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Cytomegalovirus and HIV: A Dangerous Pas de Deux

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Human immunodeficiency virus (HIV)–infected adults who take stable antiretroviral therapy (ART) are at risk for early onset of age-related diseases. This is likely due to a complex interaction between traditional risk factors, HIV infection itself, and other factors, such as underlying immune dysfunction and persistent inflammation. HIV disrupts the balance between the host and coinfecting microbes, worsening control of these potential pathogens. For example, HIV-infected adults are more likely than the general population to have subclinical bursts of cytomegalovirus (CMV) replication at mucosal sites. Production of antigens can activate the immune system and stimulate HIV replication, and it could contribute to the pathogenesis of adverse outcomes of aging, like cardiovascular disease and neurocognitive impairment. Further investigation of the relationships between CMV, immune dysfunction, and unsuccessful aging during chronic HIV infection is warranted.

Keywords. HIV; inflammation; immune dysfunction; cytomegalovirus; aging; end organ disease.

Antiretroviral therapy (ART) improves health, prolongs life, and reduces the risk of human immunodeficiency virus (HIV) transmission [1]. Nevertheless, adult ART recipients living with HIV have greater morbidity and mortality than the general population [2]. Morbidities include metabolic and vascular disorders, frailty, malignancies, and neurocognitive impairment, which have been linked in part to persistent inflammation during long-term suppressive ART [3]. Multiple mechanisms underlie the persistent inflammation, including coinfection with cytomegalovirus (CMV) and other human herpesviruses (HHVs) that lead to immune dysregulation and senescence [4, 5].

As HIV-infected adults age into their sixth decade and beyond, better understanding and management of aging-associated morbidities is an urgent priority in HIV research and clinical care. Successful aging is a multidimensional concept encompassing the avoidance of disease and disability, maintenance of high physical and cognitive function, and sustained engagement in social and productive activities [6]. Research has identified factors predictive of successful aging for HIV-infected and uninfected individuals [7–11]. Here, we review the existing literature on how CMV influences the course of HIV disease, and we summarize steps that may influence disease outcomes in adults aging with HIV disease, particularly those related to cardiovascular and neurocognitive complications.

EPIDEMIOLOGY AND PATHOGENESIS OF CMV

Human CMV is a member of the β-herpesvirus family and is common worldwide, particularly among those who have receptive sexual intercourse (women and men who have sex with men) [12, 13] or are of low socioeconomic status [13]. Primary CMV infection elicits robust innate and adaptive immune responses and can cause a febrile mononucleosis and hepatitis but is subclinical for most healthy individuals [14]. Reactivation can cause life-threatening complications in immunocompromised hosts [15]. The most common manifestation in HIV-infected subjects with advanced disease is CMV retinitis, which accounted for 85% of all CMV complications, leading to blindness in many patients [15]. Gastrointestinal tract manifestations accounted for 10% of CMV disease in AIDS patients, followed by neurological disorders, pneumonitis, hepatitis, and adrenalitis [15]. The introduction of combination ART in 1995–1996 substantially reduced the incidence of AIDS-related, CMV-associated end-organ diseases [15]. CMV still contributes to morbidity and mortality in patients who initiate ART with low $CD4^+$ T-cell counts, occasionally as a result of immune reconstitution inflammatory syndrome [16].

Many adults are initially infected with CMV during childhood or early adulthood, although the incidence continues to rise throughout adulthood, by approximately 1% annually [17]. About 70% of adults under good socioeconomic conditions and 90% under poor conditions become infected with CMV [13]. Following primary infection, the virus persists in a true latent form or in a state of low-level replication made possible by multiple immune evasion mechanisms [18, 19]. Latent CMV can reactivate in response to inflammatory stimuli and other physiologic stressors, releasing intact virions that can infect new cells, including cells in the central nervous system (CNS) [20–23] and the vascular endothelium [24, 25]. Such episodic bursts of CMV replication are typically asymptomatic, appear to occur repeatedly at unpredictable intervals, and are self-limited [13]. Subclinical shedding of CMV has been described in genital secretions, saliva, urine, blood, stool, and breast milk [13]. The frequency of CMV shedding at mucosal sites varies and is dependent on the geographical location, cohort characteristics, and detection methods [19].

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When the immune system is compromised, CMV shedding can increase dramatically. We recently showed that nearly all sexually active HIV-infected men who have sex with men (94%) in southern California have detectable DNA from ≥1 HHV over 48 weeks [26]. The most common virus was CMV (85%), followed by Epstein-Barr virus (EBV; 81%), HHV-7 (35%), HHV-6 (29%), HHV-8 (26%), and herpes simplex viruses (HSVs; 23%) [26]. Viral shedding was associated with younger age but not with $CD4^+$ T-cell count, HIV RNA levels, duration of HIV infection, or ART use. Less is known about CMV shedding in HIV-infected women. One recent study measured vaginal shedding of CMV DNA longitudinally in Uganda [27]. Vaginal CMV was detected in over three quarters (78%) at ≥1 assessment and was the highest shortly after ART initiation, which may occur because immune reconstitution increases the number of target cells for CMV.

Such asymptomatic CMV shedding is important for the horizontal transmission and for the interplay between CMV, reactivation of other viruses, differentiation of naive T cells, and monocyte/macrophage activation.

CMV AND THE HOST IMMUNE SYSTEM

Like other viruses causing chronic infection, CMV coevolved with its host over millennia, developing complex strategies to allow viral persistence and facilitate transmission [13]. CMV is one of the largest and most immunogenic viruses to infect humans [28]. A recent study using ribosome profiling and transcript analysis demonstrated that 751 unique viral messenger RNAs are translated in CMV-infected fibroblasts, suggesting an even more complex biology than previously recognized [28]. Many CMV-encoded proteins are not essential for viral replication but allow the virus to avoid immune recognition, protecting infected cells from destruction by host defenses [19]. As part of this complex host-virus relationship, CMV stimulates and maintains a high frequency of virus-specific T cells that work to control CMV replication and prevent life-threatening end-organ complications [29]. CMV-specific T cells can comprise upward of 50% of circulating $CD8^+$ T cells and 30% of $CD4^+$ T cells in HIV-uninfected donors [29], proportions that are higher in HIV-infected adults [30, 31]. Epitopes recognized by these T cells are present for CMV proteins expressed at all stages of the viral replication cycle [29], consistent with repeated exposure of the host immune response to viral antigens. While some individuals also develop clonal expansion against EBV, this is much smaller in size [32]. CMV appears to be unique among chronic viral infections in its profound effect on the T-cell repertoire [33]. Two reasons for this may be its ability to upregulate the expression of several inflammatory mediators [34–37] while encoding its own cytokine and cytokine receptor homologs, allowing it to create an environment that favors its persistence and transmission [34, 38, 39].

CMV's effects in immune-competent hosts seem to be age dependent. The effects of CMV infection on host immunity are not always deleterious, and CMV might have a beneficial effect on the immune system by providing immune protection against other pathogens (so-called heterologous immunity [40]) in younger healthy people. This could explain why humans (and many other species) tolerate the very high prevalence of this infection, and it is consistent with the notion of antagonistic pleiotropy [41–43]. Certain biological features can be selected as favorable during youth but become harmful with age (ie, during a stage of life that is neutral in terms of evolutionary selection) [44]. Improved survival over the past century has revealed a set of CMV-associated changes in the aging immune system that might be associated with multiple disorders, including cardiovascular disease and neurodegenerative disorders.

CMV, IMMUNOSENESCENCE, AND AGING

The progressive expansion of the T-cell repertoire committed to CMV (referred to as CMV-specific $CD8^+$ T-cell memory inflation [29]) can deplete naive T cells and is associated with the immune risk phenotype in the general population [45]. The immune risk phenotype includes expansion of late-differentiated $CD8^+$ T cells and an inverted $CD4^+/CD8^+$ T-cell ratio; is a strong predictor of mortality; and is rarely seen in centenarians [46]. The predominant senescent phenotype of CMV-specific $CD8^+$ T cells ($CD28^-CD57^+$) has altered function, including poor proliferative response and relative resistance to apoptosis, which can in turn lead to adverse clinical outcomes [47]. The accumulation of peripheral T cells lacking CD28 contributes to inflammation and aging by producing large amounts of interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin 1β, and interleukin 6 (IL-6) upon antigenic stimulation [48]. CMV infection together with elevated IL-6 dramatically increases the risk for frailty, a state associated with increased morbidity and mortality in older adults [49, 50]. CMV infection may also be important for telomere and telomerase dynamics, by increasing the number of highly differentiated T cells with shorter telomeres and decreased telomerase activity [51]. Aging and chronic inflammatory conditions are associated with oxidative stress, which may increase CMV reactivation [52]. In turn, CMV replication can increase oxidative stress [53, 54], setting up a possible positive feedback loop. Taken together, there is strong evidence that CMV is implicated in immunosenescence and aging [55, 56], but this is still a very dynamic topic, and the exact clinical implications remain to be defined.

HIV VERSUS CMV

HIV-infected individuals are almost universally coinfected with CMV [13], and both viral infections are associated with inflammation and aging [44]. CMV seems to exert a more dramatic effect than HIV (in HIV RNA–suppressed individuals) and might be the so-called "smoking gun" of immunosenescence among coinfected persons [57–59]. The main differential effect between CMV and HIV seems to be their impact on $CD8^+$ T cells [33]. A recent study found elevated numbers of $CD8^+$ T cells and a low $CD4^+/CD8^+$ T-cell ratio in individuals coinfected with

both viruses but not in persons infected with HIV alone or CMV alone [60]. Along the same line, HIV-infected individuals who are seronegative for CMV show greater resilience and better immune recovery following ART [61]. HIV infection seems to also exert a distinct effect on the $CD8^+$ T-cell phenotype. Unlike CMV and aging, which are associated with terminal differentiation and proliferation of effector memory $CD8^+$ T cells, HIV inhibits this process, expanding less well-differentiated $CD28^-CD8^+$ T cells and decreasing the proportion of $CD28^-CD8^+$ T cells that express CD57 [62, 63].

CMV is well known to induce high levels of multiple cytokines (particularly IFN-γ) [64], which seem to be much higher and broader than that induced by HIV in vitro (Dr Rachel Schrier, unpublished observation). Blood plasma levels of IFN-γ–inducible protein 10, TNF-RII, and D-dimer are higher in people coinfected with CMV and HIV as compared to those in HIV-monoinfected subjects, suggesting that CMV might specifically drive expression of these biomarkers [65]. No difference was observed for IL-6, interleukin 18, or soluble CD14 between the 2 groups (ie, HIV-monoinfected versus HIV/CMV-co-infected) [65]. While the complex effects of CMV and HIV on immunosenescence continue to be untangled, existing findings implicate CMV as an important contributor to T-cell activation and adverse outcomes in treated HIV disease and an attractive target for therapeutic interventions (Figure 1).

CMV, HIV, AND CLINICAL OUTCOMES

In the setting of underlying immune deficiency, CMV is associated with more-rapid HIV disease progression, more AIDS-related events [66, 67], and a wide range of serious end-organ diseases [13]. The incidence of life-threatening complications has decreased dramatically with suppressive combination ART, likely due to restoration of CMV-specific immune responses that limit CMV reactivation [68]. While the clinical importance of CMV in the setting of ART-treated HIV disease is less clear, emerging evidence links CMV to suboptimal immune response to ART [61] and increased risk of non–AIDS-related complications [69]. Interestingly, $CD8^+$ T-cell activation was reduced by valganciclovir treatment in a small clinical trial, suggesting that treatment of CMV (and other valganciclovir-susceptible viruses) might be a viable strategy to reduce immune activation in HIV-infected adults [70].

A large, longitudinal study recently established CMV as a risk factor for severe, non–AIDS-related adverse clinical events in HIV disease [69]. The event most frequently associated with CMV was cardiovascular disease, which has been described following organ transplantation [71, 72] and with HIV disease [73, 74]. Given its ubiquity as a human pathogen and its ability to infect endothelial cells and smooth-muscle cells [75], CMV is an ideal candidate pathogen for atherosclerosis [76]. Several epidemiologic and animal studies support this conclusion [59, 77–81], but

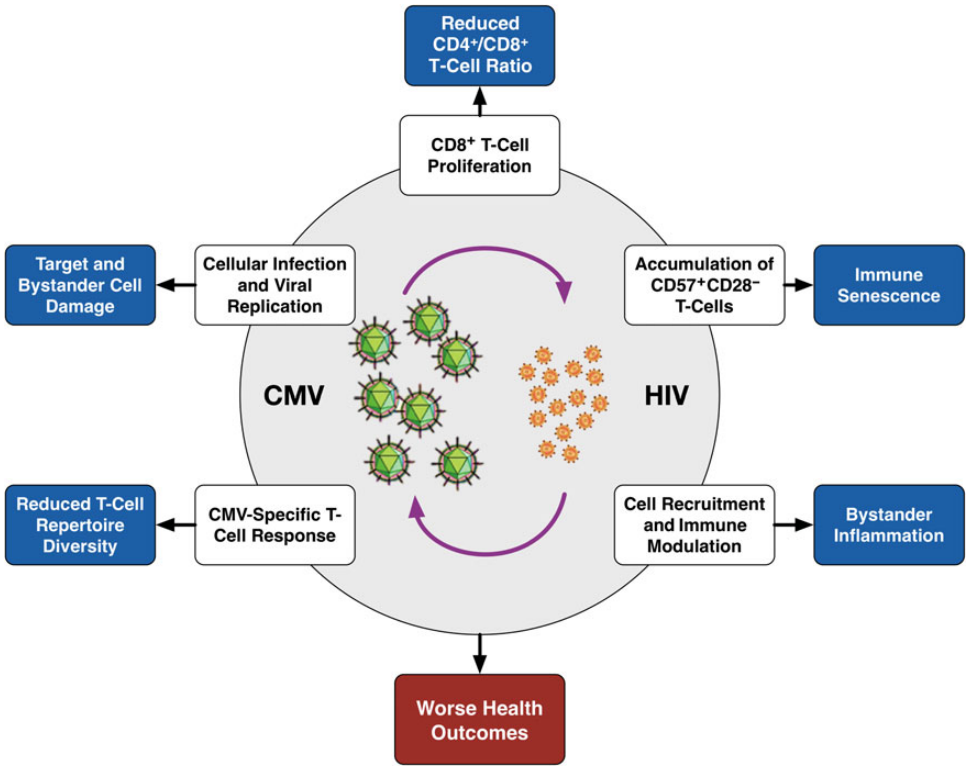

Figure 1. Proposed model connecting cytomegalovirus (CMV), human immunodeficiency virus (HIV), immune dysfunction and worse disease outcome. HIV infection induces $CD4^+$ T cell loss and dysfunction, thereby failing to provide help to $CD8^+$ T cells and permitting more CMV replication. Both viral infections contribute to inflammation, immune senescence and promote the expansion of $CD8^+$ T cells. Such $CD8^+$ T cell expansion, coupled with a loss of $CD4^+$ T cells (leading to a lower CD4/CD8 T cell ratio) are linked to morbid outcomes of CMV and HIV infections. Additionally, CMV might cause direct cellular damage to endothelial cells and other cell types further contributing to end organ damage.

the search for causal links is ongoing. CMV has been isolated from atherosclerotic plaques [82] and predicts mortality in patients with coronary artery disease [83]. Among heart transplant recipients, higher levels of anti-CMV immunoglobulin G (IgG) and CMV DNA correlate with development of cardiac allograft vascular disease and acute graft rejection [84]. When prophylaxis was given to heart transplant recipients, the incidence of posttransplantation CMV disease declined, along with the incidence of acute and chronic graft rejection [85, 86]. CMV may also contribute to coronary artery restenosis after coronary angioplasty [87].

In response to CMV infection, endothelial cells express proangiogenic factors and proinflammatory molecules (eg, IL-6 and vascular endothelial growth factor) [82, 88]. This promotes enhanced proliferation and migration of monocytes and smooth-muscle cells into the intima of the vascular wall, as well as lipid accumulation and expansion of the atherosclerotic lesion [89]. Also, CMV-infected smooth-muscle cells within vascular lesions have greater proliferation and impaired apoptosis (perhaps mediated by the CMV US28 protein [90]), which may contribute to intima media thickening, plaque formation, and restenosis [88, 89]. When peripheral blood cells from persons with strong anti-CMV T-cell response are incubated with CMV antigens, an immune cascade results in endothelial damage and increased expression of CX3CL1 and other cytokines [91, 92]. CMV-specific T cells frequently express the CX3CL1 receptor (CX3CR1), and a study linked $CD4^+$ T cells expressing CX3CR1 to carotid intima media thickness [93]. Thus, both CMV replication and the immune response to CMV may promote changes in endothelial cells that contribute to the atherogenesis [58, 91]. Similar immune-viral interactions might also underlie increased levels of inflammation linking CMV to other age-associated diseases.

CMV AND NEUROCOGNITIVE COMPLICATIONS

Similar to cardiovascular disease, multiple clues about the impact of CMV infection on the CNS come from outside the HIV field. For example, older adults with higher levels of anti-CMV IgG antibodies or CMV-specific $CD4^+$ T cells in blood had worse performance on the mini–mental status examination and worse activities of daily living [94]. Consistent evidence also came from the Sacramento Area Latino Study on Aging, a population-based study of >1200 adults aged >60 years. Again, those who had the highest anti-CMV IgG levels had the highest rate of cognitive decline over 4 years, after accounting for the effects of age, sex, education, income, and chronic health conditions [95]. In contrast, no association was found with anti–HSV-1 IgG concentrations. In a separate analysis from this cohort, higher serum anti-CMV IgG levels were associated with all-cause and cardiovascular disease–related mortality, and 2 proinflammatory cytokines, IL-6 and TNF-α, statistically mediated part of this relationship [96].

Consistent with these findings, CMV has been recently implicated in the pathogenesis of Alzheimer disease. In one study of >800 adults followed for an average of 5 years, CMV seropositivity was associated with a faster rate of cognitive decline, including a >2-fold increased risk of developing Alzheimer disease, when accounting for the influence of age, sex, race, vascular risk factors, and apolipoprotein E genotype [97]. In a study of autopsy brain tissue donated by Catholic clergy with few confounding conditions, higher serum IgG levels in life against CMV but not those against HSV-1 were associated with the presence of neurofibrillary tangles at death [98].

The direct effect of CMV on Alzheimer disease remains controversial [99, 100]. Even though CMV can infect glia, neurons, and neural precursor cells [20–23], CMV replication is rarely found within the CNS in immune-competent hosts. Distinguishing the effects of CMV from HSV-1 is important since prior studies have also linked HSV-1 to Alzheimer disease [101–103] and because the immune responses to these 2 viruses can overlap [104].

While HIV-associated neurocognitive disorder (HAND) is not a primary amyloidopathy, recent evidence has identified amyloid accumulation in brain tissue of adults dying with HIV disease [105] and low amyloid β1–42 levels in cerebrospinal fluid from HIV-infected adults who have a family history of dementia [106]. Amyloid accumulation is also associated with vascular disease, which has been in turn linked to HAND [107, 108]. Consistent with these findings, stronger CMV-specific, IFN-γ $CD8^+$ T-cell responses have been linked to worse carotid intima media thickness [73], and higher anti-CMV IgG levels have been linked to carotid atherosclerotic lesions in HIV-infected adults [74]. More recently, a large nationwide population-based cohort study in Taiwan including >22 000 people living with HIV found a significant association between CMV end-organ disease and risk of ischemic stroke [109].

Our own data from the CNS HIV Antiretroviral Therapy Effects Research cohort identified consistent results in HIV-infected adults [110]. Even though the 138 participants in this analysis were younger than in the published analyses from the general population (median age, 43 years), higher anti-CMV IgG levels were associated with worse neurocognitive performance, but only among those taking suppressive ART. In addition, the combination of higher serum anti-CMV IgG titers and higher plasma levels of the monocyte activation biomarker, soluble CD163, were strongly associated with global neurocognitive impairment (odds ratio, 5.7; positive predictive value, 83%). Another recent study of 91 HIV-infected adults taking suppressive ART found a consistent association between higher anti-CMV IgG levels and worse neurocognitive performance, although this weakened when age was included in the model [111].

In summary, there is evidence that CMV could be associated with adverse neurocognitive outcomes. CMV could injure the CNS in multiple ways, including replication-mediated cell injury and resulting inflammation, cerebrovascular disease, and perhaps neurotoxic viral proteins. Larger observational and interventional studies are needed to determine how CMV and other chronic infections influence neurocognitive health.

CMV AND HIV PERSISTENCE

The conclusion that chronic inflammation and immune activation drives HIV persistence during ART is supported by strong evidence [112, 113]. To link CMV replication, systemic inflammation, and maintenance of the HIV reservoir, recent studies have identified that the presence of subclinical CMV replication is associated with higher levels of HIV DNA in both ART-naive adults [114] and in those taking long-term suppressive ART [115]. More recently, in a longitudinal study of 108 individuals followed since the earliest phase of HIV infection, intermittent CMV and EBV replication in blood cells was associated with more HIV DNA in blood over time [116]. A recent study of 6 HIV-infected adults undergoing cytoreductive chemotherapy demonstrated that the majority of HIV DNA after immune reconstitution was detected in circulating CMV- and EBV-specific $CD4^+$ T cells (as compared to those responding to αCD3/αCD28 stimulation or not expressing interleukin 2/IFN-γ) [117]. Although the observational design of these studies does not allow causality to be inferred and they did not specifically evaluate the replication competent HIV DNA subset, the findings support the theory that asymptomatic CMV replication (especially during immune reconstitution) could drive local and systemic immune activation with a subsequent increase in the HIV DNA reservoir. The effect of latency-reversing agents and immune-modulatory therapies on CMV reactivation is currently unknown and should be evaluated in the setting of ongoing clinical trials. Activation of latent HIV DNA with immune modulatory interventions could affect replication of CMV and other HHVs, which might in turn limit HIV clearance.

CONCLUSIONS

Through millions of years of coexistence, CMV has developed multiple strategies to coexist with the human immune system [118]. The extended lifetime provided by medical and socioeconomic advantages has revealed a set of CMV-associated changes in the immune system, which are associated with multiple age-related disorders and decreased survival. These relationships are even more prominent in the setting of HIV infection. The mechanisms by which CMV raises the risk of age-related morbidities may be accelerated and more intense in the setting of HIV infection (Figure 1). A detailed knowledge of the interactions between CMV, HIV, and host immune responses is necessary to understand the complex mechanisms underlying aging-related complications during HIV infection and to develop new strategies to prevent the premature occurrence of end-organ diseases that may be linked to CMV. Also, because the prevalence of CMV increases with age and varies according to socioeconomic factors [13], distinguishing the effects of CMV on aging-related complications from the effects of other confounding variables is difficult.

Future studies should evaluate the relative contributions of CMV reactivation, CMV-specific T-cell response, and immune dysregulation to determine the best targets for intervention. Anti-CMV therapy in transplant recipients prevents long-term complications, improves graft function, and reduces the risk of other infections and overall mortality [119]. Whether this will be true for other populations, including HIV-infected people, is unclear. Clinical trials of newer, less toxic anti-CMV drugs (eg, letermovir [120]) should evaluate the effects of CMV suppression on immune activation and inflammation in the HIV-infected population. This might be particularly true during immune reconstitution in late presenters initiating ART. Similarly, clinical trials should evaluate whether CMV control during long-term suppressive ART might also prevent neurocognitive and cardiovascular complications. As these agents will not eradicate CMV, prolonged courses of therapy may be needed, particularly when effects on clinical outcomes are the end points.

Another important factor to be considered in designing future studies is the timing of each viral infection. Since CMV influences aging-related changes of the immune system, the duration of chronic CMV infection before acquisition of HIV could influence the T-cell repertoire and affect other immune system characteristics during ART.

HIV-coinfected individuals who have the strongest CMV-specific immune response may be at greater risk for adverse health outcomes, compared with those with less robust responses. Additional analyses of the quantity and quality of the CMV response and their relation to CMV replication will be needed to explore this issue. In this regard, whether strategies to enhance CMV-specific immune responses (eg, therapeutic immunization) will (1) decrease viral expression and be beneficial or (2) enhance $CD8^+$ T-cell expansion, inflammation, and non–AIDS-associated comorbidities remains to be determined. Carefully designed clinical trials targeting CMV replication and immune responsiveness will be crucial to understand the complex relationships between CMV and HIV pathogenesis and to direct the design of clinical strategies that will have a positive effect on HIV disease progression and aging-related complications.

Notes

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