Chapter 5

The Footprint of CMV Infection May Last a Lifetime

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1. Introduction

Cytomegalovirus (CMV) is a β-herpesvirus able to replicate in fibroblasts, endothelial cells and monocytes [1]. CMV infection is usually asymptomatic, but causes a mononucleosis-like illness in some individuals. CMV disease can manifest as a syndrome or as an acute infection of an organ or tissue. CMV syndrome is characterized by fever, leukopenia, hepato-splenomegaly, myalgias and occasionally pneumonitis. Sites of acute CMV infection include brain, heart, kidneys, liver and eyes. CMV colitis and CMV enteritis are manifestations of CMV disease in solid organ transplant recipients, bone marrow transplant recipients and HIV patients [2]. CMV retinitis was a common AIDS-defining illness before antiretroviral therapy (ART) became available, and remains a significant cause of blindness in HIV patients in the developing world [3]

In considering the role of CMV in human health, many studies have overlooked the fact that 50-90% of all populations are seropositive. As the virus has the capacity of latency and is known to be reactivated by "stress" (immunosuppression), it is likely that most people harbour latent virus [2]. Much of literature related to CMV is derived from studies of laboratory mice infected with a related virus Murine Cytomegalovirus (MCMV), which shares a similar genomic organisation and some sequence homology with human CMV. It is promoted as a useful model to study host-interaction because it shares similar in-vivo properties to human CMV after infection. Differences in the susceptibility of inbred strains of laboratory mice to MCMV infection has allowed several mechanisms of virological control to be characterised [4, 5], but there are several areas where extrapolation to human CMV is problematic.

1. CMV has over 200 reading frames with potential to encode proteins [1].Of the proteins characterised, many are redundant for viral replication *in vitro*. These include homologues of host genes "picked up" since mice and humans diverged during mammalian evolution. If we assume that such genes are retained because they confer a survival advantage, then

the pathogenic pathways initiated by the murine and human viruses must be subtly different. This has been demonstrated with CMV-encoded chemokines [6].

2. Susceptibility to murine CMV is MHC (murine *H-2*) dependent. This is evident in cultured cells and immunodeficient hosts so it is not related to $CD8^+$ T-cell responses. Rather some *H-2* Class I proteins appear to act as a cell surface receptor. There is no evidence that human HLA proteins have this role [7].

3. Without external immunosuppression, adult laboratory mice of susceptible strains can readily be infected with murine CMV at a dose that destroys their spleen and other organs, and may cause death [4].This is not seen in people, but has been used in many studies to examine immune responses to CMV.

4. *In vitro* infection of monocytes, macrophages and dendritic cells with murine CMV [8, 9] creates cells which remain intact but selectively loose secondary functions. This is interesting but not an important mode of immunoregulation, as only a small percentage of cells of these lineages are infected in patients or more resistant mice.

To avoid translational issues between studies of MCMV in mice and HCMV in humans, we need to look more closely at people infected with CMV. This must include primary disease and the effects of long term asymptomatic CMV infection in immune competent hosts. A lesson that we can take from MCMV is the effects on multiple cells and organs, including the adrenals, pancreas and salivary glands [4, 5, 10, 11]. Sensitive PCR-based viral load assays are now available, but these are only routinely applied to blood, urine or saliva of patients at risk of acute disease. There is little probability of detecting latent CMV. Here we present a tool to evaluate the lifetime effects of CMV on human health - the footprint of CMV. We also summarise evidence that natural killer (NK) cells may regulate the footprint of CMV. The likely impact in HIV patients is presented as Figure 1.

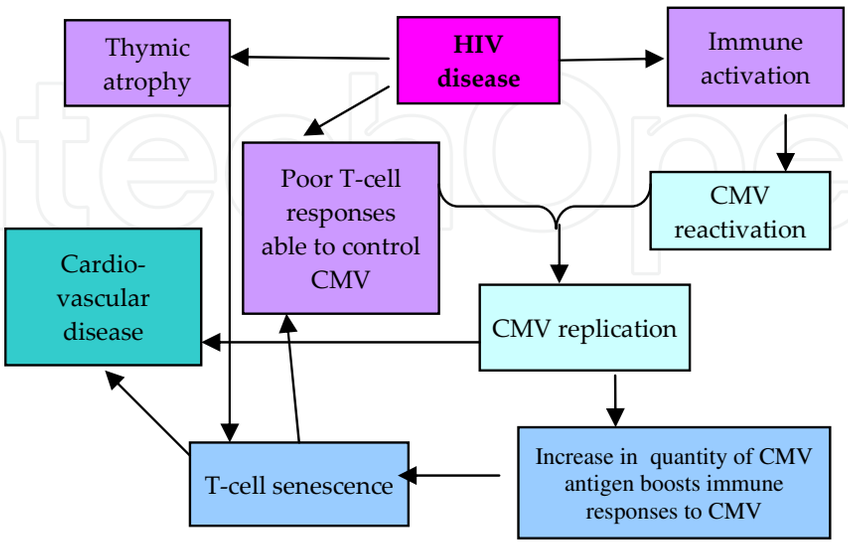

Figure 1. HIV disease has several avenues to enhance the footprint of CMV and thereby promote cardiovascular disease.

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2. Immune control of CMV

T-cell and antibody responses may reflect CMV replication rather than protect against it. CD8+ T-cell responses to CMV can be assessed by IFNγ ELISpot or using tetramers or pentamers that mark cells reacting with a particular CMV peptide presented by a particular HLA molecule (usually HLA-A2). Gamadia *et al* [12]reported that frequencies of CMV-specific $CD8^+$ T-cells were significantly higher in immunosuppressed transplant recipients than in healthy donors, suggesting that these responses may reflect exposure rather than protection. This is consistent with evidence that CMV encodes proteins that down regulate T-cell recognition of infected cells, and thus evade immune detection. This includes the degradation of HLA class I and II molecules by unique short (US) proteins and disruption of antigen processing by an infected antigen-presenting cell [13].CMV-specific cells predominantly have an effector-memory or senescent phenotype ($CD45R0^+CD27^-CCR7^-$ or $CD45RA^+CD27^-CCR7^-$, resp.). Subsequent studies suggest that a rapid $CD4^+$ T-cell response was also essential to avoid symptomatic primary CMV infection in renal transplant recipients [14], but the cells critical for the maintenance of latency have not been identified.

Extensive studies of MCMV infection in laboratory mice have mapped protective NK cell-mediated responses to the Ly49 gene cluster [equivalent to human Killer Cell Immunoglobulin-like receptor (KIR) genes]. Mouse strains have distinct Ly49 gene repertoires, which correlate with resistance to MCMV [15]. The activating receptor Ly49H is implicated in protection, and several members of the Ly49 family interact with MCMV encoded proteins [16]. In mice without a protective NK response (eg: through Ly49H), MCMV infections are eventually controlled by T-cells. $CD4^+$ T-cells are needed to control MCMV persistence in the salivary gland [17]. $CD8^+$ T-cells recognising immediate early (IE) epitopes are also implicated in control of reactivated MCMV, where frequent boosting expands specific $CD8^+$ T-cell clones. MCMV encodes genes able to regulate MHC class I expression, demonstrating an evolutionary impetus to avoid $CD8^+$ T-cell responses. Critical epitopes and *H-2* loci initiating protective $CD8^+$ T-cell responses have been identified, but it is a limitation that all studies use laboratory strains of MCMV rather than primary isolates [18]. This highlights the need to study human CMV disease.

Direct evidence that NK cells can control CMV in humans is available from a study of a congenitally T-cell deficient child with acute CMV infection and a 10-fold expansion of NK cells with restricted receptor diversity. Acute illness resolved and NK cells returned to normal levels with clearance of plasma CMV DNA [19].This fits teleological and genetic evidence that NK cells control CMV. Human and mouse CMV diverged with their host species and have independently evolved proteins able to subvert protective NK responses [20]. This includes homologues of HLA-G (UL18) and HLA-E signal peptide (UL40), which interact with NK inhibitory receptors (LIR-1 and NKG2C, resp.) (Reviewed in[21]) In support of a role for NK cells in CMV and HIV disease, we showed that heterozygous carriage of allele 2 at LIR-1 (rs1061680; LILRB1 I142T) associated with CMV disease and nadir $CD4^+$ T-cell counts [22].

A role for NK cells in the control of CMV is also consistent with evidence that carriage of more genes for activating KIR receptors protects against CMV reactivation in immunosuppressed

renal [23, 24] and bone marrow [25, 26] transplant patients. KIR receptors in man comprise both inhibitory and activating members (as do Ly49 genes in mice). The ligands for most inhibitory KIR are allelic epitopes of the classical class I HLA proteins (reviewed in[27]). In contrast, ligands for most of the activating KIR are unknown. An exception is KIR2DS1, which interacts with HLA-C2. [28, 29]. Several groups have attempted to identify the CMV-protective KIR gene, but this is complicated by linkage disequilibrium in the KIR gene complex. Inhibition of NK killing of fibroblasts infected by CMV has been demonstrated by several groups [30].This study implicated UL18 but this may depend on the NK donor's genotype. Although the roles of specific NK receptors in CMV disease are unclear, increased expression of LIR-1 [31, 32] and/or NKG2C [33, 34] is a consequence (footprint) of CMV replication. This has potential as a tool to assess a history of CMV reactivation.

3. CMV has a footprint in healthy aging and cardiovascular disease

Associations between CMV and vasculopathy have been described since 1987 [35] and attributed to immunopathological events initiated by viral replication. Our studies of MCMV in inbred mice showed that susceptible BALB/c mice develop myocarditis in which CD8+ T-cells accumulate in the myocardium and persist for 12 months despite clearance of viral antigen by day 3 [36]. In C57BL/6 mice have a protective NK response [5] and display only mild resolving myocarditis. To evaluate the evidence available in patients requires consideration of the underlying mechanisms.

Inflammation and activation of immune cells features throughout atherogenic plaque formation, which is the principle condition of cardiovascular disease (CVD). Pathogenesis of atherosclerotic plaques on vessel walls begins with acute inflammation resulting in endothelium dysfunction [37]. Many life-style risk factors can reduce the integrity of endothelium. The accumulation of low density lipoproteins (LDL) in intimal space by diffusion and its oxidation can cause endothelial cell injury and inflammation [38]. Secretion of vascular cell adhesion molecule-1 (VCAM-1) and up-regulation of selectins and integrins facilitates leukocyte adhesion to vessel walls. Inflammatory cytokines such as IL-1 and TNF-α induce expression of chemokines (eg: CCL2, CXCL8, CX3CL1) by endothelial cells, recruiting T-cells and monocytes and facilitating their transmigration into the intimal space. Monocytes internalize LDL and differentiate into macrophages which promote inflammation and leukocyte migration into developing plaques by secretion of CX3CL1/CX3CR1, interferon-γ (IFNγ) and CCL2 [39, 40] and generation of reactive oxygen species [41]. Hyperlipidemia, macrophage death and consequential irregular surfaces of vessel endothelium promote growth of the atherosclerotic lesion. Smooth muscle cells migrate from the media to intimal space aided by lytic enzymes. This contributes to plaque instability [39]. Smooth muscle cells proliferate in intimal space and also adhere to monocytes [42], thickening arterial walls and occluding the vessel. Rupture of the plaque can result in infarction. Myocardial infarcts (MI) refer to rupture of plaque in the coronary artery. The carotid artery is also a frequent site of plaque formation and thickness of the intima at this site can indicate clinical and sub-clinical CVD [43].

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Active CMV infection has been associated with the onset of autoimmune disorders in transplant patients and healthy donors. The development of autoimmune antibodies following reactivation of CMV in transplant patients has been linked to graft versus host disease and graft rejection. Hypergammaglobulinemia and autoantibody production can also be a feature of CMV-induced mononucleosis. There have been several case reports of healthy individuals developing acute CMV infection preceding vasculitis or encephalitis. In a case of encephalitis, treatment of active CMV with valganciclovir resolved symptoms, but CMV-specific $CD4^+$ and $CD8^+$ T-cells remained 10 months after disease onset [44-]. The development of autoimmune vasculitis, systemic lupus erythematosus, sclerodoma and necrotizing vasculitis have been associated with CMV replication [46]. Anti-phospholipid antibodies have been shown to activate endothelial cells and CMV transcription [47], suggesting a feedback amplification loop.

CMV seropositivity has been correlated with a greater risk of all-cause mortality in the elderly [48-]. Although it is rare for CMV to be identified as the primary cause of death, CMV prevalence in the older population can be as high as 100% [52]. An in-depth study following Latinos aged 60-101 years for a period of 9 years (n=1,468) showed that those with high CMV antibody titres were 1.43 times more likely to die and had 1.35 times greater risk of CVD-associated mortality than those with low CMV antibody titres [51]. 96% of the participants were CMV seropositive. Factors significantly ($p<0.05$) associated with mortality included age, female gender, low education level and levels of inflammatory markers (TNF, IL-6, C-reactive protein). Elderly CMV-seropositive patients respond less well to seasonal influenza vaccination than those with low or negative CMV seropositivity [50, 53]. This suggests dysfunction of the immune system and could account for the increased risk of all-cause mortality.

In older CMV-seropositive adults, up to 23% of the T-cell population can be CMV-specific. For example, NLV peptide-specific $CD8^+$ T-cells alone comprised a median 3% (range = 0.4-5.6%) of $CD8^+$ T-cells in donors aged 90 [89-96] years. CMV-specific T-cells are generally CD28-negative(an immunosenescent phenotype also associated with expression of CD57 and shortened telomeres) and have limited proliferative potential, but may produce IFNγ. Their accumulation correlates with immunologic aging or ''immunosenescence'' evident in the entire T-cell population assayed *ex vivo* [54-].The accumulation of senescent CMV-reactive T-cells was greatest in frail and institutionalized elderly donors [58].Repeated sub-clinical CMV infections may expand CMV-specific T-cells clones until they suppress homeostatic expansion of other T-cells. Alternatively the expanded clones of CMV-reactive cells may bias the population and dilute cells of other specificities - explaining why EBV-reactive T-cells do not show a senescent phenotype [54].

However chronic CMV reactivation may have wider consequences than just an aging immune system. CMV infects endothelial cells in acute stages of infection and it is proposed they could also be a site of latent infection [59, 60]. Studies of murine CMV in mice have identified endothelial cells as a site of viral latency [61], whilst several studies demonstrated human CMV in arterial walls of atherosclerotic and non-atherosclerotic patients [62, 63]. A study of tissues removed during surgery for abdominal aortic aneurysm associated the presence of CMV DNA in smooth muscle cells with expression of inflammatory mediators and implicated CMV in the pathology [64]. Accordingly higher CMV antibody titres are associated with increased diastolic and systolic blood pressure in young men [65] and CMV seropositivity is more frequent in

coronary artery disease requiring surgery[66]. Increased expression of LIR-1 on NK cells (a footprint of CMV) is also associated with atherosclerosis [67].Stronger T-cell responses to CMV also associate with severe cardiovascular changes seen in HIV patients [68].

The chemokine, fractalkine (CX3CL1) and its receptor CX3CR1 are membrane-bound proteins. CX3CL1 can be cleaved from a cell surface through TNFα signal pathways to mediate attraction and then firm adhesion of lymphocytes expressing CX3CR1 to endothelium. T-lymphocytes and monocytes express CX3CR1, whilst monocytes, endothelial cells and smooth muscle cells can be induced to express CX3CL1 by TNFα, IFNγ, IL-1 and LPS [37, 69, 70].CX3CR1 is found in atherosclerotic plaques and its role in plaque formation and mediation by inflammation is of interest in the management of CVD [69]. An *in vitro* system co-coculturing CMV infected endothelial cells and peripheral blood mononuclear cells established the principle that CMV specific CD4+ T-cells can induce CX3CL1 production in CMV infected endothelial cells. CX3CL1 aids the ingress of monocytes and NK cells which are capable of killing the CMV infected endothelial cell [71].

Monocytes in atherosclerotic plaques express higher levels of CX3CR1 and CX3CL1 promoting chemotaxis of monocytes and T-lymphocytes to the plaque [72].CX3CL1 can be expressed by epithelial cells, but vascular endothelial cells and smooth muscle cells do not normally express CX3CL1. TNFα can induce expression of CX3CR1/L1 in these tissues [70], which corresponds with detection of CX3CR1/L1 at a later stage of plaque formation. Sacre *et al*. reported that $CD4^+CX3CR1^+$T-cells produced more TNFα and IFN γ *in vitro* than $CD4^+CX3CR1^-$ T-cells. This is consistent with a potential feedback mechanism in which $CD4^+CX3CR1^+$ T-cells exacerbate plaque formation. Immuno-histochemical staining of coronary arterial wall samples from HIV patients with atherosclerosis showed a presence of CX3CR1, CD4 and CD3 at *early* stages of atherogenesis, so $CD4^+CX3CR1^+$ T-cells could initiate plaque formation [73].

4. HIV patients stable on ART have a stronger footprint of CMV

In HIV patients with suppressed HIV replication on ART, the recovery of $CD4^+$ T-cell counts is limited by replenishment from the thymus and the loss of T-cells through persistent chronic immune activation [74, 75].Persistent CD4+ T-cell deficiency is most common in patients with low nadir CD4+ T-cell counts (<100 cells/μl) even though some patients beginning ART with severe T-cell depletion achieve effective immune reconstitution [76]. Patients with abundant thymic tissue show a faster and higher return of naïve $CD4^+$ T-cells after ART. However the thymus is a site of HIV replication. Infected thymocytes may die (through necrosis or apoptosis) or survive and carry the HIV provirus to their progenies (establishing latent infection). As HIV disease progresses, the thymus becomes prematurely atrophic, with changes similar to those seen in old age. For example, the thymus of a 30 year-old with late stage AIDS may be morphologically similar to the normal atrophic thymus of a 60 year-old [77].

Thymic dysfunction and the consequent release of autoreactive T-cells into circulation are implicated in the autoimmune and immunopathological conditions normally seen in old age - conditions that are more common in HIV patients (including those with a virological response

to ART) than in the general population. This includes cardiovascular disease – which is influenced by the ART regime, life-style factors (smoking, exercise etc.) and other infections, notably CMV. CMV infection is more prominent in HIV patients, so its role in immunological aging and cardiovascular disease requires evaluation [78].

Over 50% of healthy individuals and 90% of individuals living with HIV are seropositive for CMV. Retinitis is the most common manifestation of CMV disease in HIV-infected individuals, affecting up to 40% of American AIDS patients, and many HIV patients in the developing world [3, 79].Treatment of systemic CMV disease is expensive and protracted, so prophylaxis is suspended once patients are stable on ART. As discussed earlier, CMV has the capacity for latency with frequent reactivation triggered by inflammatory mediators, including TNF [80]. Immune activation in treated and untreated HIV disease increases levels of this cytokine in circulation and tissues [81], so frequent subclinical reactivation of CMV is expected.

It appears likely that CMV and thymic insufficiency are synergistic in their effects on T-cell profiles in HIV patients. This is supported by evidence that homeostatic expansion of existing T-cells maintains T-cell numbers in the absence of thymic output, so age-related declines in immune function are accentuated in patients thymectomised in early childhood. This was clearest in individuals with strong T-cell responses to CMV IE and pp65 antigens [82].Accumulation of CMV –specific T-cells with an immunosenescent phenotype is greater in HIV patients than in age-matched controls [83, 84]. The importance of CMV in immune activation and immunosenesence in HIV patients is confirmed by evidence that immune activation was reduced when patients were treated with valgancyclovir [85].

Our studies of HIV patients also suggest that elevated T-cell and humoral responses to CMV reflect frequent reactivation. We investigated HIV patients who began antiretroviral therapy (ART) with extreme immunodeficiency and maintained a virological response until they were >50 years old. One can assume that they had a high burden of CMV pre-ART as many had experienced CMV retinitis. These HIV patients retained high titres of antibody reactive with CMV after 14 [13-16] years on ART and displayed elevated IFNγ responses to an immediate early peptide of CMV*(unpublished data).*Such patients display accelerated cardiovascular disease that correlates with responses to CMV [86].

CD4+CX3CR1+ T-cells may help explain the role of CMV-specific cells in development of atherosclerosis in HIV patients, but the mechanisms requires further investigation. Interest in CX3CR/L in atherosclerosis is focussed by three findings reported in several studies.

1. Atherosclerosis is an inflammatory disease that is more frequent in HIV patients and cannot be attributed to ART cardiotoxicity alone [87, 88, 89, 90, 91].
2. HIV patients have a high proportion of CMV-specific T-cells [82, 83, 92]
3. CX3CR1 is found in atherosclerotic lesions and is expressed by T-cells [69,70]

A study of CX3CR1+ CD4+ T-cells and their implications in CVD was conducted in HIV-infected (n=29) and uninfected (n=48) individuals. The frequency of $CD4^{+}CX3CR1^{+}$ T-cells correlated with increasing carotid intima-media thickness (cIMT) in HIV-infected individuals.

These cells were antigen primed ($CD45RA^-$, $CD27^-$), activated (HLA-DR+) and immunosenescent ($CD57^+$) [73].

It may also be important that NK function is deficient in HIV patients. HIV infection changes the proportions of NK cell subsets, and expression of their activating and inhibitory receptors. It also perturbs their cytotoxic functions and cytokine production [93].Our group has published two studies of previously immunodeficient Australian patients, stabilised for many years on ART:

1. CD4+ T-cell IFNγ responses to CMV were *inversely* related to CD4+ T-cell counts before ART in patients who began ART with <60 CD4+ T-cells/μL, but IFNγ responses of NK cells to an unrestricted target (K562 cells) were *directly* proportional to nadir CD4+ T-cell counts [94].This establishes that NK cells don't follow the same trends as CD4+ T-cells on ART and do keep the imprint of the pre-ART immune system for many years.

2. NK cell IFNγ responses and proportions of $CD56^{lo}CD16^+$ NK cells were positively correlated and lower in patients than controls (confirming persistent NK dysfunction). Proportions of $CD56^{hi}CD16^{neg}$ NK cells (a phenotype associated with cytokine production) correlated inversely with CD4+ T-cell counts after ART and expression of perforin in this NK subset was *higher* in HIV patients than healthy controls. So these NK cells may compensate for T-cell deficiency [95].

5. CMV remains an important pathogen after renal transplantation

CMV reactivation (in previously seropositive recipients) or primary infection (in any recipient) is the most common infectious complication in renal transplantation [96].In the 1970's one in three recipients experienced pathologies associated with CMV. In one study of 141 patients, 12 *died* with disseminated CMV infection [97, 98].

In Australia, prophylaxis (valganciclovir) is routinely administered for 12-26 weeks after transplantation, according to a formula that considers donor and recipient CMV seropositivity and clinical risk. Under an equivalent regime, CMV recurred in 14/43 (33%) seropositive patients and in 4/19 (21%) patients after primary infection [99]. CMV remains a significant cause of graft loss despite prophylaxis and in the longer term, CMV reactivations are implicated in deterioration in renal function [100, 101], exhaustion or senescence of T-cells and cardiovascular disease.

Cardiovascular disease is recognised as a long term complication of renal transplantation, but a recent review [102] attributed this to immunosuppression. CMV antigenaemia (pp65) in the first year post-transplant did not predict cardiovascular disease over the next 2 years [102], but the study did no assess the longer term footprint of CMV disease. It is notable that Gomez et al [103] associated cardiovascular disease with CMV seropositivity over 1 year post-transplant in patients given oral ganciclovir.

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6. Conclusions

The immune response to CMV has been studied extensively in mice and evidence is now accumulating from studies in humans. It is clear that NK cell and T cell responses are both important and that they influence each other. We propose a "footprint of CMV" as a tool to investigate the short and long term effects of CMV infection.

The footprint may include

1. CMV DNA detected by a sensitive PCR assay of blood, saliva or urine.
2. CMV-peptide/HLA tetramer positive CD8 T cells: The number of these cells in the blood is thought to reflect an accumulation of cells responding to CMV replication.
3. IFN-γ responses of $CD4^+$ and $CD8^+$ T-cells to CMV antigens enumerated by ELISPOT or flow cytometry.
4. Anti-CMV antibody detected by ELISA
5. Expression of NKG2C and LIR-1 on NK cells and T cells: NKG2C is expressed on a very small proportion of NK cells in CMV-seronegative subjects but expressed on a substantial proportion of NK cells from CMV seropositive subjects [31,32,33]and is considered a hallmark of CMV exposure. This probably reflects expansion of a small NK cell population in response to CMV infection. LIR-1 expression is also increased in subjects with higher titres of CMV antibody.

The resulting holistic view of the immune response in man will be a foundation for future studies aimed at identifying phenotypes associated with protection and those individuals who will benefit most from CMV prophylaxis.

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