Title

Partners in Crime: The Role of CMV in Immune Dysregulation and Clinical Outcome During HIV Infection.

Journal

Current HIV/AIDS Reports, 13(1)

Authors

Freeman, Michael

Lederman, Michael

Gianella, Sara

Publication Date

2016-02-01

DOI

10.1007/s11904-016-0297-9

Peer reviewed

HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2016 October 25.

Published in final edited form as:

Curr HIV/AIDS Rep. 2016 February ; 13(1): 10–19. doi:10.1007/s11904-016-0297-9.

Partners in Crime: The Role of CMV in Immune Dysregulation and Clinical Outcome During HIV Infection

Michael L. Freeman[1], **Michael M. Lederman**[1], and **Sara Gianella**[2]

Sara Gianella: gianella@ucsd.edu

[1]Case Western Reserve University/University Hospitals Case Medical Center, 2109 Adelbert Road, BRB 1048B, Cleveland, OH 44106, USA

[2]University of California, San Diego, 9500 Gilman Drive MC 0679, La Jolla, CA 92093-0679, USA

Abstract

In the current era of combination antiretroviral therapy (ART), human immunodeficiency virus (HIV)-infected individuals are living longer and healthier lives. Nevertheless, HIV-infected persons are at greater risk for age-related disorders, which have been linked to residual immune dysfunction and inflammation. HIV-infected individuals are almost universally co-infected with cytomegalovirus (CMV) and both viruses are associated with inflammation-related morbidities. Therefore, a detailed investigation of the relationship between CMV and aging-related morbidities emerging during chronic HIV infection is warranted. Here, we review the literature on how CMV co-infection affects HIV infection and host immunity and we discuss the gaps in our knowledge that need elucidation.

Keywords

CMV infection; HIV infection; Inflammation; Aging; Immune response

Introduction

Antiretroviral therapy (ART) can control HIV replication indefinitely in most HIV-infected individuals who adhere to their medications [1]. Nevertheless, and depending on timing of ART initiation, HIV-infected persons may experience greater morbidity and mortality than the HIV-uninfected do. These morbidities include non-AIDS defining disorders such as cardiovascular disease, a spectrum of malignancies, frailty, and neurocognitive impairment that are also seen as people age [2]. This increased morbidity and mortality has been associated with residual immune dysfunction which persists in some individuals despite long term suppressive ART [3]. The mechanisms of residual immune dysfunction are incompletely understood and most likely multifactorial in origin. Persistent co-infections

Correspondence to: Sara Gianella, gianella@ucsd.edu.

This article is part of the Topical Collection on *HIV Pathogenesis and Treatment*

Conflict of Interest Michael L. Freeman, Michael M. Lederman, and Sara Gianella declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

with other pathogens are common in HIV infection, and likely contribute to overall immune dysfunction during HIV disease [4, 5]. For example, HIV-infected individuals are nearly universally co-infected with cytomegalovirus (CMV), and both HIV and CMV infections are independently associated with increased inflammation and inflammation-related morbidities [6]. Therefore, a detailed investigation of the relationship between CMV and aging-related morbidities emerging during chronic HIV infection is warranted.

Epidemiology, Life Cycle, and Pathogenesis of CMV Infection

Cytomegalovirus (CMV, also known as human herpesvirus 5 or HHV-5) is a widespread β-herpesvirus that causes persistent infection and is often acquired during childhood or during sexual debut. CMV seroprevalence can vary from 40 to 100 % in the adult population depending on age, socioeconomic status, and geographical region [7–9]. Primary CMV infection in immunocompetent hosts is often asymptomatic or minimally symptomatic, but morbidity and mortality dramatically increase during immunodeficiency (particularly among transplant recipients and HIV-infected people) [7, 8]. After primary infection, the virus establishes episomal latency in pluripotent CD34+ hematopoietic stem cells in the bone marrow [10]. As these cells differentiate along the myeloid lineage to monocytes and macrophages, latent CMV can reactivate and be released in response to different (often inflammatory) stimuli to infect new cellular targets. Other non-hematopoietic sites of latency have been suggested, particularly in epithelial cells, but this is still controversial since most in vivo studies failed to distinguish between true latency (no productive infection) and persistence (low-level productive infection in the absence of cytopathic effects) [10]. In fact, episodic bursts of asymptomatic CMV reactivation are frequently documented (particularly among HIV-infected persons) and are rapidly controlled by cell-mediated immune-surveillance [11]. One very common site of CMV shedding is the genital tract. The frequency of CMV shedding in genital secretions varies substantially across different studies and is strongly dependent on the geographical location, cohort characteristics, and detection methods used [9]. When an infected person has a compromised immune system, shedding of CMV increases dramatically. For example, in Southern California, almost half of HIV-infected men who have sex with men asymptomatically shed CMV in their genital tract, regardless of CD4+ T cell count or use of ART [12–14]. Less is known about the frequency of CMV shedding in the genital tract of HIV-infected women. Two studies of HIV-infected women conducted in the USA with partial uptake of ART found that CMV DNA was detected infrequently (3–7 %) in cervicovaginal lavage [15, 16]. In a study of HIV-infected Kenyan women not on ART, CMV was detected in 59 % of provider-collected cervical swabs [17]. Another recent study quantified vaginal shedding of CMV DNA longitudinally among 96 HIV-infected women starting ART in Rakai, Uganda. Vaginal CMV was detected in 75 of 96 women (78.0 %) and in 379 of 1080 individual visits (35.1 %). Compared to shedding pre-ART, CMV shedding increased, peaking from month two to four after ART initiation, suggesting a possible immune reconstitution inflammatory syndrome (IRIS). Other sites of CMV reactivation are the following: oral mucosa (where CMV may be found in 15–30 % of HIV-infected persons) [18, 19], peripheral blood mononuclear cells (PBMC) (where CMV may be found in 13–20 % of HIV-infected persons), urine (where CMV may be found in 10–30 % of HIV-infected persons), stool, and breast milk [20–22]. Such

asymptomatic shedding at different mucosal sites is likely important for the natural history and transmission dynamics of CMV itself, and also for the interplay of CMV with other co-infecting viruses (e.g., HIV) and with the host immune environment.

CMV Infection and the Host Immune Environment

CMV has established a powerful interaction with the immune system, having infected humans since our species arose [9]. In a complex host-virus relationship, CMV elicits and maintains a high frequency of virus-specific T cells that engage in a lifelong effort to restrain CMV replication and prevent life-threatening disease [23]. In HIV-uninfected individuals, approximately 10 % of both CD4 and CD8 memory T cells in the circulation target CMV antigens, and these frequencies can increase to about one third of CD4+ T cells and nearly half of CD8+ T cells in older persons [23, 24]. In HIV-infected adults, CMV-specific CD8 and CD4 T cell numbers are further elevated, similar to proportions observed in the HIV-uninfected elderly, and remain high even after ART-mediated suppression of HIV replication [25, 26]. With a large 230-kB genome, CMV is one of the largest viruses to infect humans. A recent study using ribosomal profiling to determine the protein-coding capacity of CMV showed that as many as 751 CMV open-reading frames are translated into CMV proteins in virus-infected cells [27•], suggesting that the CMV proteome is far more complex than hitherto recognized. Interestingly, many of these proteins were not essential for CMV replication and are thought to allow the virus to avoid immune recognition, protecting reactivating cells from attack and destruction by host defenses. Since CMV replication is enhanced by inflammatory stimuli, it is not surprising that the virus also developed ingenious strategies to induce and augment inflammation [28]. In fact, CMV is able to directly upregulate the expression of several cytokines and inflammatory mediators in host cells, including IL-1β, IL-6, and type I interferon, thereby exacerbating the inflammatory response [29–32]. CMV infection has also recently been shown to be associated with an increase of IL-15 in plasma [33]. Although there is little evidence of direct upregulation of IL-15 by CMV, other herpesviruses have been shown to directly induce IL-15 production [34]. The elicitation of IL-15 and other common γ-chain cytokines (including IL-2 and IL-7) is of particular interest, as these cytokines can drive antigen non-specific activation, proliferation, and expansion of naïve and memory CD4 and CD8 T cells [35]. In addition, CMV encodes its own cytokines and chemokine homologs as well as cytokine receptor homologs that can further modulate levels of human cytokines, chemokines, and growth factors [29, 36, 37]. While regulating inflammatory responses to benefit its own replication, CMV has also developed mechanisms to avoid immune recognition and protect infected cells from attack by host defenses. For example, CMV impairs antigen presentation by inhibiting the expression of HLA class I and class II molecules; CMV can also induce immune-inhibitory pathways (for example PD-1 and IL-10) and can inhibit activation of natural killer (NK) cells by virus-encoded HLA class I homologs and NK cell immune evasion proteins, thereby impairing destruction of infected cells [36–41]. Strategies of immune evasion and immune subversion by CMV are summarized in Table 1.

CMV Infection Drives CD8 T Cell Expansion

As noted above, CMV reactive T cells comprise a substantial proportion of the effector memory T cell repertoire and this appears to increase with age [25, 26]. Since CMV replication tends to occur in effector tissues rather than in inductive lymphoid tissues, the exact anatomical sites of interaction between immune cells and CMV (for both CMV-antigen specific and nonspecific interactions) are not well defined. One possibility is that many of these events occur in the draining lymph nodes, as many cytokines (including IL-1β, IL-2, and IL-15) are increased in lymph tissue or are elicited from lymph node histocultures of HIV-infected persons [42, 43]. In support of this hypothesis, recent evidence in mouse models suggests that murine (m)CMV can directly infect macrophages and non-hematopoietic cells in lymph nodes [44], selectively inducing proliferation of CD8 T cells [45, 46]. This so-called "$CD8^+$ T cell memory inflation" is characterized by the accumulation of high-frequency functional antigen-specific $CD8^+$ T cells with an effector-memory phenotype, which are typically enriched in peripheral organs. Although persistence of antigens is considered essential, the mechanism of this inflation is not completely understood, and it is not clear if similar mechanisms play a role also in the setting of human CMV infection [47]. One recent study investigated the clonal and phenotypic relations between T cells obtained from peripheral blood and lymph nodes during primary and latent human CMV infection to understand what cells sustain the circulating CMV-specific effector pool [48]. Interestingly, new clones that appear after primary CMV infection or during CMV reactivation seldom originated from peripheral blood or lymph nodes, suggesting that the precursors of the new CMV-specific clones are probably located elsewhere (e.g., in other secondary lymphoid tissues) or are recruited directly from the naïve CD8+ T cell pool.

Does "Occupancy" of the T Cell Repertoire by CMV-Reactive Cells have Impact on Immune Potential?

As CMV-infected persons age, an increasing proportion of their T cell repertoire becomes CMV-reactive and these cells are characteristically more differentiated (presumably as a result of repeated exposure to CMV peptides) and have a phenotype characteristic of replicative exhaustion and senescence [49]. The expansion of the T cell repertoire committed to CMV may compromise the ability to respond de novo to antigens by decreasing the diversity of the remaining naïve T cells or out-competing the naïve T cells for resources [50–53]. Other studies, however, found that the entrance of CMV-specific CD8+ T cells expanded the antigen-primed $CD8^+$ T cell pool rather than competing for space with pre-existing memory T cells specific for persistent or cleared viruses [54, 55]. Furthermore, as predicted by their maturation phenotype, CMV-specific $CD8^+$ T cells are negligibly present in the lymph nodes and thus do not limit immunologic "space" at sites where immune reactions are initiated [55]. These different findings might reflect the variability among humans in the magnitude of CMV-specific T cell responses that in turn reflect differences in CMV dosage, antigen exposure during shedding, and/or the immune competence of the host [56]. In support of this model, there is reason to suspect more profound influence of CMV infection on the immune repertoire in thymectomized individuals where the naïve T cell

repertoire is already diminished due to reduced thymic output, [57] and perhaps too in the elderly who have survived decades of thymic involution [58].

CMV Infection in the Young and the Old

Because the prevalence of CMV infection increases with age and also varies according to socio-economic factors [59], it has been difficult to distinguish the effects of CMV infection on aging-related complications from the effect of other confounding variables. To assess the relative contribution of heritable versus non-heritable factors, Brodin, et al. performed an elegant system-level analysis of 210 healthy monozygotic twins between 8 and 82 years of age [60•], measuring over 200 different immunologic indices, including cell population frequencies, cytokine responses, and serum proteins. The authors found that over three quarters (77 %) of these parameters were dominated and over half (58 %) were almost completely determined by non-heritable influences. Interestingly, in twins discordant for CMV serostatus, more than half of all these indices were affected, providing strong evidence that CMV co-infection has a profound effect on the immune system in healthy individuals. Large population studies in Scandinavia demonstrated that infection with CMV makes a significant contribution to the so-called immune risk profile (IRP), which is predictive of an increased mortality in very old individuals [61]. This immune risk profile (including expansion of CD8+ CD28 T cells and inverted CD4/CD8 T cell ratio) was rarely seen in Swedes who survived into their eleventh decade [62]. Other epidemiological studies in the USA suggested that CMV infection itself might have a negative impact on survival [63, 64], and higher levels of anti-CMV antibody were correlated to poor survival in older adults with stable cardiovascular disease [65, 66]. What different antibody titers actually reflect is however unclear and one recent study found that high CMV IgG levels were associated with less CMV replication [67], suggesting that CMV IgG levels are not simply a correlate of replication burden.

In summary, there is increasing evidence that CMV has a broad impact on human immunity: in older adults, it might exacerbate the aging processes contributing to the development of age-related morbidities that have been linked to immune senescence, such as frailty, cancer, neurocognitive impairment, and cardiovascular disease [2, 61, 68]. The effects of CMV infection on host immunity, however, are not always deleterious, and a recent study suggested that CMV might even have a beneficial effect on the immune system in younger healthy people, which could help to explain why humans and many other species tolerate the very high prevalence of this infection [69•].

Bidirectional Interaction Between HIV and CMV Replication

As described above, CMV is able to maintain an inflammatory environment that is beneficial for its own replication and survival and it has concurrently developed numerous strategies to control immune function so that CMV-reactive immune cells and other effectors are less able to eradicate virus-infected cells. It is reasonable to hypothesize that other co-infecting pathogens (for example HIV) could take advantage of this particular immune environment to protect their own persistence and replication.

Several studies have suggested that both direct and indirect interactions between CMV and HIV could influence their replication and the resulting disease pathogenesis. Several mechanisms could play a role including the following: (i) direct interaction between CMV-encoded regulatory proteins and the HIV long terminal repeat (LTR) region resulting in transactivation of viral gene expression [70, 71], (ii) enhanced HIV replication stimulated through a release of CMV-induced inflammatory cytokines and chemokines [72], (iii) upregulation of CCR5 expression in central memory T cells, which has been recently described in cord blood mononuclear cells exposed in vitro [73] and might be mediated by enhanced (CMV-induced) interferon production [74], and (iv) clonal expansion of HIV-infected T cells through CMV-induced inflammatory cytokines and chemokines [75]. This relationship between CMV and HIV has been widely documented in the genital tract, where presence of detectable CMV DNA has been repeatedly associated with increased genital shedding of HIV RNA [12, 13, 76–79] and with increased HIV transmission [11, 14, 76]. Additionally, presence of detectable CMV DNA was also associated with increased levels of HIV DNA in peripheral blood cells in both treated and untreated HIV infected individuals [20, 21, 75].

Impact of CMV Co-infection on the Course of HIV Infection

In the setting of underlying immune deficiency, CMV is associated with a wide range of serious clinical diseases, such as retinitis, pneumonitis, colitis, and other end organ disease [9], as well as with indication of more rapid HIV disease progression and increased occurrence of AIDS-related events [80, 81]. The incidence of these life-threatening conditions has decreased dramatically with the advent of ART. These changes are likely the consequence of a restoration of CMV-specific immune responses that result in diminished CMV expression and viremia [82]. While the clinical importance of CMV co-infection in the setting of ART-treated HIV infection is less clear, emerging evidence links CMV to determinants of both clinical risk [59] and immune pathogenesis [19, 75] during well-controlled HIV infection. Indeed, CMV co-infection is linked to a more inflammatory profile [83], including increased circulating levels of Interferon gamma-induced protein (IP)-10 and D-dimer, and to a profound expansion of circulating CD8 T cells and a reduced CD4/CD8 ratio that characterize treated HIV infection, [83, 84] and that is linked to an increased morbidity and mortality [85, 86].

Even in the setting of ART-treated HIV infection, asymptomatic shedding of CMV was linked to increased levels of T cell activation, proliferation, and exhaustion [19, 75]. In HIV/CMV co-infected individuals, more CD8 T cells express the marker of cellular senescence CD57 and fewer express the co-stimulatory molecule CD28, compared to CD8 T cells of age-matched monoinfected persons [84, 86]. As discussed above, one of the main hallmarks of CMV infection is a demonstrable expansion of CD8 T cells (referred to as “memory T cell inflation”) [23, 87–90], which is particularly prominent and appears at younger age within the HIV co-infected populations [84, 91]. This ongoing recruitment, activation, and apparent dysfunction of virus-specific CD8 T cells fails to eliminate or effectively control CMV replication and results in an expanded pool of effector CD8 T cells, and consequently a low CD4:CD8 ratio that is associated with an increased risk of non-AIDS morbidity and mortality [85, 86]. Since both aging and CMV contribute to immune

senescence [52, 92], it is not surprising that the importance of CMV co-infection becomes increasingly recognized as co-morbid conditions complicate the extended lifespan of the ART-treated HIV-infected population. A proposed simplified summary of the interactions between HIV infection, CMV replication, CD4, and CD8 T cells is shown in Fig. 1.

Recent epidemiological studies suggest a direct connection between CMV infection (or the magnitude of CMV-antibody response) and non-AIDS associated morbidities during ART-treated HIV infection, including neurocognitive impairment, cancer, and cardiovascular disease [59, 93]. The most frequent association is between CMV and cardiovascular disease, which has been described in the setting of post-transplant atherosclerosis [94, 95] and HIV infection [66, 96]. Both CMV replication itself and the immune response against CMV can promote changes in endothelial cells that might contribute to the pathogenesis of atherosclerosis [97, 98]. Possible mechanisms include the secretion of pro-angiogenic factors through CMV-infected endothelial cells (e.g., IL-6, GM-CSF) and direct endothelial damage through CMV-induced inflammation. Additionally, immune cells responding to CMV infection can activate immune cascades resulting in endothelial damage and aggravating the effect of CMV replication. For example, there is increasing evidence to support a key role for fractalkine-fractalkine receptor (CX3CR1) interactions in the host inflammatory response leading to vascular injury [98, 99]. Interestingly, the expression of the host chemokine fractalkine (a key marker of inflammation in endothelial cells) is strongly upregulated in the presence of PBMCs from donors with a high frequency of CMV-specific T cells [99]. The fractalkine-CX3CR1 interaction results in recruitment of natural killer cells, monocytes and possibly also CX3CR1+ CD8+ T cells [100] that may participate in driving vascular inflammation, coagulation, and the formation of atheromas. The cardiovascular complications associated with CMV infection are most likely multifactorial, and include consequences of direct effect of CMV replication driving activation of immune cells and cytokine/chemokine-mediated effects as an additional risk factor for development of chronic inflammation and endothelial cell injury.

Conclusions

Through millions of years of co-existence, CMV has developed a number of strategies to adapt and synergistically coexist with the human immune system. A detailed knowledge of the interactions among 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 infection. For example, it will be important to understand the directional relationships among CMV reactivation, inflation of the CMV-specific T cell response, and immune dysregulation to determine where intervention should be targeted to affect these outcomes. Newer less toxic drugs with activity against CMV (e.g., Brincidofovir [101] and Letermovir [102]) could be applied in clinical trials to evaluate first the effects of CMV suppression on immune activation and inflammation. As these agents will not eradicate CMV, prolonged courses of therapy may be needed, particularly when effects on clinical outcomes are the endpoints. It remains to be seen if attenuation of CMV expression will be sufficient to reverse the inflammatory process initiated by CMV infection.

Conceivably, HIV co-infected individuals with the most brisk CMV-specific immune response are at greater risk for morbid outcomes while persons with less robust CMV-specific T-cell responses are not. Additional analyses stratified on the basis of the quantity and quality of the CMV response and in relation to markers of CMV replication will be needed to explore this issue. These analyses should not only include the T-cell compartment but should also encompass other immune defenses affected by CMV infection such as B cells and NK cells. Another intriguing open question is why CMV, uniquely among all human herpes viruses, is able to drive such dramatic expansion of virus specific T cells, while other common persistent viruses such as EBV do not.

In this regard, it is not clear whether strategies to enhance CMV-specific immune responses such as via therapeutic immunization will decrease viral expression and provide indication of benefit or on the other hand, might further enhance the CD8 T cell expansion and inflammation that have been linked to non-AIDS-related co-morbidities during HIV infection.

Carefully designed clinical trials targeting CMV replication and immune responsiveness may help to understand the complex interrelationships between CMV and HIV pathogenesis and also may direct the design of interventional strategies that will have a positive effect on HIV disease progression and aging-related complications.

Acknowledgments

This work was supported by the Department of Veterans Affairs and grants from the National Institutes of Health: AI43638, AI100665, MH097520, DA034978, AI036214, AI007384, AI027763, AI106039, AI074621, AI110181, 7-UM1 AI068636-07, AI-36219, P30-AI027763, amfAR grant 108537 with support from FAIR, UL1TR000100, the James B. Pendleton Charitable Trust.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

1. Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006; 43:27–34. [PubMed: 16878047]
2. Hunt PW. HIV and inflammation: mechanisms and consequences. Curr HIV/AIDS Rep. 2012; 9:139–47. [PubMed: 22528766]
3. Deeks SG, Verdin E, McCune JM. Immunosenescence and HIV. Curr Opin Immunol. 2012; 24:501–6. [PubMed: 22658763]
4. Unemori P, Leslie KS, Hunt PW, et al. Immunosenescence is associated with presence of Kaposi's sarcoma in antiretroviral treated HIV infection. AIDS. 2013; 27:1735–42. [PubMed: 23435301]
5. Appay V, Fastenackels S, Katlama C, et al. Old age and anti-cytomegalovirus immunity are associated with altered T-cell reconstitution in HIV-1-infected patients. AIDS. 2011; 25:1813–22. [PubMed: 21412126]
6. Durier N, Ananworanich J, Apornpong T, et al. Cytomegalovirus viremia in Thai HIV-infected patients on antiretroviral therapy: prevalence and associated mortality. Clin Infect Dis. 2013; 57:147–55. [PubMed: 23511301]
7. Fishman JA. Overview: cytomegalovirus and the herpesviruses in transplantation. Am J Trans Off J Am Soc Trans Am Soc Trans Surg. 2013; 13:1–8.

8. Richman, DD. Clinical Virology. 3. ASM Press; Jan 1. 2009 p. 1408
9. Gianella S, Massanella M, Wertheim JO, Smith DM. The sordid affair between human herpesvirus and human immunodeficiency virus. J Infect Dis. 2015; 212(6):845–52. [PubMed: 25748324]
10. Sinclair J, Sissons P. Latency and reactivation of human cytomegalovirus. J Gen Virol. 2006; 87:1763–79. [PubMed: 16760381]
11. Barnabas RV, Celum C. Infectious co-factors in HIV-1 transmission herpes simplex virus type-2 and HIV-1: new insights and interventions. Curr HIV Res. 2012; 10:228–37. [PubMed: 22384842]
12. Gianella S, Morris SR, Anderson C, et al. Herpesviruses and HIV-1 drug resistance mutations influence the virologic and immunologic milieu of the male genital tract. AIDS. 2013; 27:39–47. [PubMed: 22739399]
13. Lisco A, Munawwar A, Introini A, et al. Semen of HIV-1-infected individuals: local shedding of herpesviruses and reprogrammed cytokine network. J Infect Dis. 2012; 205:97–105. [PubMed: 22107749]
14. Gianella S, Scheffler K, Mehta SR, et al. Seminal shedding of CMV and HIV transmission among men who have sex with Men. Int J Environ Res Publ Health. 2015; 12:7585–92.
15. Mitchell C, Hitti J, Paul K, et al. Cervicovaginal shedding of HIV type 1 is related to genital tract inflammation independent of changes in vaginal microbiota. AIDS Res Hum Retrovir. 2011; 27:35–9. [PubMed: 20929397]
16. Schoenfisch AL, Dollard SC, Amin M, et al. Cytomegalovirus (CMV) shedding is highly correlated with markers of immunosuppression in CMV-seropositive women. J Med Microbiol. 2011; 60:768–74. [PubMed: 21393456]
17. Mostad SB, Kreiss JK, Ryncarz AJ, et al. Cervical shedding of cytomegalovirus in human immunodeficiency virus type 1-infected women. J Med Virol. 1999; 59:469–73. [PubMed: 10534728]
18. Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. J Infect Dis. 2008; 198:23–30. [PubMed: 18491970]
19. Hunt PW, Martin JN, Sinclair E, et al. Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy. J Infect Dis. 2011; 203:1474–83. [PubMed: 21502083]
20. Gianella S, Anderson CM, Vargas MV, et al. CMV DNA in semen and blood is associated with higher levels of proviral HIV DNA. J Infect Dis. 2012; 207:898–902. [PubMed: 23275608]
21. Gianella, S.; Anderson, C.; Var, SR., et al. 22th Conference on Retroviruses and opportunistic infections (CROI). Seattle: 2015. Detectable CMV in PBMC Is Associated with Slower HIV DNA Decay during Suppressive ART. Under Review
22. Reitter A, Buxmann H, Haberl AE, et al. Incidence of CMV co-infection in HIV-positive women and their neonates in a tertiary referral centre: a cohort study. Med Microbiol Immunol. 2015; doi: 10.1007/s00430-015-0427-9
23. Sylwester AW, Mitchell BL, Edgar JB, et al. Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects. J Exp Med. 2005; 202:673–85. [PubMed: 16147978]
24. Li H, Margolick JB, Bream JH, et al. Heterogeneity of CD4+ and CD8+ T-cell responses to cytomegalovirus in HIV-infected and HIV-uninfected men who have sex with men. J Infect Dis. 2014; 210:400–4. [PubMed: 24532602]
25. Stone SF, Price P, Khan N, Moss PA, French MA. HIV patients on antiretroviral therapy have high frequencies of CD8 T cells specific for Immediate Early protein-1 of cytomegalovirus. AIDS. 2005; 19:555–62. [PubMed: 15802973]
26. Naeger DM, Martin JN, Sinclair E, et al. Cytomegalovirus-specific T cells persist at very high levels during long-term antiretroviral treatment of HIV disease. PLoS One. 2010; 5:e8886. [PubMed: 20126452]
27•. Stern-Ginossar N, Weisburd B, Michalski A, et al. Decoding human cytomegalovirus. Science. 2012; 338:1088–93. The results of this study revealed an unanticipated complexity to the HCMV coding capacity and illustrate the role of regulated changes in transcript start sites in generating this complexity. [PubMed: 23180859]

28. Soderberg-Naucler C. Treatment of cytomegalovirus infections beyond acute disease to improve human health. Expert Rev Anti-Infect Ther. 2014; 12:211–22. [PubMed: 24404994]
29. Lisco A, Vanpouille C, Margolis L. War and peace between microbes: HIV-1 interactions with coinfecting viruses. Cell Host Microbe. 2009; 6:403–8. [PubMed: 19917495]
30. Almeida GD, Porada CD, St Jeor S, Ascensao JL. Human cytomegalovirus alters interleukin-6 production by endothelial cells. Blood. 1994; 83:370–6. [PubMed: 8286737]
31. Suni MA, Ghanekar SA, Houck DW, et al. CD4(+)CD8(dim) T lymphocytes exhibit enhanced cytokine expression, proliferation and cytotoxic activity in response to HCMV and HIV-1 antigens. Eur J Immunol. 2001; 31:2512–20. [PubMed: 11500836]
32. Iwamoto GK, Monick MM, Clark BD, Auron PE, Stinski MF, Hunninghake GW. Modulation of interleukin 1 beta gene expression by the immediate early genes of human cytomegalovirus. J Clin Invest. 1990; 85:1853–7. [PubMed: 2161430]
33. Saghafian-Hedengren S, Sohlberg E, Theorell J, et al. Epstein-Barr virus coinfection in children boosts cytomegalovirus-induced differentiation of natural killer cells. J Virol. 2013; 87:13446–55. [PubMed: 24089567]
34. Fawaz LM, Sharif-Askari E, Menezes J. Up-regulation of NK cytotoxic activity via IL-15 induction by different viruses: a comparative study. J Immunol. 1999; 163:4473–80. [PubMed: 10510389]
35. Overwijk WW, Schluns KS. Functions of gammaC cytokines in immune homeostasis: current and potential clinical applications. Clin Immunol. 2009; 132:153–65. [PubMed: 19428306]
36. Chang WL, Baumgarth N, Yu D, Barry PA. Human cytomegalovirus-encoded interleukin-10 homolog inhibits maturation of dendritic cells and alters their functionality. J Virol. 2004; 78:8720–31. [PubMed: 15280480]
37. Kotenko SV, Saccani S, Izotova LS, Mirochnitchenko OV, Pestka S. Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10). Proc Natl Acad Sci U S A. 2000; 97:1695–700. [PubMed: 10677520]
38. Soderberg-Naucler C. Human cytomegalovirus persists in its host and attacks and avoids elimination by the immune system. Crit Rev Immunol. 2006; 26:231–64. [PubMed: 16928188]
39. Powers C, DeFilippis V, Malouli D, Fruh K. Cytomegalovirus immune evasion. Curr Top Microbiol Immunol. 2008; 325:333–59. [PubMed: 18637515]
40. Dan J, Massanella M, Spina C, et al. Effect of cytomegalovirus and HIV transcription on CD57 and PD-1 Tcell expression during suppressive ART. JAIDS. 2016 In press.
41. Johnson DC, Hegde NR. Inhibition of the MHC class II antigen presentation pathway by human cytomegalovirus. Curr Top Microbiol Immunol. 2002; 269:101–15. [PubMed: 12224504]
42. Shive CL, Mudd JC, Funderburg NT, et al. Inflammatory cytokines drive CD4+ T-cell cycling and impaired responsiveness to interleukin 7: implications for immune failure in HIV disease. J Infect Dis. 2014; 210:619–29. [PubMed: 24585897]
43. Biancotto A, Grivel JC, Iglehart SJ, et al. Abnormal activation and cytokine spectra in lymph nodes of people chronically infected with HIV-1. Blood. 2007; 109:4272–9. [PubMed: 17289812]
44. Farrell HE, Davis-Poynter N, Bruce K, et al. Lymph node macrophages restrict murine cytomegalovirus dissemination. J Virol. 2015; 89:7147–58. [PubMed: 25926638]
45. Torti N, Walton SM, Brocker T, Rulicke T, Oxenius A. Non-hematopoietic cells in lymph nodes drive memory CD8 T cell inflation during murine cytomegalovirus infection. PLoS Pathog. 2011; 7:e1002313. [PubMed: 22046127]
46. Torti N, Oxenius A. T cell memory in the context of persistent herpes viral infections. Viruses. 2012; 4:1116–43. [PubMed: 22852044]
47. Lang A, Brien JD, Nikolich-Zugich J. Inflation and long-term maintenance of CD8 T cells responding to a latent herpesvirus depend upon establishment of latency and presence of viral antigens. J Immunol. 2009; 183:8077–87. [PubMed: 20007576]
48. Remmerswaal EB, Klarenbeek PL, Alves NL, et al. Clonal evolution of CD8+ T cell responses against latent viruses: relationship among phenotype, localization, and function. J Virol. 2015; 89:568–80. [PubMed: 25339770]

49. Fletcher JM, Vukmanovic-Stejic M, Dunne PJ, et al. Cytomegalovirus-specific CD4+ T cells in healthy carriers are continuously driven to replicative exhaustion. J Immunol. 2005; 175:8218–25. [PubMed: 16339561]
50. Almanzar G, Schwaiger S, Jenewein B, et al. Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-cell repertoire, which may be the basis for an imbalance in the cytokine production profile in elderly persons. J Virol. 2005; 79:3675–83. [PubMed: 15731261]
51. Cicin-Sain L, Brien JD, Uhrlaub JL, Drabig A, Marandu TF, Nikolich-Zugich J. Cytomegalovirus infection impairs immune responses and accentuates T-cell pool changes observed in mice with aging. PLoS Pathog. 2012; 8:e1002849. [PubMed: 22916012]
52. Mekker A, Tchang VS, Haeberli L, Oxenius A, Trkola A, Karrer U. Immune senescence: relative contributions of age and cytomegalovirus infection. PLoS Pathog. 2012; 8:e1002850. [PubMed: 22916013]
53. Smithey MJ, Li G, Venturi V, Davenport MP, Nikolich-Zugich J. Lifelong persistent viral infection alters the naive T cell pool, impairing CD8 T cell immunity in late life. J Immunol. 2012; 189:5356–66. [PubMed: 23087407]
54. van Leeuwen EM, Koning JJ, Remmerswaal EB, van Baarle D, van Lier RA, ten Berge IJ. Differential usage of cellular niches by cytomegalovirus versus EBV- and influenza virus-specific CD8+ T cells. J Immunol. 2006; 177:4998–5005. [PubMed: 17015682]
55. Remmerswaal EB, Havenith SH, Idu MM, et al. Human virus-specific effector-type T cells accumulate in blood but not in lymph nodes. Blood. 2012; 119:1702–12. [PubMed: 22207739]
56. Arens R, Remmerswaal EB, Bosch JA, van Lier RA. 5(th) International Workshop on CMV and Immunosenescence—a shadow of cytomegalovirus infection on immunological memory. Eur J Immunol. 2015; 45:954–7. [PubMed: 25857239]
57. Sauce D, Larsen M, Fastenackels S, et al. Evidence of premature immune aging in patients thymectomized during early childhood. J Clin Invest. 2009; 119:3070–8. [PubMed: 19770514]
58. Harris JM, Hazenberg MD, Poulin JF, et al. Multiparameter evaluation of human thymic function: interpretations and caveats. Clin Immunol. 2005; 115:138–46. [PubMed: 15885636]
59. Lichtner M, Cicconi P, Vita S, et al. Cytomegalovirus coinfection is associated with an increased risk of severe non-AIDS-defining events in a large cohort of HIV-infected patients. J Infect Dis. 2015; 211:178–86. [PubMed: 25081936]
60•. Brodin P, Jojic V, Gao T, et al. Variation in the human immune system is largely driven by non-heritable influences. Cell. 2015; 160:37–47. By studying twins, this study found that non-heritable influences (inclusive CMV serostatus) explain much of the variation in immune measurements. [PubMed: 25594173]
61. Olsson J, Wikby A, Johansson B, Lofgren S, Nilsson BO, Ferguson FG. Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. Mech Ageing Dev. 2000; 121:187–201. [PubMed: 11164473]
62. Strindhall J, Nilsson BO, Lofgren S, et al. No immune risk profile among individuals who reach 100 years of age: findings from the Swedish NONA immune longitudinal study. Exp Gerontol. 2007; 42:753–61. [PubMed: 17606347]
63. Dowd JB, Aiello AE, Alley DE. Socioeconomic disparities in the seroprevalence of cytomegalovirus infection in the US population: NHANES III. Epidemiol Infect. 2009; 137:58–65. [PubMed: 18413004]
64. Simanek AM, Dowd JB, Pawelec G, Melzer D, Dutta A, Aiello AE. Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. PLoS One. 2011; 6:e16103. [PubMed: 21379581]
65. Strandberg TE, Pitkala KH, Tilvis RS. Cytomegalovirus antibody level and mortality among community-dwelling older adults with stable cardiovascular disease. JAMA. 2009; 301:380–2. [PubMed: 19176439]
66. Parrinello CM, Sinclair E, Landay AL, et al. Cytomegalovirus immunoglobulin G antibody is associated with subclinical carotid artery disease among HIV-infected women. J Infect Dis. 2012; 205:1788–96. [PubMed: 22492856]

67. Gianella S, Morris SR, Tatro E, et al. Virologic Correlates of Anti-CMV IgG Levels in HIV-1 Infected Men. J Infect Dis. 2014; 209(3):452–6. [PubMed: 23964106]
68. Hadrup SR, Strindhall J, Kollgaard T, et al. Longitudinal studies of clonally expanded CD8 T cells reveal a repertoire shrinkage predicting mortality and an increased number of dysfunctional cytomegalovirus-specific T cells in the very elderly. J Immunol. 2006; 176:2645–53. [PubMed: 16456027]
69•. Furman D, Jojic V, Sharma S, et al. Cytomegalovirus infection enhances the immune response to influenza. Sci Transl Med. 2015; 7:281ra43. This study found that latent CMV infection could be beneficial in that it enhanced the development of an influenza vaccine-specific antibody response in young, but not aged, individuals.
70. Skolnik PR, Kosloff BR, Hirsch MS. Bidirectional interactions between human immunodeficiency virus type 1 and cytomegalovirus. J Infect Dis. 1988; 157:508–14. [PubMed: 2830343]
71. Yuan R, Bohan C, Shiao FC, Robinson R, Kaplan HJ, Srinivasan A. Activation of HIV LTR-directed expression: analysis with pseudorabies virus immediate early gene. Virology. 1989; 172:92–9. [PubMed: 2549725]
72. Lisco A, Vanpouille C, Margolis L. Coinfecting viruses as determinants of HIV disease. Curr HIV/AIDS Rep. 2009; 6:5–12. [PubMed: 19149991]
73. Johnson EL, Howard CL, Thurman J, Pontiff K, Johnson ES, Chakraborty R. CMV upregulates expression of CCR5 in central memory TCM cord blood mononuclear cells which may facilitate in utero HIV-1 transmission. J Infect Dis. 2015; 211(2):187–96. [PubMed: 25081935]
74. Stoddart CA, Keir ME, McCune JM. IFN-alpha-induced upregulation of CCR5 leads to expanded HIV tropism in vivo. PLoS Pathog. 2010; 6:e1000766. [PubMed: 20174557]
75. Gianella S, Massanella M, Richman DD, et al. Cytomegalovirus replication in semen is associated with higher levels of proviral HIV DNA and CD4+ T cell activation during antiretroviral treatment. J Virol. 2014; 88:7818–27. [PubMed: 24789781]
76. Gianella S, Morris SR, Vargas MV, et al. The role of seminal shedding of herpesviruses in HIV-1 transmission. J Infect Dis. 2012; 207:257–61. [PubMed: 23148284]
77. Gianella S, Strain MC, Rought SE, et al. Associations between virologic and immunologic dynamics in blood and in the male genital tract. J Virol. 2012; 86:1307–15. [PubMed: 22114342]
78. Kim HN, Wang J, Hughes J, et al. Effect of acyclovir on HIV-1 set point among herpes simplex virus type 2-seropositive persons during early HIV-1 infection. J Infect Dis. 2010; 202:734–8. [PubMed: 20649426]
79. Gianella S, Smith DM, Vargas MV, et al. Shedding of HIV and human herpesviruses in the semen of effectively treated HIV-1-infected men who have sex with men. Clin Infect Dis. 2013; 57:441–7. [PubMed: 23595831]
80. Webster A, Lee CA, Cook DG, et al. Cytomegalovirus infection and progression towards AIDS in haemophiliacs with human immunodeficiency virus infection. Lancet. 1989; 2:63–6. [PubMed: 2567870]
81. Detels R, Leach CT, Hennessey K, et al. Persistent cytomegalovirus infection of semen increases risk of AIDS. J Infect Dis. 1994; 169:766–8. [PubMed: 8133089]
82. Deayton J, Mocroft A, Wilson P, Emery VC, Johnson MA, Griffiths PD. Loss of cytomegalovirus (CMV) viraemia following highly active antiretroviral therapy in the absence of specific anti-CMV therapy. AIDS. 1999; 13:1203–6. [PubMed: 10416523]
83. Freeman ML, Mudd JC, Shive CL, et al. M CD8 T cell expansion and inflammation linked to CMV co-infection in ART-treated HIV infection. Clin Infect Dis. 2016; 62(3):392–6. [PubMed: 26400999]
84. Barrett L, Stapleton SN, Fudge NJ, Grant MD. Immune resilience in HIV-infected individuals seronegative for cytomegalovirus. AIDS. 2014; 28:2045–9. [PubMed: 25265072]
85. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog. 2014; 10:e1004078. [PubMed: 24831517]
86. Lee SA, Sinclair E, Hatano H, et al. Impact of HIV on CD8+ T cell CD57 expression is distinct from that of CMV and aging. PLoS One. 2014; 9:e89444. [PubMed: 24586783]

87. Moss P, Khan N. CD8(+) T-cell immunity to cytomegalovirus. Hum Immunol. 2004; 65:456–64. [PubMed: 15172445]

88. Khan N, Shariff N, Cobbold M, et al. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. J Immunol. 2002; 169:1984–92. [PubMed: 12165524]

89. Khan N, Cobbold M, Cummerson J, Moss PA. Persistent viral infection in humans can drive high frequency low-affinity T-cell expansions. Immunology. 2010; 131:537–48. [PubMed: 20722762]

90. Ouyang Q, Wagner WM, Zheng W, Wikby A, Remarque EJ, Pawelec G. Dysfunctional CMV-specific CD8(+) T cells accumulate in the elderly. Exp Gerontol. 2004; 39:607–13. [PubMed: 15050296]

91. Chidrawar S, Khan N, Wei W, et al. Cytomegalovirus-seropositivity has a profound influence on the magnitude of major lymphoid subsets within healthy individuals. Clin Exp Immunol. 2009; 155:423–32. [PubMed: 19220832]

92. Pawelec G, Derhovanessian E. Role of CMV in immune senescence. Virus Res. 2011; 157:175–9. [PubMed: 20869407]

93. Letendre S, Bharti A, Perez-Valero I, et al. Higher Anti-CMV IgG Concentrations are Associated with Worse Neurocognitive Functioning in People Living with HIV Disease. 2013 Under review.

94. Bruning JH, Persoons M, Lemstrom K, Stals FS, De Clercq E, Bruggeman CA. Enhancement of transplantation-associated atherosclerosis by CMV, which can be prevented by antiviral therapy in the form of HPMPC. Trans Int Off J Eur Soc Organ Trans. 1994; 7(Suppl 1):S365–70.

95. Watkins RR, Lemonovich TL, Razonable RR. Immune response to CMV in solid organ transplant recipients: current concepts and future directions. Expert Rev Clin Immunol. 2012; 8:383–93. [PubMed: 22607184]

96. Hsue PY, Hunt PW, Sinclair E, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. AIDS. 2006; 20:2275–83. [PubMed: 17117013]

97. Barrett L, Fowke KR, Grant MD. Cytomegalovirus, aging, and HIV: a perfect storm. AIDS Rev. 2012; 14:159–67. [PubMed: 22833059]

98. Bolovan-Fritts CA, Spector SA. Endothelial damage from cytomegalovirus-specific host immune response can be prevented by targeted disruption of fractalkine-CX3CR1 interaction. Blood. 2008; 111:175–82. [PubMed: 17895402]

99. Bolovan-Fritts CA, Trout RN, Spector SA. High T-cell response to human cytomegalovirus induces chemokine-mediated endothelial cell damage. Blood. 2007; 110:1857–63. [PubMed: 17519388]

100. Combadiere B, Faure S, Autran B, Debre P, Combadiere C. The chemokine receptor CX3CR1 controls homing and anti-viral potencies of CD8 effector-memory T lymphocytes in HIV-infected patients. AIDS. 2003; 17:1279–90. [PubMed: 12799549]

101. Marty FM, Winston DJ, Rowley SD, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med. 2013; 369:1227–36. [PubMed: 24066743]

102. Verghese PS, Schleiss MR. Letermovir treatment of human cytomegalovirus infection antiinfective agent. Drugs Future. 2013; 38:291–8. [PubMed: 24163496]

103. Jones TR, Sun L. Human cytomegalovirus US2 destabilizes major histocompatibility complex class I heavy chains. J Virol. 1997; 71:2970–9. [PubMed: 9060656]

104. Jones TR, Wiertz EJ, Sun L, Fish KN, Nelson JA, Ploegh HL. Human cytomegalovirus US3 impairs transport and maturation of major histocompatibility complex class I heavy chains. Proc Natl Acad Sci U S A. 1996; 93:11327–33. [PubMed: 8876135]

105. Ahn K, Gruhler A, Galocha B, et al. The ER-luminal domain of the HCMV glycoprotein US6 inhibits peptide translocation by TAP. Immunity. 1997; 6:613–21. [PubMed: 9175839]

106. Lehner PJ, Karttunen JT, Wilkinson GW, Cresswell P. The human cytomegalovirus US6 glycoprotein inhibits transporter associated with antigen processing-dependent peptide translocation. Proc Natl Acad Sci U S A. 1997; 94:6904–9. [PubMed: 9192664]

107. Jones TR, Hanson LK, Sun L, Slater JS, Stenberg RM, Campbell AE. Multiple independent loci within the human cytomegalovirus unique short region down-regulate expression of major histocompatibility complex class I heavy chains. J Virol. 1995; 69:4830–41. [PubMed: 7609050]

108. Park B, Spooner E, Houser BL, Strominger JL, Ploegh HL. The HCMV membrane glycoprotein US10 selectively targets HLA-G for degradation. J Exp Med. 2010; 207:2033–41. [PubMed: 20713594]
109. Tomazin R, Boname J, Hegde NR, et al. Cytomegalovirus US2 destroys two components of the MHC class II pathway, preventing recognition by CD4+ T cells. Nat Med. 1999; 5:1039–43. [PubMed: 10470081]
110. Hegde NR, Tomazin RA, Wisner TW, et al. Inhibition of HLA-DR assembly, transport, and loading by human cytomegalovirus glycoprotein US3: a novel mechanism for evading major histocompatibility complex class II antigen presentation. J Virol. 2002; 76:10929–41. [PubMed: 12368336]
111. Miller DM, Zhang Y, Rahill BM, Waldman WJ, Sedmak DD. Human cytomegalovirus inhibits IFN-alpha-stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN-alpha signal transduction. J Immunol. 1999; 162:6107–13. [PubMed: 10229853]
112. Paulus C, Krauss S, Nevels M. A human cytomegalovirus antagonist of type I IFN-dependent signal transducer and activator of transcription signaling. Proc Natl Acad Sci U S A. 2006; 103:3840–5. [PubMed: 16497831]
113. Taylor RT, Bresnahan WA. Human cytomegalovirus IE86 attenuates virus- and tumor necrosis factor alpha-induced NFkappaB-dependent gene expression. J Virol. 2006; 80:10763–71. [PubMed: 17041226]
114. Beck S, Barrell BG. Human cytomegalovirus encodes a glycoprotein homologous to MHC class-I antigens. Nature. 1988; 331:269–72. [PubMed: 2827039]
115. Cosman D, Mullberg J, Sutherland CL, et al. ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. Immunity. 2001; 14:123–33. [PubMed: 11239445]
116. Chalupny NJ, Rein-Weston A, Dosch S, Cosman D. Downregulation of the NKG2D ligand MICA by the human cytomegalovirus glycoprotein UL142. Biochem Biophys Res Commun. 2006; 346:175–81. [PubMed: 16750166]
117. Stern-Ginossar N, Elefant N, Zimmermann A, et al. Host immune system gene targeting by a viral miRNA. Science. 2007; 317:376–81. [PubMed: 17641203]
118. Tomasec P, Wang EC, Davison AJ, et al. Downregulation of natural killer cell-activating ligand CD155 by human cytomegalovirus UL141. Nat Immunol. 2005; 6:181–8. [PubMed: 15640804]
119. Arnon TI, Achdout H, Levi O, et al. Inhibition of the NKp30 activating receptor by pp 65 of human cytomegalovirus. Nat Immunol. 2005; 6:515–23. [PubMed: 15821739]
120. Fielding CA, Aicheler R, Stanton RJ, et al. Two novel human cytomegalovirus NK cell evasion functions target MICA for lysosomal degradation. PLoS Pathog. 2014; 10:e1004058. [PubMed: 24787765]
121. Wyrwicz LS, Rychlewski L. Cytomegalovirus immediate early gene UL37 encodes a novel MHC-like protein. Acta Biochim Pol. 2008; 55:67–73. [PubMed: 18320076]
122. Knoblach T, Grandel B, Seiler J, Nevels M, Paulus C. Human cytomegalovirus IE1 protein elicits a type II interferon-like host cell response that depends on activated STAT1 but not interferon-gamma. PLoS Pathog. 2011; 7:e1002016. [PubMed: 21533215]
123. Luttichau HR. The cytomegalovirus UL146 gene product vCXCL1 targets both CXCR1 and CXCR2 as an agonist. J Biol Chem. 2010; 285:9137–46. [PubMed: 20044480]
124. Penfold ME, Dairaghi DJ, Duke GM, et al. Cytomegalovirus encodes a potent alpha chemokine. Proc Natl Acad Sci U S A. 1999; 96:9839–44. [PubMed: 10449781]
125. Neote K, DiGregorio D, Mak JY, Horuk R, Schall TJ. Molecular cloning, functional expression, and signaling characteristics of a C-C chemokine receptor. Cell. 1993; 72:415–25. [PubMed: 7679328]
126. Benedict CA, Butrovich KD, Lurain NS, et al. Cutting edge: a novel viral TNF receptor superfamily member in virulent strains of human cytomegalovirus. J Immunol. 1999; 162:6967–70. [PubMed: 10358135]
127. Zhu H, Shen Y, Shenk T. Human cytomegalovirus IE1 and IE2 proteins block apoptosis. J Virol. 1995; 69:7960–70. [PubMed: 7494309]

128. Chiou SH, Yang YP, Lin JC, et al. The immediate early 2 protein of human cytomegalovirus (HCMV) mediates the apoptotic control in HCMV retinitis through up-regulation of the cellular FLICE-inhibitory protein expression. J Immunol. 2006; 177:6199–206. [PubMed: 17056549]

129. Skaletskaya A, Bartle LM, Chittenden T, McCormick AL, Mocarski ES, Goldmacher VS. A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. Proc Natl Acad Sci U S A. 2001; 98:7829–34. [PubMed: 11427719]

130. Goldmacher VS, Bartle LM, Skaletskaya A, et al. A cytomegalovirus-encoded mitochondria-localized inhibitor of apoptosis structurally unrelated to Bcl-2. Proc Natl Acad Sci U S A. 1999; 96:12536–41. [PubMed: 10535957]

131. Smith W, Tomasec P, Aicheler R, et al. Human cytomegalovirus glycoprotein UL141 targets the TRAIL death receptors to thwart host innate antiviral defenses. Cell Host Microbe. 2013; 13:324–35. [PubMed: 23498957]

132. Reeves MB, Davies AA, McSharry BP, Wilkinson GW, Sinclair JH. Complex I binding by a virally encoded RNA regulates mitochondria-induced cell death. Science. 2007; 316:1345–8. [PubMed: 17540903]

133. Iwamoto GK, Konicek SA. Cytomegalovirus immediate early genes upregulate interleukin-6 gene expression. J Investig Med. 1997; 45:175–82.

134. Smith PD, Saini SS, Raffeld M, Manischewitz JF, Wahl SM. Cytomegalovirus induction of tumor necrosis factor-alpha by human monocytes and mucosal macrophages. J Clin Invest. 1992; 90:1642–8. [PubMed: 1331170]

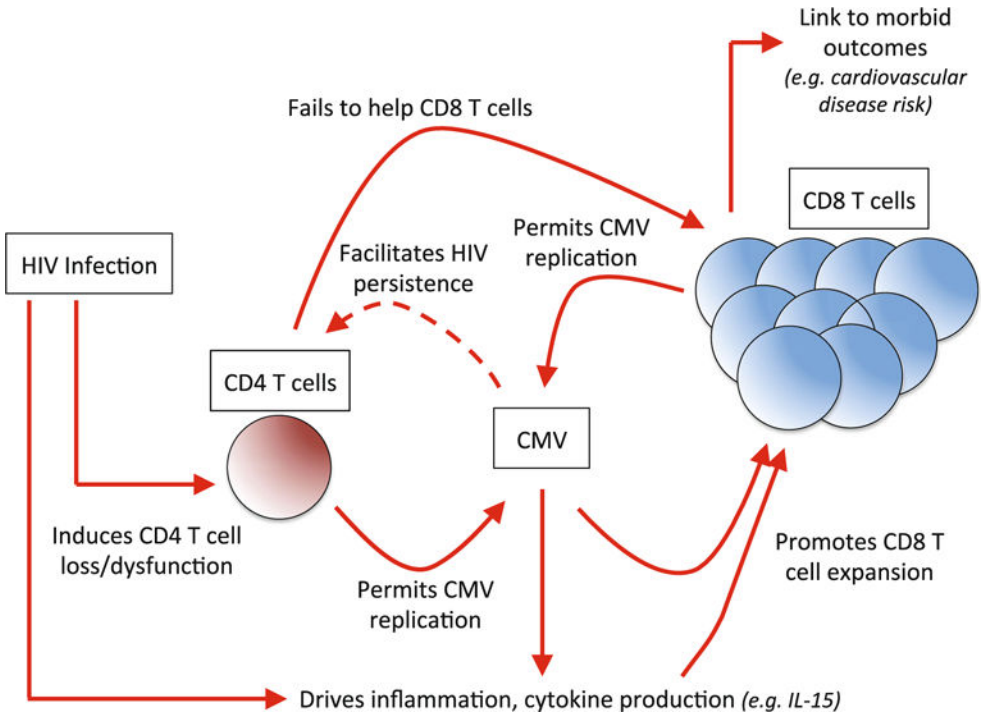

Fig. 1.

Proposed model connecting CMV, HIV, CD4 T cell dysfunction, and CD8 T cell expansion. We propose a model where HIV infection itself drives inflammation and cytokine production (for example IL-15) promoting $CD8^+$ T cell expansion. HIV infection also induces $CD4^+$ T cell loss and dysfunction, thereby failing to provide help to $CD8^+$ T cells and permitting more CMV replication, which contributes to inflammation and further promotes the expansion of $CD8^+$ T cells. Signals from CMV infection may also promote HIV persistence in $CD4^+$ T cells (dotted line). Expanded $CD8^+$ T cells are unable to control CMV replication, contributing to the vicious cycle. In addition, $CD8^+$ 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, including cardiovascular risk (and other non AIDS events)

Table 1

Summary of strategies of immune evasion and immune subversion/hijacking by CMV

Category	Strategy	Function	CMV protein/gene	References
Immune evasion	MHC class I inhibition	Destabilizes heavy chains	US2	[103]
		Impairs heavy chain transport and maturation	US3	[104]
		Inhibits peptide translocation by TAP	US6	[105, 106]
		Downregulates MHC-I heavy chains	US11	[107]
		Downregulates nonclassical HLA-G surface expression	US10	[108]
	MHC class II inhibition	Induces degradation of HLA-DR and HLA-DM	US2	[109]
		Reduces peptide-loaded MHC-II complexes	US3	[110]
	Interruption of interferon signaling	Blocks multiple levels of IFNα signal transduction	UL83	[111]
		Inhibits Stat2 signaling	IE1	[112]
		Inhibits NFκB binding to DNA	IE2	[113]
	NK cell evasion	MHC-I homolog	UL18	[114]
		Prevents surface expression of NKG2D	UL16	[115]
		Downregulates MICA, leading to NKG2D reduction	UL142	[116]
		Downregulates MICB, leading to NKG2D reduction	miR UL112	[117]
		Downregulates NK cell activating ligand CD155	UL141	[118]
		Inhibits NKp30 activating receptor	UL83 (pp65)	[119]
		Promotes lysosomal degradation of MICA	US18	[120]
		Promotes lysosomal degradation of MICA	US20	[120]
		Encodes an MHC-like protein	UL37	[121]
Immune Hijacking	Interferon stimulation	Mimics IFNγ-mediated host gene expression	IE1	[122]
	Cytokine and chemokine homologs	IL-10 homolog	UL111A	[37]
		CXCL1 homolog	UL146	[123]
		CXCL2 homolog	UL147	[124]
		CC chemokine receptor homolog	US28	[125]
		TNFR homolog	UL144	[126]
	Blocks apoptosis of infected Cells	Prevents apoptosis	IE1	[127]
		Upregulates antiapoptotic molecule c-FLIP	IE2	[128]
		Inhibitor of caspase-8 mediated apoptosis	UL36	[129]
		Mitochondria-localized inhibitor of apoptosis	UL37	[130]
		Downregulates TRAILR1 and TRAILR2	UL141	[131]
		Stabilizes mitochondrial membrane potential	RNA 2.7	[132]
	Host cytokine induction	IL-6, IL-1β	IE genes	[32, 133]
		TNFα, IFNγ, IL-15	Unknown	[33, 134]

MHC major histocompatibility complex, *NK cells* natural killer cells, *IFN* Interferon