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Impact of antiretroviral therapy (ART) timing on chronic immune activation/inflammation and end-organ damage

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Abstract

Purpose of review—The purpose of this review was to summarize recent studies on the effect of early antiretroviral therapy (ART) in HIV-infected patients on markers of immune activation/inflammation, viral persistence and serious non-AIDS events.

Recent findings—Early ART, initiated within days to months of HIV infection, was associated with marked reduction in T-cell activation often reaching levels observed in HIV-uninfected individuals. However, the impact of early ART on markers of innate immune activation, microbial translocation and inflammation/coagulation was less clear. Early ART has also been associated with a significant reduction in the frequency of latently infected cells, which was greater if ART was initiated within days to weeks rather than months following infection. However, few studies have evaluated the relationship between immune activation and viral reservoirs, specifically following early ART. Early ART may potentially reduce serious non-AIDS events and associated mortality, but most of these studies have extrapolated from changes in surrogate markers, such as CD4 : CD8 ratio.

Summary—Early ART was associated with beneficial effects on multiple markers of immune activation, inflammation and viral persistence. Longer term prospective studies are still needed to determine whether early ART translates to a significant reduction in serious non-AIDS events and mortality.

Keywords

CD4:CD8 ratio; early antiretroviral therapy; immune activation; serious non-AIDS events; viral persistence

INTRODUCTION

Immune activation and inflammation are hallmarks of chronic untreated HIV disease and have been associated with a range of clinical endpoints and serious non-AIDS events (SNAEs) ([1,2,3], recent review in [4]). Immune activation can be measured as changes in the adaptive and innate immune systems, markers of microbial translocation and systemic markers of inflammation and coagulation (reviewed in [5]). Although antiretroviral therapy (ART) leads to a significant reduction in multiple markers of immune activation, immune activation following ART still remains significantly elevated compared with uninfected controls [6–8]. Several studies have also shown a clear relationship between markers of immune activation and persistence of HIV on ART in blood or tissue [9,10]; however, it is currently unclear whether immune activation drives virus persistence on ART or whether virus persistence drives immune activation.

Here, we review recent studies that have assessed the effects of early ART, defined by time postinfection and not CD4⁺ T-cell count at ART initiation, on markers of immune activation, viral persistence and clinical end-points and discuss future directions of research to better understand the clinical impact of early ART.

EARLY ART AND CHRONIC IMMUNE ACTIVATION/INFLAMMATION

Multiple recent studies have assessed the impact of early ART on immune activation (summarized in Table 1) [11,12,13,14,15,16,17,18,19,20–23], but few studies [12,13,17] have directly compared early and delayed ART. In general, studies of early ART and immune activation have largely been small and observational, have only compared outcomes to HIV-uninfected [11,16] or historical controls [17] and, therefore, have had significant limitations.

T-cell activation

The impact of early ART on T-cell activation markers [measured as CD38/human leukocyte antigen (HLA-DR) or Ki-67] has consistently shown a decline, following ART [12,14,16,19,21] as observed following ART in chronic infection [7,24], but whether these markers eventually reach levels of uninfected controls is unclear. Some studies [16,19,21] of early ART have shown that ART within 45 days of infection and continued for at least 12 months, resulted in a reduction in CD8⁺ T-cell activation (CD38⁺HLA-DR⁺CD8⁺ T cells) which reached similar levels to uninfected controls, whereas other studies [12,14] have shown that levels of T-cell activation remain above that observed in uninfected controls. The differences between these studies may potentially be explained by differences in the timing of ART (days vs. months following infection) and the degree of immunodeficiency at ART initiation (CD4⁺ T cells > or <500 cells/μl). In studies wherein levels of T-cell activation remained elevated following early ART, lower CD4⁺ T-cell nadir was associated with

higher after combination ART CD4⁺ T-cell activation, whereas CD8⁺ T-cell activation was associated with both nadir CD4⁺ T-cell counts and cumulative viremia prior to ART [12], implying that in some patients, immunological damage sustained prior to ART may be persistent and irreversible despite early treatment.

Studies of T-cell activation markers in gut-associated lymphoid tissue (GALT) following initiation of ART during acute HIV infection (Fiebig I–V) found that T-cell activation (measured as expression of CD38/HLA-DR or Ki-67) [22,23] declined to levels seen in HIV-uninfected controls, although reconstitution of CD4⁺ T cells in the lamina propria remained impaired even after 24 months of suppressive ART [23]. Taken together, these studies demonstrate that initiation of early ART significantly reduces T-cell activation markers and in patients with preserved immune function at ART initiation, activation levels may normalize both in the periphery and GALT.

CD4 : CD8 ratio

The ratio of CD4 : CD8 has traditionally been described as a marker of immunosenescence in the general population [25,26], and is an emerging marker of interest in HIV-infected individuals as it has been shown to identify individuals with persistent immunological dysfunction who are at greater risk of AIDS, non-AIDS events and mortality despite normalization of CD4⁺ T-cell counts on ART [3,17,27]. Numerous studies [13,16,17,28] have found that early ART was associated with more rapid increases in CD4⁺ T-cell counts, as well as increases in the CD4 : CD8 ratio. However, in a study [17] on HIV-infected individuals treated within 6 months compared with 2 years after seroconversion, low CD4 : CD8 ratios persisted and did not normalize in the early treatment group.

Innate immune activation and microbial translocation

Early ART initiated within 1 year of seroconversion was found to decrease soluble (s)CD163, a marker of monocyte activation, and the proportion of the inflammatory monocytes that express CD14⁺ and CD16⁺; however, levels of sCD14 unexpectedly increased with no change reported in plasma lipopolysaccharide levels [11]. Two studies [16,18] on patients initiating ART during acute HIV infection (within Fiebig I–V) showed neither a change in markers of microbial translocation (lipopolysaccharide, 16S ribosomal DNA, or peptidoglycan levels) nor monocyte/macrophage activation (sCD14 or interleukin-1 receptor antagonist or C-X-C motif chemokine 10 [CXCL10]), whereas one study [19] of early ART reported a decline and normalization of sCD14 levels. The reasons for these mixed results are unclear but may be related to differences in timing of initiation of ART, duration on ART and possibly route of acquisition or other comorbidities, such as hepatitis C virus, which is also associated with elevated levels of immune activation [29].

Very early ART – within days to weeks, as opposed to early ART, – within weeks to months, may be important in maintaining mucosal integrity and consequent effects on immune activation. The subset of T helper 17 cells, which have been shown to be important in mucosal repair [30], was found to remain unchanged when measured in peripheral blood

[16]; however, when measured in GALT, were found to be preserved, at least in patients initiating ART in Fiebig I–II [22]. In contrast, in patients treated with Fiebig III infection, ART led to an increase in T helper 17 cells in the GALT, but this did not reach levels seen in uninfected patients [22].

Systemic inflammation and coagulation

Studies of the impact of early ART on systemic inflammatory markers are limited. Levels of D-dimer and interferon- α declined when ART was initiated during acute HIV infection, but it was unclear whether these levels normalized because a control group of HIV-uninfected patients was not included in this study [18■■■]. Interleukin-6 and highly sensitive C-reactive protein are two markers that when measured pre-ART and on-ART have been shown to predict subsequent mortality and SNAEs [1■■■,31,32]. These biomarkers interestingly did not decline significantly after 6 months of early ART [11,18■■■]. Given that pre-ART levels of interleukin-6 and highly sensitive C-reactive protein, independent of on-ART levels, have both been associated with SNAEs, it is possible that even early ART may have limited impact on the risk of SNAEs on ART [1■■■,31].

IMMUNE ACTIVATION AND VIRUS PERSISTENCE

Numerous studies [10,33] have now shown a significant correlation between markers of both adaptive and innate immune activation and virus persistence on ART in patients treated in chronic infection, and more recently in patients treated during acute infection [12■,34]. Immune activation and virus persistence may be associated through multiple mechanisms (Fig. 1 and recently reviewed in [35]). In brief, the association between immune activation and virus persistence may be a result of the following factors. First, ongoing virus replication in blood or tissue in activated CD4⁺ T cells. Second, ongoing infection of resting CD4⁺ T cells in the setting of high levels of inflammatory chemokines, such as CXCL10 [36]. Third, trafficking of susceptible cells to tissue, such as the gastrointestinal tract, in which there is impaired penetration of some antiretroviral drugs [37]. Fourth, enhanced transcription of viral DNA from latently infected cells. Fifth, homeostatic proliferation of infected resting memory T cells [38,39] and possibly activated memory T cells on ART [34].

CD4⁺ T-cell recovery following ART may also play an important role, given the clear inverse relationship between CD4⁺ T-cell count on ART and integrated DNA and multiple markers of immune activation [10,38,40]. The very clear inverse relationship between CD4⁺ T-cell counts and markers of immune activation makes it difficult to tease out which is the most significant or driving factor in this potentially three-way interaction.

Given that the treatment of acute infection is associated with a reduction in a range of markers of immune activation and maintenance of higher CD4⁺ T cells, both factors may contribute to the lower frequency of latently infected cells in patients on ART treated during acute infection compared with chronic infection [15]. Very early treatment, that is, within days to weeks in contrast to months can clearly have a profound effect on the number of latently infected cells and distribution of infection with preferential infection of short-lived cells, such as effector memory, in contrast to long-lived central memory T cells [18■■■,

20,41,42]. How the size and distribution of the viral reservoir relate to markers of immune activation or numbers of activated T-cells in both blood and tissue at the time of infection or at the time of early ART remain unknown, but could potentially be addressed in the informative macaque models now being used to study early ART [41].

There have been few studies that have directly explored the relationship between immune activation and virus persistence in patients treated following acute infection. One recent study [12■] demonstrated that early ART (<6 months after infection) compared with later ART (>2 years of infection) was associated with lower CD8⁺ and CD4⁺ T-cell activation and lower cell-associated HIV DNA and RNA. The authors conclude that ART timing (early vs. late) rather than pre-ART cumulative viremia or CD4⁺ T-cell count was the primary determinant of cell-associated HIV DNA levels [12■]. Given the very significant effect of early ART on the number of latently infected cells [41,43,44], further work is needed to define what role early control of immune activation may play in limiting the establishment and/or maintenance of latently infected cells.

IMPACT OF EARLY ART ON THE DEVELOPMENT OF END-ORGAN DAMAGE

There have been a limited number of studies that have addressed the impact of early ART on the development of end-organ diseases.

Serious non-AIDS events

In a recent review [45■] of all-cause mortality between 1999 and 2011 in 49 731 HIV-infected patients in the data collection on adverse events of anti-HIV Drugs cohort, non-AIDS cancers, cardiovascular disease, renal dysfunction and liver disease accounted for 40% of all deaths. However, the benefit of ART initiation close to the time of HIV infection, or at a predefined CD4⁺ T-cell count upon the incidence and outcome of SNAEs has not yet been fully elucidated.

Serrano-Villar *et al.* [17■] utilized four separate clinical cohorts and data from three clinical trials to investigate the CD4:CD8 ratio on ART on patients' immunological and clinical outcomes, including SNAEs. Utilizing the OPTIONS cohort, which comprised patients with acute/early HIV infection, they reported that ART initiated within 6 months ($n = 33$) vs. more than 2 years ($n = 35$) was associated with a significantly greater likelihood of obtaining a CD4:CD8 ratio greater than 1.0 after 1 year of ART. Next, they reported on a nested case-control analysis of 33 HIV-infected treated patients with CD4⁺ T cells of at least 500 cells/μl from the Madrid HIV outpatient cohort who had developed SNAEs (cases) and matched each case with one control. After adjusting for age, gender, ART duration and nadir and proximal CD4⁺ T-cell counts, they found that for every 10% decrease in the CD4:CD8 ratio, there was a 48% increased incidence in SNAEs [17■]. The authors examined the relationship between the CD4:CD8 ratio and mortality in the Study of the Ocular Complications of AIDS cohort, which is composed of patients who initiated ART at the time of an AIDS diagnosis. Using 62 cases matched with 121 controls, they found in adjusted

analyses that for every 10% increase in the CD4:CD8 ratio, there was a 15% decrease in the risk of death, most of which were from SNAEs [17■■■].

The authors conceptually linked the findings from these three cohorts to suggest that early ART was associated with a decreased risk of SNAEs and SNAE-related mortality [17■■■]. However, the findings were derived by dichotomizing ART initiation from time of HIV infection between less than 6 months compared with a median of more than 3 years, which may have skewed the likelihood of finding a significant difference between the timing of ART initiation. Further, the study utilized three cohorts from two different countries, and there were a low number of evaluable cases, hence unmeasured confounders may have been present.

Given the limited numbers of studies that directly assessed clinical end-points with early ART, we have also reviewed studies that assessed the impact of high and low CD4⁺ T-cell counts prior to ART and clinical end-points. In the HIV Prevention Trials Network 052 study, HIV-infected patients with CD4⁺ T-cell counts between 350 and 500 cells/μl were randomized to receive early or delayed ART, in which patients in the delayed arm commenced ART if CD4⁺ T-cell counts fell to less than 250 cells/μl or AIDS illnesses developed [46■]. In a post-hoc analysis, after a median of 2.1 years of follow-up, 21 SNAEs occurred, with no significant differences between the delayed and early arms. A longer follow-up time may be required to see any differences between the two arms [46■]. In a retrospective Spanish cohort of 675 antiretroviral-naïve patients with CD4⁺ T cells more than 500 cells/μl, the crude incidence rate of SNAES and SNAE-related mortality was 1.4 per 100 persons-years of follow-up [47]. In those patients whose CD4⁺ T-cell nadir was more than 350 cells/μl, there was a significant decrease in the crude incidence rate of SNAES and SNAE-related mortality before and after initiation of ART (2.5; 95% confidence interval 1.9–3.2 and 0.6; 95% confidence interval 0.3–1.0 per 100 persons-years of follow-up, respectively). However, in this study, SNAES may have been underreported because only those SNAEs requiring hospital admission were recorded. Furthermore, the study's analyses were not adjusted for smoking, hypertension, renal function or lipid levels, hence the level of risk of SNAEs in relation to the CD4⁺ T-cell nadir may have been lower than reported [47].

HIV-associated neurocognitive disorders

Primary HIV infection is associated with an inflammatory response in the central nervous system [48], but whether early ART attenuates this response or reduces the risk of HIV-associated neurological disease is unknown. In a study on patients re/commencing ART with CD4⁺ T-cell counts less than 200 cells/μl, elevated cerebrospinal fluid neopterin levels persisted in 41% of neurologically asymptomatic patients after a median of 84.7 months of virologically suppressive ART, suggesting that ART initiated in patients with low CD4⁺ T-cell counts does not fully mitigate HIV-associated inflammation in the central nervous system [49■■■].

Non-AIDS defining cancers

In a cohort of 11 485 HIV-infected patients in the USA, whose median CD4⁺ T-cell count at ART initiation was 202 cells/μl [interquartile range 61–338], the incidence of AIDS-defining and non-AIDS-defining cancers (NADC) was similar and that the commonest overall NADC was anal cancer (69 per 100 000 person-years) and in women, breast cancer (128 per 100 000 person-years) [50]. The incidence of liver cancer was 37 per 100 000 person-years. A lower CD4⁺ T-cell count at the time of ART initiation was associated with an increased risk of all cancers except the nonlymphoma and non-human papillomavirus NADCs. These findings suggest that the risk of NADC was not reflected by a single measure of immunity, the CD4⁺ T-cell count. A functional marker of immune dysfunction, such as lower CD4:CD8 ratio, has also been associated with increased risk of NADCs [17■■■]. Taken together, these data suggest that CD4⁺ T-cell count alone at ART initiation may not fully predict the risk of NADCs and further work is needed to determine the impact of early ART on long-term risk of NADCs.

CONCLUSION

There are multiple observational nonrandomized studies showing that early ART can significantly reduce multiple markers of both adaptive and innate immune activation, microbial translocation and systemic inflammation, as well as markers of virus persistence, although timing of ART initiation and duration of ART are important factors. Long-term, large randomized studies are still needed to determine whether there are significant benefits on the risk of SNAEs and end-organ damage with early treatment over and above treatment at higher CD4⁺ T-cell counts. Given the logistic difficulties of identifying early HIV infection, it will be important to determine whether there really is an added benefit of early or very early ART. With the widespread uptake of regular testing and ‘test and treat’ strategies in many countries now, long-term cohort studies of early ART with clinical outcome data may potentially answer these important questions.

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KEY POINTS

- Early ART is associated with a clear decline in markers of T-cell activation, but the impact on markers of innate immune activation, microbial translocation, systemic inflammation and coagulation need to be confirmed in larger studies that specifically compare early and delayed ART.
- ART within days as compared to weeks or months is associated with reduced frequency of latently infected cells, but it remains unclear whether this is a consequence of any beneficial effects of lower levels of immune activation.
- In some cohort studies, early ART was associated with a decreased risk of SNAEs and related mortality and improved normalization of the CD4 : CD8 ratio, but longer prospective studies with clinical endpoints are still needed to determine the benefits of early ART.

FIGURE 1.

Potential mechanisms driving interactions between immune activation and virus persistence on ART. Early ART leads to reduction in activated CD4⁺ T cells, enhanced CD4⁺ T-cell recovery and reduced tissue damage that may potentially contribute to reduced virus persistence on ART. ART, antiretroviral therapy; IL7, interleukin 7; TNF- α , tumor necrosis factor- α .

Table 1
Changes in immune activation, inflammation and the HIV reservoir in blood and tissue following early ART (within 1 year of HIV infection)

Study design	Time of ART following infection				Microbial translocation		Immune activation			Inflammation and coagulation					Functional markers					
Reference	Sample size, <i>n</i>	Duration on ART	Viral reservoir ^a	EndoCAb, 16S rDNA, peptidoglycan	I-FABP	IFN-α	sCD14	sCD163	Neopterin	IP-10	%CD14 ⁺ CD16 ⁺	CD38 ⁺ HLA-DR ⁺	Ki-67 on T cells	TNF-α	IL-6	Hs-CRP	D-dimer	CD4:CD8 ratio	%Th17 cells	K _{ym} /Trp ratio
Blood																				
[11]	<i>n</i> =14	<12 months		↔			↑	↘			↓	↑								
[12■]	<i>n</i> =66	<6 months vs. >2 years	More ↓ in early vs. late									↑								
[13■■■]	<i>n</i> =35	<2 months vs. >2 years	More ↓ in early vs. late															↑		
[14■]	<i>n</i> =31	<43 days										↓								
[15]	<i>n</i> =307	<4 months vs. CHI	More ↓ in early vs. late															↑		
[16]	<i>n</i> =10	<42 days		↔	↑		↔					↘						↑	↔	
[17■■■]	<i>n</i> =68	<6 months vs. >2 years																↑		
[18■■■]	<i>n</i> =15	Fiebig stages I–IV	↓ But higher than EC	↔		↓	↔			↓						↔	↓			
[19■]	<i>n</i> =34	<45 days	↓				↘					↘								
[20]	<i>n</i> =47	Fiebig stages I to III	↓																	
[21]	<i>n</i> =17	<12 months	Not stated									↘								↘
Tissue																				
[22]	<i>n</i> =38	Fiebig stage I–III										↔ in I, II, ↓ in FIII	↔ in I, II, ↓ in FIII						↔ in I, II, ↓ in FIII	
[23]	<i>n</i> =30	Fiebig stage I–V											↘	↘						

[↓] decrease to levels in HIV-uninfected controls, ART, antiretroviral therapy; CHI, chronic HIV infection; EC, elite controllers; EndoCAb, endotoxin core antibody; F, Fiebig; GI, gastrointestinal; I-FABP, intestinal fatty acid-binding proteins; IFN, interferon; Hs-CRP, highly sensitive C-reactive protein; IL-6, interleukin-6; IP-10, interferon gamma-induced protein 10; Kyn/Trp, kynurenine/tryptophan; LPS, lipopolysaccharide; rDNA, ribosomal DNA; SC, seroconversion; TNF-tumor necrosis factor, Th, T helper.

^a Viral reservoirs measured by cell associated total or integrated HIV DNA, cell-associated HIV RNA or infectious units per million resting CD4 T cells.