HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2021 May 01; 16(3): 168–176. doi:10.1097/COH.0000000000000678.

CMV and Persistent Immune Activation in HIV

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Abstract

Purpose of review: Despite antiretroviral therapy (ART)-mediated viral suppression, people with HIV (PWH) have increased morbidity and mortality. Immune activation and inflammation persist on antiretroviral therapy and predicts these complications. Over 90% of PWH have cytomegalovirus (CMV) co-infection, and CMV is considered a plausible contributor to this persistent immune activation.

Recent findings: A detailed understanding of the link between CMV and multimorbidity is needed, particularly as research moves toward identifying potential targeted therapeutics to attenuate inflammation-mediated morbidity and mortality in treated HIV. We review the literature on the association between CMV and immune activation as well as multiple end-organ complications including cardiovascular disease, venous thromboembolic disease, metabolic complications, gastrointestinal dysfunction, central nervous system involvement, birth sex-related differences, and the relation to the HIV reservoir. We conclude with a discussion of ongoing therapeutic efforts to target CMV.

Summary: As CMV is a plausible driver of multiple comorbidities through persistent immune activation in treated HIV, future research is needed and planned to address its causal role as well as to test novel therapeutics in this setting.

Keywords

CMV; inflammation; immune activation; cardiovascular disease; letermovir

Introduction

Among viruses, cytomegalovirus (CMV) has one of the most dynamic and comprehensive interactions with the human immune system. CMV elicits and maintains a high frequency of CMV-specific T cells – nearly 10% of the entire memory T cell repertoire - that are engaged in a lifelong effort to restrict CMV replication and prevent life-threatening disease [1–3]. As people age with CMV, repeated immune activation and response to CMV can drive T cells toward a more differentiated and senescent phenotype [4–6]. Senescent T cells are enriched for CMV-specific cells, and the abundance of senescent T cells has been associated with negative outcomes in older adults including frailty, cardiovascular disease, and systemic infections [7–13]. These inflammatory effector CD8+ T cells typically migrate to tissues

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where they—along with low-level CMV replication itself—may contribute to local inflammation and chronic disease. A recent review has addressed CMV and immune dysfunction, particularly with CMV's interaction with human immunodeficiency virus (HIV) as a coinfection, which is further relevant given co-infection prevalence in HIV over 90% [14]. This review will focus on the various end-organ disease manifestations associated with CMV in treated HIV, as well as prior and ongoing interventional approaches aimed at CMV as one of the putative drivers of persistent immune activation.

CMV and Immune Activation

Asymptomatic CMV replication is induced by inflammation *in vivo*. It has long been recognized that inflammation can trigger lytic CMV replication in latently CMV-infected myeloid cells. Inflammatory signaling through TNFα receptors in latently CMV-infected myeloid cells activates the NF-κB pathway, which in turn binds to the immediate early enhancer region of CMV, initiating virus transcription [15, 16]. This phenomenon appears to explain why CMV DNA, which is typically undetectable in the peripheral blood in immunocompetent CMV-seropositive individuals, becomes detectable in inflammatory states such as sepsis, myocardial infarction, and even atopic dermatitis [15, 17–21]. That said, asymptomatic CMV replication is also a cause of systemic inflammation *in vivo*. Even asymptomatic CMV infection in immunocompetent adults is associated with measurable increases in systemic inflammation [22]. One study in critically ill HIV-negative CMV-seropositive participants with sepsis and acute respiratory distress syndrome found that while ganciclovir therapy improved oxygenation and shortened the time requiring mechanical ventilation, even though it failed to significantly reduce plasma IL-6 levels (though this may not have been the most appropriate biomarker to reflect CMV-induced inflammation) [23]. In the context of treated HIV, CMV seropositive adults also have higher markers of inflammation, greater CD8+ T cell expansion, and lower CD4+/CD8+ T cell ratios than CMV-seronegative adults [23–29]. We also previously assessed the contribution of asymptomatic CMV replication to systemic inflammation in a randomized placebo-controlled trial of valganciclovir in asymptomatic CMV-seropositive people with HIV (PWH) with incomplete CD4+ T cell recovery on antiretroviral therapy (ART) [30]. The trial showed a reduction in T cell immune activation in those randomized to valganciclovir after 8 weeks of therapy that was sustained for 4 weeks following treatment cessation. Recent analysis of samples from this trial further revealed nearly an entire quartile reduction in sTNFR2 as well as significant reductions in sCD163 and sCD14 levels in the valganciclovir arm [31, 32].

CMV and Cardiovascular Disease

CMV may play a modest role in cardiovascular disease (CVD) in the general population but is likely to play a far greater role in immunocompromised populations, including those with HIV. Mechanistically, CMV can replicate in macrophages and endothelial and smooth muscle cells within the vasculature, attracting inflammatory CX3CR1+ T cells and monocytes, which may all contribute to atherogenesis [24, 33]. Indeed, activated CD8+ T cells may promote not just atherosclerosis, but also monocyte tissue factor expression and coagulation via a TNF-dependent mechanism in non-human primate models of HIV

infection [34]. In the general population, 82% of atherosclerotic plaques obtained from HIV-uninfected individuals undergoing endarterectomy had detectable CMV DNA [18, 35]. Observational data also suggest a modest role of CMV in increasing CVD risk in the general population; a recent meta-analysis including nearly 35,000 participants reported that CMV serostatus was associated with a 1.22-fold increased risk of incident CVD after adjustment for traditional risk factors [36]. A more recently published meta-analysis of 5 European cohorts did not find CMV to be associated with all-cause or cardiovascular mortality and more limited evidence of higher CMV IgG quartile as associated with all-cause mortality compared to seronegative controls [37].

The evidence for a role of CMV in contributing to vascular disease in immunocompromised populations – particularly those with T cell defects - is much stronger. In one clinical trial, just 28 days of ganciclovir appeared to cause a 2-fold decreased risk of post-transplant atherosclerosis 48 weeks after heart transplantation [38]. While associated with more subtle degrees of immunodeficiency than solid organ transplantation, treated HIV infection is associated with extremely high CMV prevalence (>90%) and much higher levels of mucosal CMV shedding than in HIV-uninfected CMV-seropositive individuals [39, 40]. Higher levels of CMV-specific CD8+ T cells and CMV-specific IgG are associated with atherosclerosis in treated HIV infection [11, 41, 42]. In fact, after adjusting for CMV-specific CD8+ T cell frequencies, HIV-infected participants no longer had greater atherosclerosis (by carotid intima-media thickness) than HIV-uninfected individuals, an early clue that CMV may mediate the increased CVD risk in HIV infection [42]. ART-suppressed CMV-seropositive PWH also had a 2.3-fold higher incidence of cardiovascular events than CMV-seronegative PWH in the ICONA cohort [43]. Recent work has demonstrated that not just CMV serostatus, but CMV IgG titer is associated with type 1 and type 2 myocardial infarction (MI), with a stepwise increase in hazard by IgG quartile [44]. It is also important to note that valganciclovir-mediated suppression of asymptomatic CMV replication (and potentially other herpesviruses) in our recent clinical trial of PWH with incomplete CD4+ T cell recovery also decreased inflammatory biomarkers that strongly predict MI and arterial inflammation by FDG-PET/CT in other studies of ART-suppressed PWH (i.e., sTNFR2, sCD163, and sICAM-1) [31, 45–48].

CMV and Venous Thromboembolic Disease

CMV also stimulates thrombogenic activity on cells independent of vascular damage as well as cell-independent thrombin production, converting resting cells from an anticoagulant to a procoagulant state via factor Xa generation [9, 49–51]. This may plausibly lead to a higher risk of venous thromboembolism (VTE) in treated HIV. In one published study on predictors of VTE in HIV addressing CMV, a prior history of CMV end-organ disease and CMV viremia were strong predictors of subsequent VTE in participants with AIDS on suppressive ART [52]. In our more recent case-cohort study of ART-suppressed PWH, CMV IgG titer was associated with incident VTE, with a stepwise increase in hazard by IgG quartile similar to MI above [44].

CMV and Metabolic Complications

CMV may also plausibly contribute to adipose tissue inflammation and fibrosis, insulin resistance, and visceral obesity. Type 2 diabetes (T2DM) is one of the most frequently occurring comorbidities in treated HIV infection, occurring at a rate of approximately one case for every 100 person-years in the NA-ACCORD cohort [53], much higher than the adult population without HIV [54–57]. Several mechanistic studies in animal models suggest a causal role of CMV in contributing to these complications: in both murine and non-human primate models, CMV infects adipose tissue and induces inflammatory and fibrotic responses and insulin resistance [58–62]. CMV is also known to preferentially replicate in adipose tissue in humans [63]. Inflammation in adipose tissue and the resultant fibrosis restricts adipocyte growth, preventing these cells from accumulating lipid during states of nutrient excess; consequently, lipids that should be stored in subcutaneous fat stores are forced into visceral adipose tissue, the liver, and epicardium—all harbingers of insulin resistance and the metabolic syndrome [64]. Less is known about the causal role of CMV in insulin resistance and visceral adiposity in humans. A recent meta-analysis including over 1,300 kidney transplant recipients found CMV infection carried a nearly 2-fold increased risk of post-transplant new-onset diabetes [65]. CMV has also been associated with metabolic syndrome in otherwise healthy normal weight women [66]. The plasma inflammatory markers that most strongly predict incident diabetes in treated HIV (sTNFR1, sTNFR2, sCD163) are also the same markers that were profoundly suppressed by treating asymptomatic CMV replication in our prior valganciclovir trial [30]. In a recent adipose tissue sampling study among people with treated HIV and CMV co-infection, a striking infiltration of subcutaneous fat by terminally differentiated effector T cells expressing CX3CR1+ and GPR56+, two markers frequently seen on CMV-specific T cells, was observed [67]. These cells tend to express a highly cytotoxic and proinflammatory transcriptome. While more data is needed to link CMV to these metabolic complications in PWH, these studies suggest that CMV may plausibly be associated with multiple metabolic complications in this setting.

CMV and Gut Dysfunction

The GI tract is a major site of CMV disease in immunocompromised individuals, including those with HIV. While CMV esophagitis and colitis are more common manifestations in those profoundly immunosuppressed, even asymptomatic CMV replication may contribute to microbial translocation across a leaky gut barrier, leading to other end-organ dysfunction [27]. CMV targets endothelial, stromal, and intestinal epithelial cells, weakening intercellular tight junctions that maintain barrier function. CMV persistence in rectosigmoid tissues of asymptomatic CMV seropositive individuals with both untreated and ART-suppressed HIV has been associated with gut epithelial barrier dysfunction [68]. In fact, in model systems independent of HIV, CMV disrupted tight junctions of polarized epithelial cells, enhancing barrier permeability and leading to immune cell infiltration [68]. Activated immune cells accelerate further disruption of the intestinal barrier, leading to persistent inflammation in the gut of ART-suppressed PWH [27, 69, 70]. This effect was mediated in part by CMV-induced inflammation and letermovir, an anti-CMV-specific drug, preserved barrier function [68]. In other observational studies, CMV seropositivity is strongly

associated with circulating markers of microbial translocation, which have been linked to end-organ dysfunction [27]. Intriguingly, although CMV infection elicits a large and expanding pool of CMV-specific CD4+ and CD8+ T cells, CMV-specific CD8+ T cells appear to be quite rare in colorectal mucosa [5, 71]. The basis for the failure of CMV-specific T cells to traffic to the gut is unclear, but their near-absence or dysfunction likely contributes to CMV persistence and its associated systemic immune activation in this setting.

CMV and the Central Nervous System

The central nervous system (CNS) is a long-recognized site of CMV end-organ disease in advanced AIDS (e.g., retinitis, periventriculitis). CMV may also be relevant to CNS disease in the general population. CMV-infected individuals in the early stages of multiple sclerosis showed greater generalized brain atrophy over time than CMV-negative participants [72]. CMV may also play a role in psychiatric diseases like depression and sleep disturbance [73], and several earlier studies have linked psychological stress to CMV reactivation [74–79]. In people with HIV, higher anti-CMV IgG titer was associated with greater neurocognitive impairment, similar to findings in HIV-uninfected elderly individuals [80–83]. CMV DNA was detected in several cerebrospinal fluid (CSF) samples in the small, cross-sectional HIV study, but the role for migrating CMV-specific CD8+ T cells or low-level CMV replication in the brain has not been excluded. Additionally, higher plasma anti-CMV IgG concentrations were associated with higher HIV RNA and sCD163 in the CSF, indicating that the CMV-related immune response at least indirectly influences pathologic events in the CNS, perhaps driven by migration of activated monocytes or infected CD4 T-cells into this compartment. Some additional data from PWH has linked the immune activation pathways thought to be driven by CMV to depression in HIV [84]. Even in the absence of advanced immune suppression, mental health complications such as depression and neurocognitive impairment still occur more commonly in PWH than in the general population and seem to be less responsive to standard therapy [67, 85–88]. Further work is needed to determine whether inhibiting low-level CMV shedding improves neuroinflammation, neuronal injury, neurocognitive performance, and mood.

CMV and Frailty

In addition to the above neurocognitive effects associated with CMV, chronic CMV infection has also been associated with frailty, in part through greater CMV-associated inflammation [89–91]. Even with long-term effective ART, impairments in physical function and frailty are more common than expected among people aging with HIV and have been associated with an increased risk of falls, hospitalizations, and mortality [92–94]. Furthermore, the combination of both HIV infection and impaired physical function is associated with a greater risk of mortality than the presence of HIV infection or impaired function alone [95, 96]. CMV seropositivity, as measured by qualitative or quantitative CMV IgG titers or CMV-associated T-cell responses have been associated with frailty in the general geriatric population, and frailty and physical function impairment in PWH [89–91, 97].

Sex Differences in Asymptomatic CMV Infection

Women tend to have more robust innate immune responses to viral infections, with increased type I interferon production related to the X-chromosome's TLR7 [98, 99]. Little is known about sex differences related to CMV in particular. Two US-based studies in women with HIV demonstrated relatively low levels of detection of CMV DNA in cervicovaginal lavage (3–7%) compared to men, but those rates have varied in studies outside the US [100–103]. Women with ART-suppressed HIV have been found to have lower levels of CMV DNA (from oral, vaginal, or urine samples) compared to ART-suppressed men who have sex with men (in oral or semen samples) but without associated differences in cellular HIV DNA [104]. In a more recent study, women were observed to have significantly higher plasma CMV IgG titer compared to men after multivariate adjustment [44]. We do not know whether higher CMV IgG titers reflect a greater burden of CMV replication in tissues or a greater inflammatory response to it, but it is likely that there are clinically relevant sex-based differences in CMV and subsequent immune activation.

CMV and the HIV Reservoir

Chronic inflammation and immune activation contribute to maintenance of the HIV reservoir during ART [105, 106]. Recent studies have demonstrated that asymptomatic CMV seminal shedding is associated with higher levels of total HIV DNA in both ART-naïve individuals and in individuals suppressed on long-term ART [26, 107]. In a large longitudinal study of individuals followed since the earliest phase of HIV infection, CD4+ T cell associated HIV DNA in blood was associated with the frequency of detectable CMV DNA in blood cells over time [108]. A recent study has even linked subclinical CMV shedding measured in peripheral blood mononuclear cells to increasing molecular diversity of the HIV DNA reservoir [109]. Although the observational design of these studies does not allow causal inference, the findings do support the possibility that asymptomatic CMV replication drives local and systemic immune activation with a subsequent maintenance or increase in the latent HIV reservoir. Targeting drivers of chronic inflammation like CMV could thus potentially contribute to HIV curative strategies.

Therapeutic Approaches to Asymptomatic CMV Infection

Given the growing evidence for CMV as a plausible driver of persistent immune activation and associated end-organ disease, particularly in treated HIV, multiple therapeutic approaches to treat asymptomatic CMV infection are being evaluated in this setting. One prior trial to date has assessed the causal role of asymptomatic CMV infection in systemic inflammation in treated HIV [30]. In this study of treated PWH with incomplete CD4 recovery (all CD4 <350), participants (n=30) randomized to valganciclovir for 8 weeks were observed to have a nearly entire quartile reduction in sTNFR2 and significant reductions in sCD163 and sCD14 compared to placebo [30, 31]. Moreover, administration of valganciclovir led to a sustained reduction in CMV shedding after just 8 weeks that persisted for at least 4 weeks after discontinuation. Despite these findings, the study was limited in that only 70% of the participants had HIV RNA suppression on ART (though there was a significant effect on immune activation even in the ART-suppressed subset) and the sample

size was small. There were several limitations that precluded moving forward with clinical endpoint trials of valganciclovir in this setting. First, valganciclovir's toxicity (cytopenias and teratogenicity) creates challenges for long-term use. Second, insufficient evidence was generated to definitively conclude that key inflammatory pathways that predict disease outcome or cardiovascular surrogate markers were affected. The trial's short 8-week duration also limited the analysis of longer-lived T cell subsets like effector and senescent T cells. TEMRA CD8+ T cells appear quite long-lived in simian immunodeficiency virus models using similar direct measures of cellular turnover [110, 111]. Thus, many months of suppression of CMV replication may be required to stop or reverse the negative contribution of CMV-specific effector CD8+ T cells to end-organ disease. Additionally, the trial was limited to individuals with incomplete CD4+ T cell recovery on ART, and it remains unclear whether inhibiting CMV shedding would benefit immune activation in individuals with normal CD4+ T cell count recovery on ART. Lastly, there were very few female participants in the trial, and as the effects of chronic viral infections on the immune system likely differ by sex with recent evidence revealing significantly higher CMV IgG titer in women after multivariate adjustment, it is unclear whether treating CMV would have the same effect in women [44].

The above issues have been specifically addressed in the forthcoming ACTG trial (A5383) of letermovir, a CMV DNA terminase complex inhibitor that is FDA-approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of allogeneic hematopoietic stem cell transplant (HSCT) [68, 112, 113]. Letermovir demonstrated significant benefit compared to placebo in regard to clinically significant CMV disease through week 24 post-HSCT (18.9% vs 44.3% cumulative rate, stratified log-rank $p<0.001$). Letermovir also has a better safety profile than valganciclovir from this existing data, and fewer adverse events in the letermovir arm were observed versus placebo in the trial among HSCT recipients. In a pending phase II, double-blind, randomized, placebo-controlled multicenter US trial, total of 180 participants 40 years and older with ART-mediated viral suppression for at least 4 years and who meet eligibility criteria will be randomized to receive letermovir or placebo for 48 weeks, followed by 12 weeks of observation on ART alone. Randomization will be stratified by CD4 count (<350 and >350) to allow for a more direct comparison to the earlier valganciclovir trial and to explore whether there may be a role for CMV suppression to reduce immune activation not just among those with incomplete CD4 T cell recovery, but also among those with preserved CD4 T cell counts. Participants will also be stratified by sex since sex differences in immune response to viral infections have been described. The primary outcome for this trial is a reduction in sTNFR2 with secondary outcomes related to drug tolerability, reduction in CMV mucosal shedding, and reduction in sCD163. Multiple sub-studies are planned to include measures of the proviral HIV reservoir, proteomics, adipose tissue aspiration, FDG-PET/CT assessment of arterial inflammation, lumbar puncture for markers of neuronal injury, and neurocognitive assessments.

A trial of a therapeutic CMV vaccine will also start soon in the ACTG to characterize the safety and immunogenicity of a modified vaccinia Ankara-based anti-CMV vaccine (A5355) [114]. A total of 90 participants will be randomized in a 2:1 ratio to receive either two injections of the trial vaccine or placebo at trial entry and at week 4. Eligibility criteria

includes adults ages 18–65 years with both HIV and asymptomatic CMV co-infection who are ART-suppressed with current and nadir CD4 T cell counts >250 and >100, respectively. Primary endpoints will include cellular immunogenicity (anti-CMV CD8+ T cell responses between entry and study week 12) and week 48 plasma sTNFR2, with the hypothesis that the vaccine will stimulate B cell and T cell responses to generate a CMV-specific immune response that will decrease sub-clinical shedding, and thus lead to lower levels of systemic immune activation. Other cellular biomarkers will also be assessed.

Conclusion

CMV has learned to adapt to evade the human immune system, and while it may have modest or minimal clinical implications in the general population, it has been found to be significantly associated with numerous end-organ disease manifestations in those with varying degrees of immunosuppression. While more work is needed to link serum markers of CMV infection with the true burden of CMV disease in site-specific tissues, varying measures of CMV (serostatus, IgG titer, specific T cells, etc.) have been associated with numerous end-organ disease manifestations in PWH despite ART-mediated viral suppression, including cardiovascular disease, VTE, gastrointestinal and metabolic dysfunction, neurocognitive impairment, and other CNS disease. The one randomized trial to date assessing the causal role for CMV in persistent immune activation found evidence that treating CMV co-infection may lead to reduced levels of inflammation. Given this trial's design and participant recruitment, more questions remain about the possibility of differential effects by sex as well as by degree of immune recovery. With this trial and the growing evidence base supporting CMV's role as a putative driver in inflammation and end-organ disease in PWH, future trials are planned to more definitively assess this relationship as well as guide the development of pragmatic surrogate clinical endpoints, given CMV's manifold effects. Finally, given the findings of CMV's impact in the immunosuppressed population with more significant T cell immunodeficiency than treated HIV, these ongoing studies will be broadly pertinent to the solid organ transplant setting as well.

Acknowledgements

Financial support and sponsorship

This study was supported by the following NIH grants: R38HL143581 (SRS), R01HL152957 (PWH), K24 AI145806 (PWH), R01 HL128156 (PWH), R01DK112304 (PWH), and P30 AI027763 (PWH).

Conflicts of interest

SRS has no conflicts of interest. PWH has received research funding from Gilead Sciences, honoraria from Gilead, Viiv, and Janssen, and consulting fees from Biotron and Viiv.

Abbreviations:

CMV	cytomegalovirus
HIV	human immunodeficiency virus
PWH	people with HIV

ART	antiretroviral therapy
CVD	cardiovascular disease
MI	myocardial infarction
VTE	venous thromboembolism
T2DM	type 2 diabetes mellitus
CNS	central nervous system
CSF	cerebrospinal fluid
HSCT	hematopoietic stem cell transplant

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Key Points

- While antiretroviral therapy reduces morbidity and mortality in people with HIV, they face elevated rates of multiple comorbidities due at least in part to systemic inflammation.
- CMV is a plausible root driver of persistent immune activation and inflammation in treated HIV.
- Asymptomatic CMV infection in treated HIV is associated with numerous end-organ diseases, including cardiovascular disease, VTE, gastrointestinal and metabolic dysfunction, and neurocognitive impairment.
- Only one trial to date of valganciclovir has assessed the causal role of asymptomatic CMV infection in treated HIV but was limited by drug toxicity, limited duration of treatment, and limited enrollment of key subgroups.
- Future trials are planned to assess the causal role of asymptomatic CMV infection in treated HIV and to test novel oral and vaccine therapeutics in this setting.