-6 decreases were delayed in the abacavir group whereas hsCRP levels decreased in the tenofovir arm [69*]. Switching individuals from abacavir- to tenofovir-based regimens led to improvements of lipids after 48 weeks in people on boosted PIs and not those on raltegravir [70*,71*]. The mechanisms by which specific antiretroviral drugs affect inflammatory or coagulation pathways, independent of virologic and lipid effects, need to be further elucidated. From a practical standpoint, the effects of different antiretroviral drugs on inflammation may become an important determinant in individualizing ART regimens, in addition to considerations of resistance mutations, drug interactions, dosing schedules, and side effect profiles.

Could early ART eliminate residual inflammation and immune activation and improve clinical outcomes?

Although inflammatory biomarkers predict serious non-AIDS events after adjusting for CD4 T cell counts, current or nadir CD4 T cell counts still have prognostic value. Recent studies demonstrated that AIDS-defining events do not plateau until CD4 T cell counts reach 750 cells/ μ L [72**], yet all-cause mortality seems comparable to HIV-uninfected individuals once CD4 T cell counts are above 500 cells/ μ L in treated subjects [73*,74]. However, despite years of viral suppression, immunologic non-responders are still at increased risk of non-AIDS events [75*].

Nadir CD4 T cell counts may be as predictive as proximal CD4 T cell counts. Individuals initiating ART at CD4 T cell nadirs above 350 cells/ μ L have fewer non-AIDS events and complications compared to those starting at lower counts [76*]. The decrease in cardiovascular events in particular may be related to improved vascular function in

individuals with nadir CD4 T cell counts above 350 cells/ μ L [77**]. In addition, lower nadir CD4 T cell counts have been shown to correlate with greater bone mineral density loss after 96 weeks of ART [78*]. As immunologic response clearly depends on age at ART initiation and nadir CD4 count, it is feasible that earlier ART at higher CD4 counts (and consequently also at younger age) could lead to more robust CD4 T cell restoration and lower morbidity and mortality. Indeed, individuals that initiated ART less than 4 months post-infection with CD4 T cell counts greater than 500 cells/ μ L were more likely to attain CD4 T cell counts greater than 800 cells/ μ L than those that started later [79**].

Several studies have assessed whether early ART alone can decrease immune activation. Individuals treated during acute infection experienced a dramatic decrease in the frequency or number of activated (CD38⁺HLA-DR⁺ or CD38⁺⁺) CD8 T cells after 12 [20] or 28 weeks [22] to levels lower than in untreated individuals. This decrease coincided with a rapid viral load decrease and a decrease in cell-associated HIV DNA and RNA levels, particularly among those with low baseline activated CD8 T cell counts [20,22,80]. Studies conflict as to whether the frequency of activated CD38⁺HLA-DR⁺ CD8 T cells can eventually normalize in individuals treated during acute HIV infection [81,82*]. Higher CD8 T cell activation was associated with greater peak viral load, time to viral suppression, and pre-ART CD8 T cell activation even after 96 weeks [82*]. In the Options Project, the frequency of activated HLA-DR⁺CD38⁺ CD8 T cells decreased to a greater extent and cell-associated HIV DNA and RNA were lower in individuals starting ART within 6 months of infection compared to those starting at least 2 years post-infection [83**]. Higher CD8 T cell activation was associated with higher cumulative viremia and lower pre-ART CD4 T cell count in the delayed ART group. Together, these studies suggest that early ART results in less cell-associated virus, less cumulative viremia, and subsequently lower CD8 T cell activation during chronic HIV infection.

The effects of early ART on biomarkers of inflammation are heterogeneous. Levels of IFN α , D-dimer, and IP-10 but not sCD14, decreased while CD4 T cell counts increased with ART initiated during acute HIV infection [84*]. This decrease in inflammatory markers was accompanied by a decrease in cell-associated HIV DNA. Similarly, ART initiated within 1 year of infection normalized levels of sCD163, a monocyte activation marker correlated with noncalcified arterial plaque and neurocognitive impairment, but not if initiated later [18,85,86*]. In contrast, sCD14 levels increased in the early ART group while remaining unchanged in the later group [18], suggesting that early ART may not affect all inflammatory pathways similarly.

Even transient early ART can decrease T cell activation in chronic infection. In the VISCONTI study, subjects that took ART for 3 years starting 1.6 months post-infection had, after discontinuation, lower levels of cell-associated HIV DNA and comparable CD8 T cell activation to those still taking ART during chronic infection and maintained virologic suppression and steady CD4 T cell counts for over 7 years [87**]. In a similar study, 14 individuals that received 1-2 years of ART initiated within 3 months of infection maintained virologic suppression for about 4.5 years and steady CD4 T cell counts for up to 8 years [88*]. These subjects had higher CD4 T cell counts at baseline and at ART interruption and lower CD38⁺ CD8 T cell frequencies than the 136 post-ART non-controllers. Together,

these studies identify a population of post-treatment controllers that maintain small HIV reservoirs, low CD8 T cell activation, and high CD4 T cell counts, reflecting the association of viral replication, T cell activation, and CD4 depletion.

In sum, initiating ART during the first year of HIV infection results in reduced T cell activation and numerous biomarkers of inflammation, predictors of progression to AIDS [13,18,21,24,26*], cardiovascular disease [85,89], and mortality [28]. However, whether initiating ART during acute HIV infection is more beneficial on inflammation and immune activation, potentially because of an early effect on the viral reservoir, than starting ART during chronic HIV infection with a high CD4 T cell count is unknown. In addition, while decreasing viral replication may decrease inflammation, as noted above, long-term exposure to some antiretroviral drugs may contribute to hyperlipidemia, inflammation, and potentially end-organ disease. Furthermore, the optimal way to quantify viral replication and the viral reservoir is unclear, and these viral measurements have not been directly correlated with the biomarkers of interest (D-dimer, sCD14, IL-6, hsCRP, sCD163, etc) or validated as independent clinical predictors through the robustness of a large database.

It is possible that early ART will not completely eliminate inflammation, and it may not be feasible for all patients. Other modalities that target inflammation directly may be necessary to improve clinical outcomes. Studies of aspirin, statins, and methotrexate, among others, in HIV-uninfected individuals have demonstrated a decrease in inflammatory biomarkers such as IL-6, hsCRP, and D-dimer and subsequently a reduction in cardiovascular events [90-94].

Recent studies of agents to decrease immune activation and inflammation in HIV-infected individuals have been modestly successful. Prebiotic oligosaccharide administration to HIV-infected individuals not taking ART decreased plasma sCD14 levels [95], and celecoxib [96] and valganciclovir targeting CMV co-infection [97] decreased CD8 T cell activation in both studies and hsCRP in the valganciclovir study. The optimal approach may be to target either multiple drivers of inflammation simultaneously, i.e. residual viral replication, microbial translocation, and co-infections, or the final common pathway, i.e. possibly monocyte activation or the intersection of the inflammation and coagulation pathways. Numerous ongoing studies aim to decrease inflammation in HIV-infected individuals using aspirin, statins, rifaximin, sevelamer, angiotensin-receptor blockers, methotrexate, and other agents [48,98-100]. The results of these studies will provide a better understanding of both the inflammatory pathways with their related biomarkers and their role in end-organ disease in HIV-infected individuals.

Conclusion

Early ART in chronic infection would clearly benefit certain HIV-infected persons (with hepatitis B or C co-infection, high cardiovascular risk, risk for TB acquisition, older age), and accumulating evidence suggests that early ART could attenuate at least some aspects of the chronic inflammatory state of treated HIV infection. Whether this reduction in inflammation would result in fewer non-AIDS events, as data from studies from the HIV-uninfected population suggest, remains unclear. The link of biomarkers or their modification with clinical events may be further unraveled in new clinical endpoint studies such as

START and TEMPRANO that will help support or disprove the hypothesis. Despite the controversy of how early to start, the frustrating reality is that throughout the past decade, the average CD4 count at diagnosis has remained below 350 cells/ μ L [101*]. Earlier diagnosis and treatment, at least in accordance with existing guidelines, represents the first and foremost attainable task in the near future.

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Abbreviations

ART	Antiretroviral therapy
IP-10	IFN γ -induced protein 10
IFN-I	Type I interferon
IL-6	Interleukin 6
hsCRP	High-sensitivity C-reactive protein
sCD14	Soluble CD14
sCD163	Soluble CD163
MCP-1	Monocyte chemotactic protein-1

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expression of protease-activated receptor (PAR)-1 was increased in CD8 T cells of HIV-infected subjects. Thrombin, via PAR-1, induced increased mobility and expression of IFN γ by CD8 T cells. This study couples the coagulation system with the adaptive immune system and more specifically the activated effector CD8 T cells that typically remain expanded after prolonged ART.]

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decreased after 24 weeks, suggesting that low-level viral replication persists even in individuals on long-term ART with good immunologic response, and suppression of this replication could further decrease inflammation.]

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total and LDL cholesterol levels and were more likely to have desirable triglyceride levels, but there were no significant differences between groups in inflammatory biomarkers. Again, these data suggest a potential adverse synergistic effect of abacavir with protease inhibitors on lipid profiles.]

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- 76*. Ho JE, Scherzer R, Hecht FM, et al. The association of CD4+ T-cell counts and cardiovascular risk in treated HIV disease. Nadir CD4 T cell counts < 350 cells/ μ L were associated with lower flow-mediated dilation, representing higher cardiovascular disease risk whereas proximal CD4 T cell counts were not. This study suggests that initiating ART before nadir CD4 T cell counts fall below 350 cells/ μ L could decrease subsequent risk of cardiac events. *AIDS*. 2012; 26:1115–20.
- 77**. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. 2012; 26:465–74. [PubMed: 22112603] [The study included 3068 patients in the observational AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort after 2 years of starting HAART and evaluated morbidity and mortality based on immune recovery. Predictors of poor immune recovery were older age, lower nadir CD4 T cell counts, and lower baseline plasma HIV viremia. Patients with the poorest CD4 T cell recovery had the highest incidence of morbidity and mortality, including cardiovascular events.]
- 78*. Grant PM, Kitch D, McComsey GA, et al. Low Baseline CD4+ Count is Associated with Greater Bone Mineral Density Loss after ART Initiation. *Clin Infect Dis*. 2013 doi: 10.1093/cid/cit538. [Not only do low baseline CD4 T cell counts predict greater bone mineral density loss, but the degree of this loss is also dependent on ART regimen. Previous observations of the association of tenofovir with bone mineral density loss were confirmed, and an association between protease inhibitor use and bone mineral density loss was established. Whether this is related to increased inflammatory markers is unclear, but regardless, this study argues that early ART, with select regimens, could help preserve bone density.]
- 79**. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013; 368:218–30. [PubMed: 23323898] [Individuals starting ART within 4 months of the estimated date of infection were most likely to recover high CD4 T cell counts and to do so quickly, followed by those within 12 months of infection, compared to those that started more than 12 months post-infection. Thus, initiating ART during acute or early infection has the greatest likelihood of effective and fast CD4 T cell recovery, potentially abolishing the risk of HIV-associated end-organ diseases.]

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- 82*. Vinikoor MJ, Cope A, Gay CL, et al. Antiretroviral therapy initiated during acute HIV infection fails to prevent persistent T-cell activation. *J Acquir Immune Defic Syndr*. 2013; 62:505–8. [PubMed: 23314410] [In individuals starting ART a median of 43 days post-infection, CD8 T cell activation decreased but remained elevated compared to healthy controls. The decrease was associated with a shorter time to virus suppression and longer duration of ART. Thus, early, continuous ART with a regimen that would achieve rapid virus suppression in a given patient would decrease immune activation.]
- 83**. Jain V, Hartogensis W, Bacchetti P, et al. Antiretroviral Therapy Initiated Within 6 Months of HIV Infection Is Associated With Lower T-Cell Activation and Smaller HIV Reservoir Size. *J Infect Dis*. 2013 doi: 10.1093/infdis/jit311. [ART within 6 months of infection with a median CD4 T cell count of 533 cells/μl reduces the HIV reservoir and decreases T cell activation to a greater extent than ART after 2 years of infection with a median CD4 T cell count of 325 cells/μl. The higher the CD4 T cell count and the less time the virus replicates unchecked, the lower the T cell activation and the better the CD4 T cell recovery, which is, in turn, a determinant of future end-organ disease.]
- 84*. Ananworanich J, Schuetz A, Vandergeeten C, et al. Impact of multi-targeted antiretroviral treatment on gut T cell depletion and HIV reservoir seeding during acute HIV infection. *PLoS One*. 2012; 7:e33948. [PubMed: 22479485] [Initiation of ART during acute HIV infection resulted in a smaller HIV reservoir than in individuals starting ART during chronic infection and an overall reduction in inflammatory markers such as IP-10 and D-dimer with longer duration on ART. These data suggest that early, continuous ART can improve both CD4 recovery (IP-10) and biomarkers (D-dimer) associated with morbidity and mortality.]
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- 86*. Burdo TH, Weiffenbach A, Woods SP, et al. Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. *AIDS*. 2013; 27:1387–95. [PubMed: 23435298] [Increased monocyte/macrophage activation is associated with neurocognitive impairment in HIV-infected individuals, suggesting interventions to decrease this monocyte activation may improve neurocognitive functionality in individuals with long-term disease.]
- 87**. Saez-Cirion A, Bacchus C, Hocqueloux L, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog*. 2013; 9:e1003211. [PubMed: 23516360] [14 individuals that received about 36 months of ART starting a median of 1.6 months post-infection remained aviremic with steady CD4 T cell counts for a median of 89 months after ART interruption These individuals had smaller HIV reservoirs than the non-controllers and less CD8 T cell activation, consistent with HIV replication driving CD8 T cell activation.]
- 88*. Goujard C, Girault I, Rouzioux C, et al. HIV-1 control after transient antiretroviral treatment initiated in primary infection: role of patient characteristics and effect of therapy. *Antivir Ther*. 2012; 17:1001–9. [PubMed: 22865544] [14 of 164 individuals starting ART at a median of 3.2 weeks post-infection and treated for a median of 20 months maintained undetectable plasma HIV RNA levels and stable CD4 T cell counts and 14 had low-level viremia for a median of 4.5 years. These two groups had higher CD4 T cell counts prior to starting ART (median 582 and 583 cells/μl compared to 485 cells/μl in the noncontrollers) and lower CD38+ CD8 T cell percentages during ART treatment, establishing another correlation between low CD8 T cell activation and CD4 T cell stability. These data suggest starting ART at higher CD4 T cell counts and decreasing T cell activation may result in higher, stable CD4 T cell populations.]
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Key points

- Inflammatory markers have been identified as independent predictors of disease progression and clinical events in acute and chronic HIV infection.
- Specific antiretroviral drugs or their combinations may have differential effects on inflammatory biomarkers, and the clinical implications of these effects ought to be further investigated.
- It is possible, yet presently unclear, that early ART may substantially decrease or eliminate residual inflammation in chronic treated infection by diminishing residual virus and preserving a more intact T cell pool.