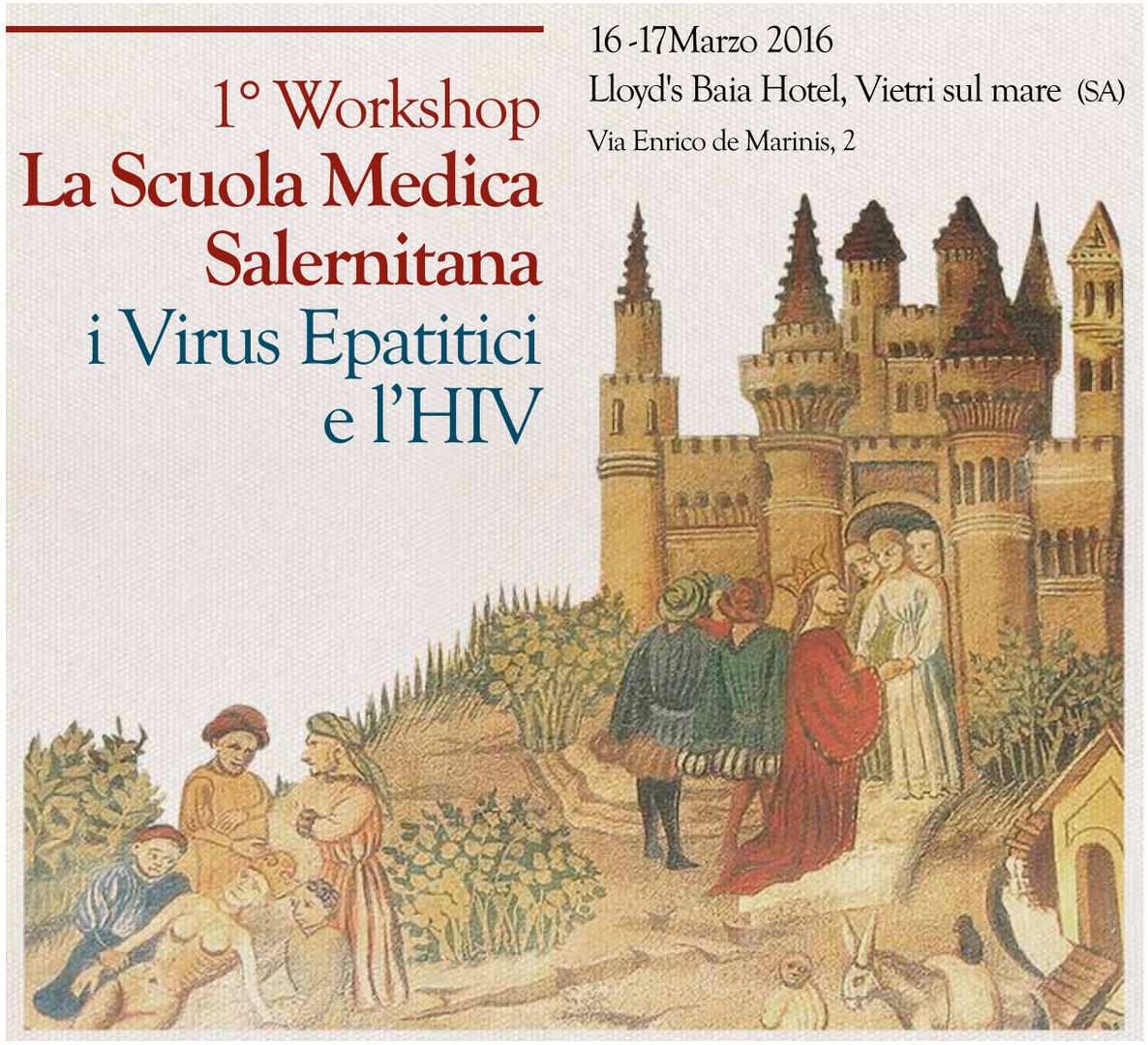


il ruolo del CMV nell'infezione da HIV

Giustino Parruti
UOC Malattie Infettive
Pescara

FONDAZIONE ONLUS
CAMILLO DE LELLIS
per l'innovazione e la ricerca in medicina

Azienda USL di pescara

index of topics

- hCMV features: why such an interesting complexity
- immune activation and modulation mechanisms in hCMV mono-infection
- HIV - CMV relationships
- CMV relevance on clinical outcomes of HIV infection in the era of HAART

which virus is hCMV

- 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

- Primary CMV infection in immunocompetent hosts is often asymptomatic or minimally symptomatic, but morbidity and mortality dramatically increase during immunodeficiency (particularly transplant recipients and HIV-infected people)

frontiers in Microbiology

MINI REVIEW
published: 24 September 2015
doi: 10.3389/fmicb.2015.01016

Ongoing burden of disease and mortality from HIV/CMV coinfection in Africa in the antiretroviral therapy era

Emily Adland[1], Paul Klenerman[2,3,4], Philip Goulder[1,5] and Philippa C. Matthews[2,3]*

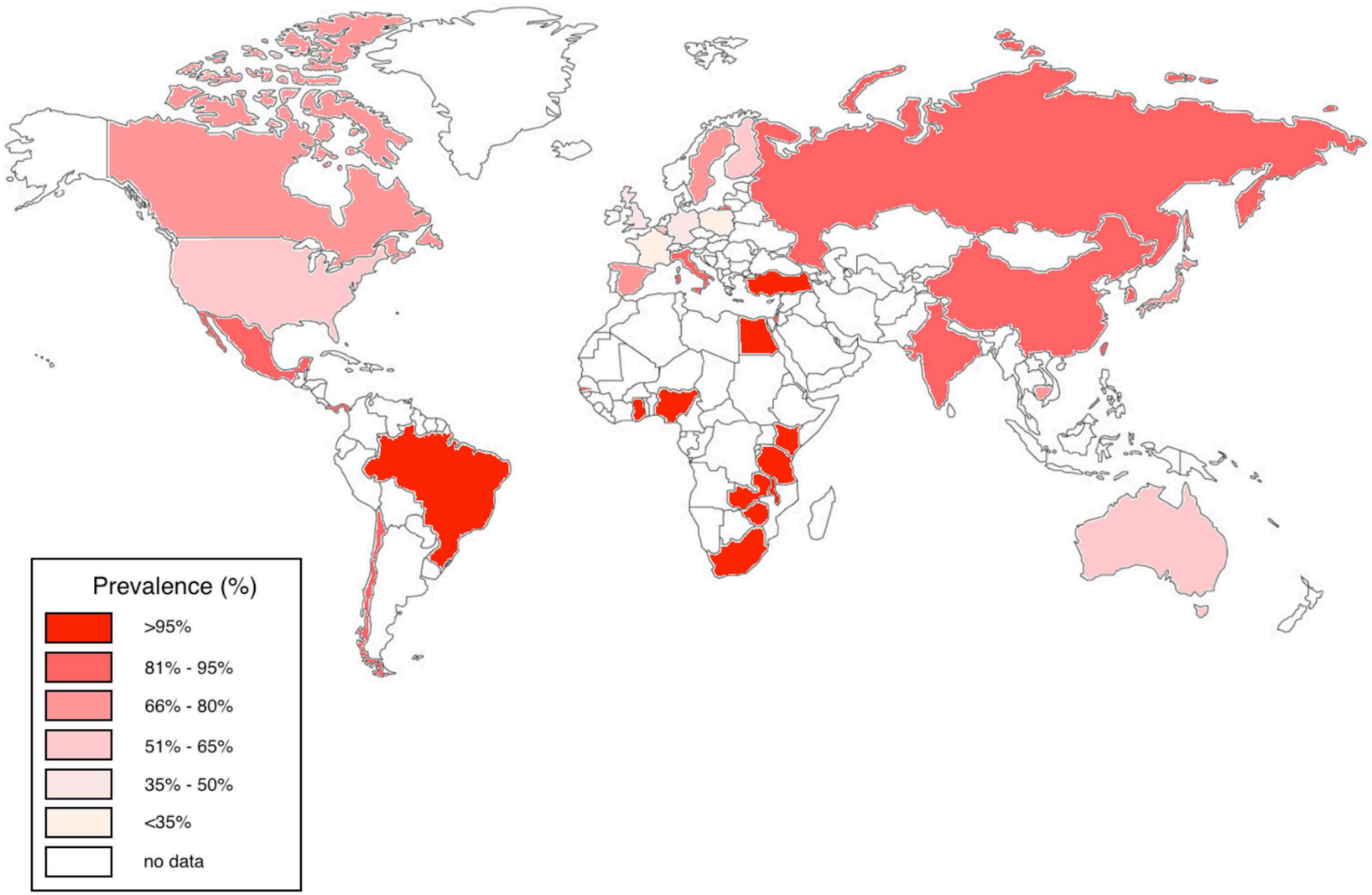


FIGURE 1 | Worldwide CMV seroprevalence rates in adults. We have represented studies of adults aged 16–50 years published between 2005 and 2015 from Australia, Belgium, Brazil, Canada, Cambodia, Chile, China, Finland, France, Gambia, Germany, Ghana, India, Israel, Italy, Japan, Kenya, Mexico, Nigeria, Panama, South Africa, Spain, Sweden, Taiwan, Tanzania, Turkey, UK, USA, Zambia, and Zimbabwe (Chakraborty et al., 2003; Schlesinger et al., 2005; Miles et al., 2007, 2008; van der Sande et al., 2007; Zhang et al., 2007; Dar et al., 2008; Alao et al., 2009; Compston et al., 2009; Micol et al., 2009; Pass et al., 2009; Cannon et al., 2010; Chakravarti et al., 2010; Fielding et al., 2011; Brantsæter et al., 2012; Hsiao et al., 2013; Manicklal et al., 2013, 2014; Gumbo et al., 2014; Lanzieri et al., 2014; Mwaanza et al., 2014; Schaftenaar et al., 2014; Lichtner et al., 2015; Tembo et al., 2015; Viljoen et al., 2015).

CMV latency and co-existance

- After primary infection, **the virus establishes episomal latency in pluripotent CD34+ hematopoietic stem cells in the bone marrow**

- **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

- CMV can infect **a host of different cell types**, including fibroblasts, endothelial cells, muscle cells, and brain-derived pericytes

- Recent studies have added perivascular mesenchymal stroll cells that encircle capillaries and vessels throughout the body

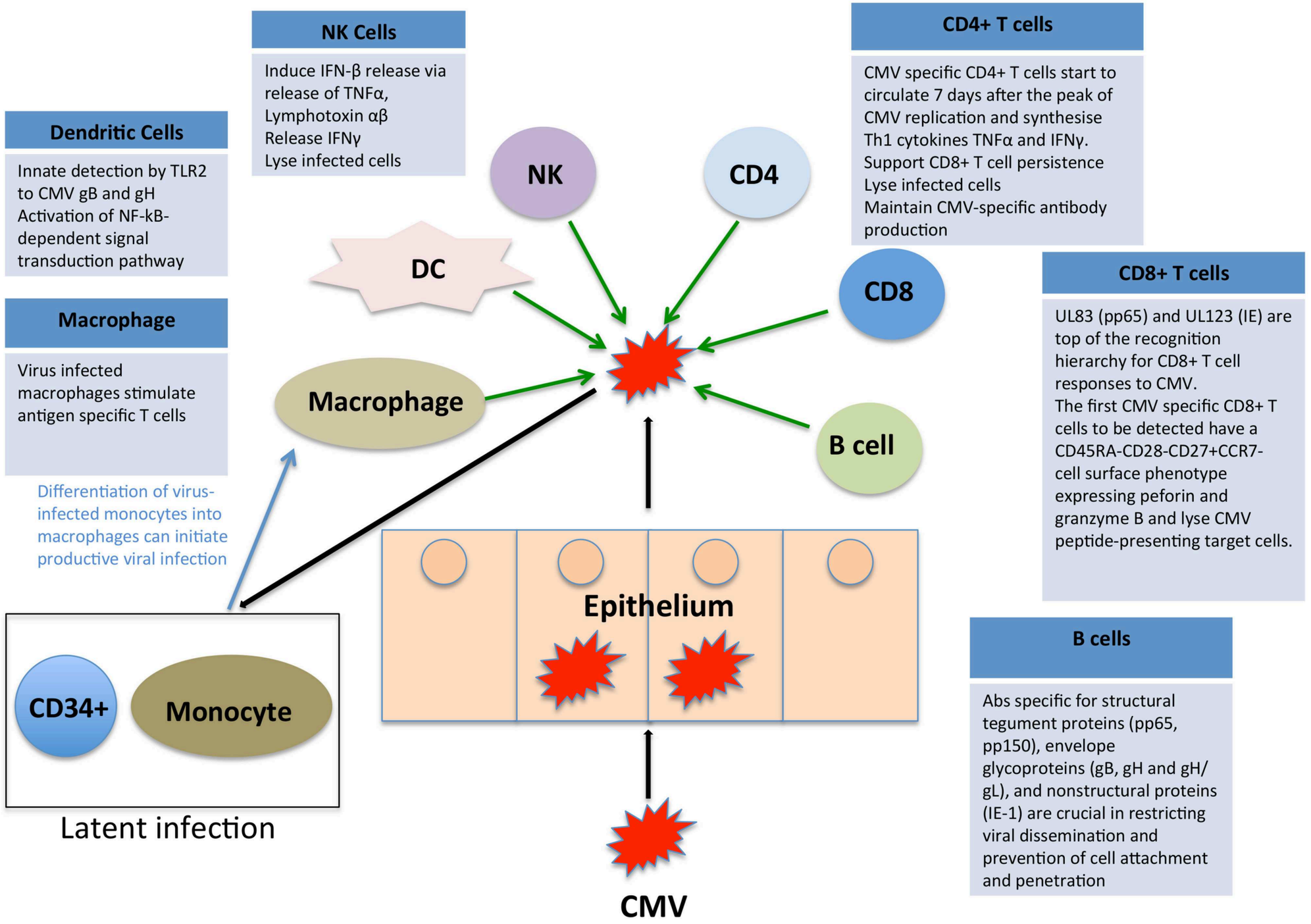


FIGURE 2 | Impact of the immune system on CMV. CMV immune control is reliant on both the innate and adaptive arms of the immune system. We have here summarized the key elements, highlighting the complex interplay of multiple limbs of the immune system in containing CMV infection.

CMV latency and co-existance

- Episodic bursts of asymptomatic CMV reactivation are frequently documented in the **genital tract and in saliva** and are rapidly controlled by cell-mediated immune-surveillance

- When an infected person has **a compromised immune system, shedding of CMV increases dramatically**.

- Almost half HIV-infected homosexual men asymptomatically shed CMV in their genital tract, regardless of CD4+ T cell counts or use of ART, at any time of their life

where does CMV reactivate?

- Other sites of CMV reactivation are:
  - oral mucosa in 15-30% of HIV
  - peripheral blood mononuclear cells in 13–20% of HIV
  - urine, in 10–30% of HIV
  - stool and breast milk - relevant to post-natal infection
- **Asymptomatic shedding** at different mucosal sites is important for the natural history and transmission dynamics of CMV, and also for the **interplay of CMV with other co-infecting viruses as HIV**

CMV genetics

- With a large 230-kB genome, CMV is one of the largest viruses to infect humans

- CMV has as many as **751 CMV open-reading frames translated into CMV proteins** in virus-infected cells, suggesting that the CMV proteome is far more complex than recognized

- many of these proteins are 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

strategies of CMV persistence in the human host

- success of CMV to persist in the human population is based on **complex strategies of immune evasion**, rather than rapid mutation of target proteins

- Nonetheless, there is genetic and antigenic heterogeneity among CMV isolates, which likely affects and makes more complicated their interaction with the human host

- Since **CMV replication is enhanced by inflammatory stimuli,** it is not surprising that the **virus developed ingenious strategies to induce and augment inflammation** in the host

CMV - cytokine interactions

- 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

- CMV infection has also been associated with **increase of IL-15** in plasma, as other herpesviruses

- The elicitation of IL-15 and other common γ-chain cytokines including IL-2 and IL-7 can **drive antigen non-specific activation**, proliferation, and **expansion of naïve and memory** CD4 and CD8 T cells

- 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

complex CMV immune modulation

- CMV has also developed mechanisms to avoid immune recognition and protect infected cells from attack by host defenses

- **CMV impairs antigen presentation** by inhibiting the expression of HLA class I and class II molecules

- CMV can also **induce immune-inhibitory pathways (PD-1 and IL-10)** and inhibit activation of natural killer (NK) cells by virus-encoded HLA class I homologs and NK cell immune evasion proteins

Table 1 Summary of strategies of immune evasion and immune subversion/hijacking by CMV

Category	Strategy	Function	CMV protein/gene
Immune evasion	MHC class I inhibition	Destabilizes heavy chains	US2
		Impairs heavy chain transport and maturation	US3
		Inhibits peptide translocation by TAP	US6
		Downregulates MHC-I heavy chains	US11
		Downregulates nonclassical HLA-G surface expression	US10
	MHC class II inhibition	Induces degradation of HLA-DR and HLA-DM	US2
		Reduces peptide-loaded MHC-II complexes	US3
	Interruption of interferon signaling	Blocks multiple levels of IFNα signal transduction	UL83
		Inhibits Stat2 signaling	IE1
		Inhibits NFκB binding to DNA	IE2
	NK cell evasion	MHC-I homolog	UL18
		Prevents surface expression of NKG2D	UL16
		Downregulates MICA, leading to NKG2D reduction	UL142
		Downregulates MICB, leading to NKG2D reduction	miR UL112
		Downregulates NK cell activating ligand CD155	UL141
		Inhibits NKp30 activating receptor	UL83 (pp65)
		Promotes lysosomal degradation of MICA	US18
		Promotes lysosomal degradation of MICA	US20
		Encodes an MHC-like protein	UL37
Immune Hijacking	Interferon stimulation	Mimics IFNγ-mediated host gene expression	IE1
	Cytokine and chemokine homologs	IL-10 homolog	UL111A
		CXCL1 homolog	UL146
		CXCL2 homolog	UL147
		CC chemokine receptor homolog	US28
		TNFR homolog	UL144
	Blocks apoptosis of infected Cells	Prevents apoptosis	IE1
		Upregulates antiapoptotic molecule c- FLIP	IE2
		Inhibitor of caspase-8 mediated apoptosis	UL36
		Mitochondria-localized inhibitor of apoptosis	UL37
		Downregulates TRAILR1 and TRAILR2	UL141
		Stabilizes mitochondrial membrane potential	RNA 2.7
	Host cytokine induction	IL-6, IL-1β	IE genes
		TNFα, IFNγ, IL-15	Unknown

is CMV role “that bad”?

- CMV had millions of years to optimize its interaction with *homo sapiens* and it is possible that beneficial effects during reproductive age might have favored its persistence

- studies comparing young and old CMV-infected adults showed **possible beneficial features in the youth**, including:
  - increased antibody response to influenza vaccination
  - elevated levels of IFN gamma and increased CD8 Tcell sensitivity

- as lifelong interaction between CMV and the host not only controls viral reactivation, but also modulates the immune system, the term **“normal” immune system might include persistent infections** as CMV

a costly equilibrium

- CMV elicits and maintains a high frequency of virus-specific T cells that engage in a life-long effort to restrain CMV replication and prevent life-threatening disease

- In HIV-uninfected individuals, **approximately 10% of both CD4 and CD8 memory T cells** in the circulation target CMV antigens; these frequencies increase to about one third of CD4+ T cells and nearly half of CD8+ T cells in older persons

- In HIV-infected adults, CMV-specific CD8 and CD4 T cell numbers are further elevated, similar to the proportions observed in the HIV-uninfected elderly, and **remain high even after suppression of HIV replication**

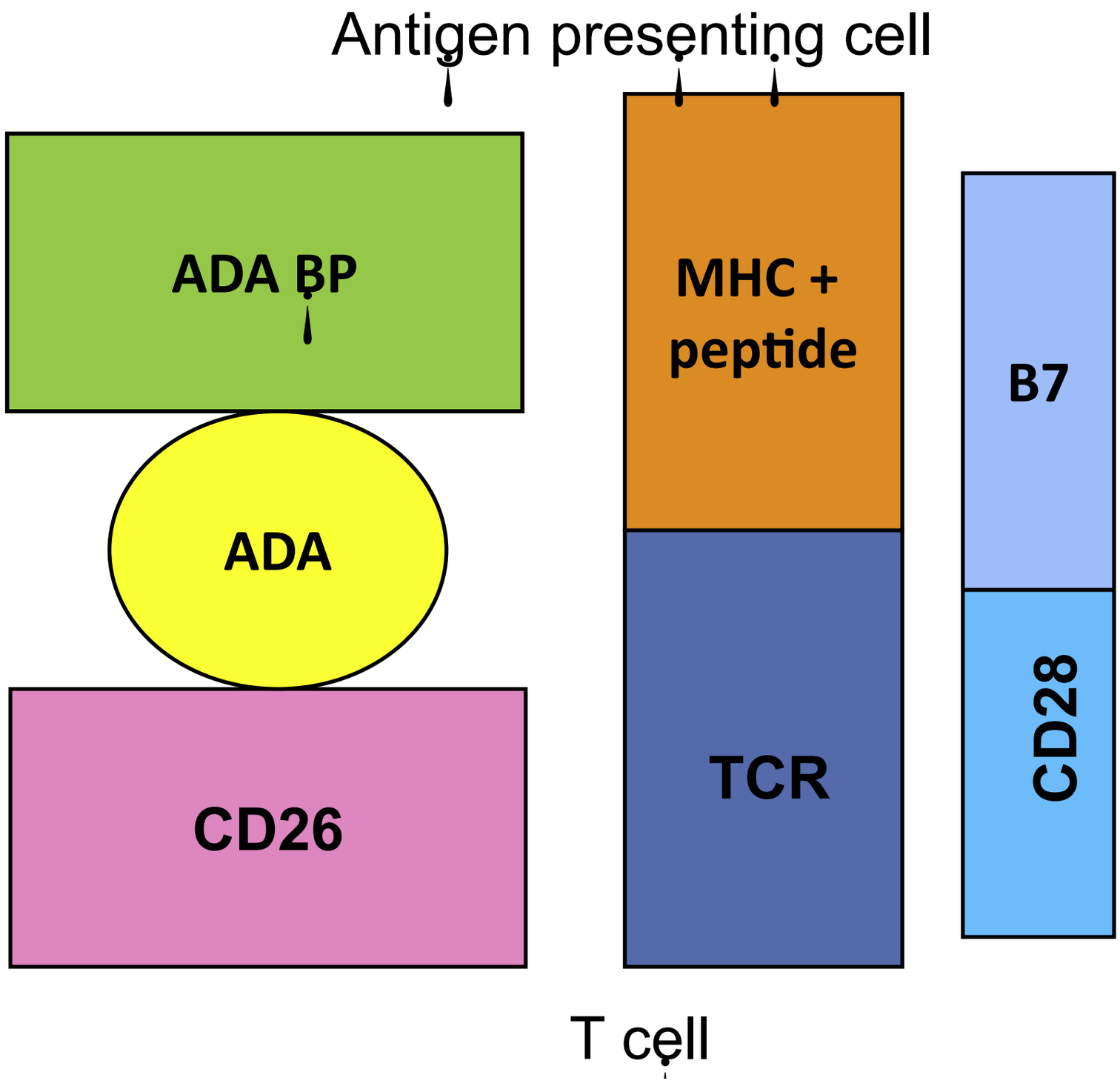
a huge army for life long

- As CMV-infected persons age, an increasing proportion of their T cell repertoire becomes CMV-reactive

- as a result of repeated exposure to CMV peptides, these cells have **a replicative exhaustion and senescence phenotype** (loss of CD28 and the complex ADA/CD26)

- in some individuals, the expansion of the T cell repertoire committed to CMV **may compromise** the ability to respond de novo to other antigens by decreasing **diversity of naïve T cells**

- more profound influence of CMV infection occur in thymectomized individuals and in the elderly surviving decades of thymic involution


Antigen presenting cell
ADA BP
ADA
CD26
MHC +
peptide
TCR
B7
CD28
T cell

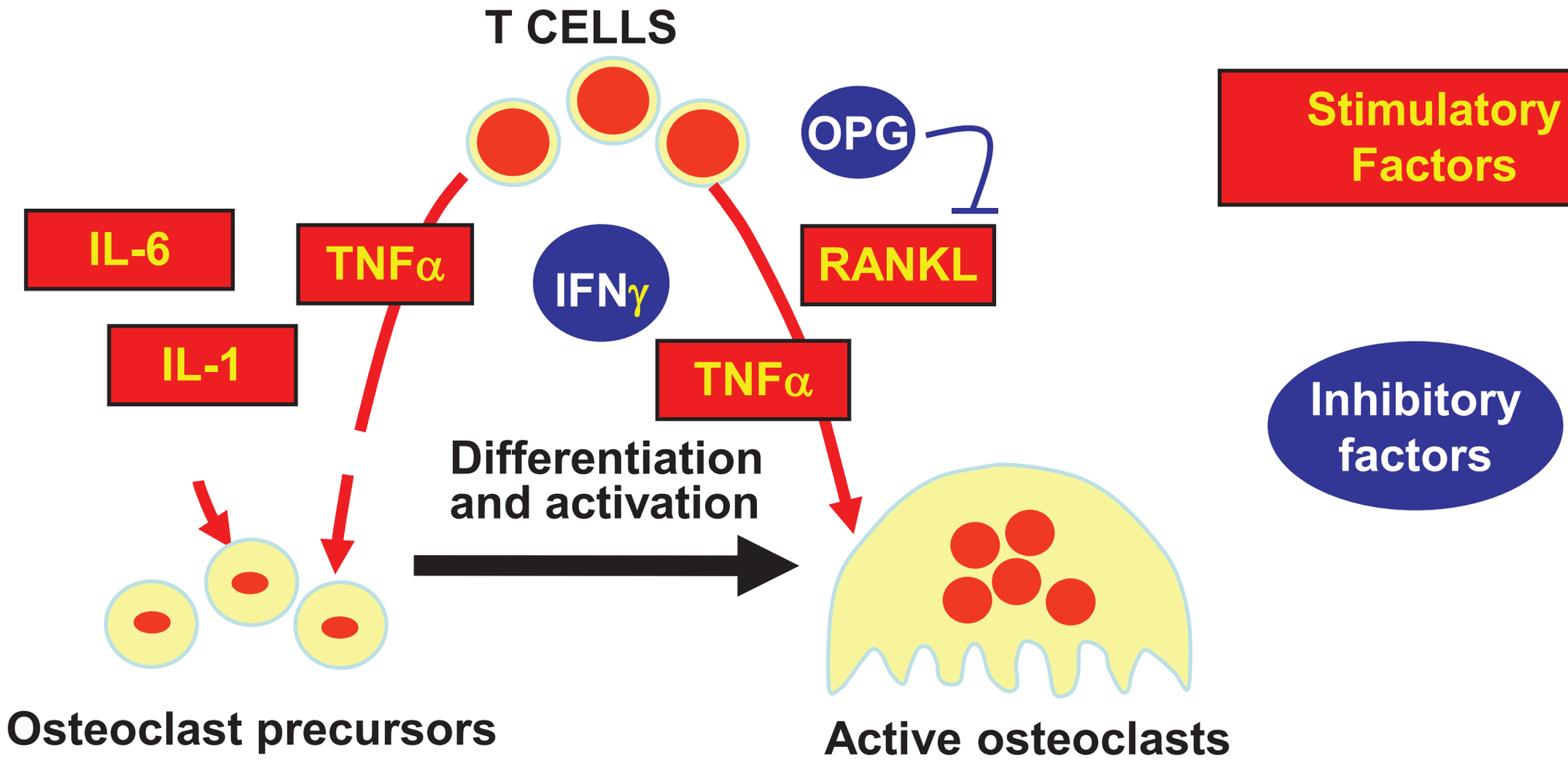
aging and CMV pathogenesis

- Large population studies in Scandinavia demonstrated that infection with CMV makes a significant contribution to the so-called immune risk profile (IRP), predictive of increased mortality in old individuals

- **IRP includes expansion of CD8+ CD28 deficient T cells and inverted CD4/CD8 T cell ratio**

- Two studies in the USA suggest that CMV infection itself might have a negative impact on survival, as higher levels of anti-CMV antibodies were correlated to poor survival in older adults with stable cardiovascular disease

Senescent CD8+ T cells: ↑TNFα, IL-6, RANKL; ↓IFNγ



CMV - HIV interactions

- Several studies suggested direct and indirect interactions between CMV and HIV influencing their replication and the resulting disease pathogenesis, through:

  - direct interaction between CMV-encoded regulatory proteins and the HIV LTR region, with **transactivation of HIV gene expression**
  - **enhanced HIV replication through CMV-induced inflammatory** cytokines and chemokines
  - **upregulation of CCR5** expression in central memory T cells, by enhanced CMV-induced interferon production
  - **clonal expansion** of HIV-infected T cells through CMV-induced inflammatory cytokines and chemokines

CMV ed HIV: culprits in crime

- in the genital tract, the presence of **detectable CMV DNA** has been repeatedly associated with **increased genital shedding of HIV RNA and increased HIV transmission**

- **detectable CMV DNA** was associated with **increased levels of HIV DNA** in peripheral blood cells

- this has been observed in both treated and untreated HIV infected individuals

Epstein–Barr and Cytomegalovirus DNA Salivary Shedding Correlate with Long-Term Plasma HIV RNA Detection in HIV-Infected Men Who Have Sex With Men

Renzo Scaggiante,[1] Samantha Andreis,[2] Monica Basso,[2] Elisa Franchin,[2] Marzia Franzetti,[1] Claudia Del Vecchio,[2] Carlo Torti,[3] Carlo Mengoli,[2] Mario Cruciani,[4] Loredana Sarmati,[5] Giorgio Palù,[2] and Saverio Giuseppe Parisi[2]*

[1]*Infectious Disease Unit, Padova Hospital, Padova, Italy*
[2]*Department of Molecular Medicine, University of Padova, Padova, Italy*
[3]*Unit of Infectious Diseases, University "Magna Graecia", Catanzaro, Italy*
[4]*Center of Diffusive Diseases, Verona, Italy*
[5]*Clinical Infectious Diseases, Tor Vergata University, Rome, Italy*

The aim of the study was to evaluate cytomegalovirus (CMV) and Epstein–Barr virus (EBV) DNA salivary shedding in HIV-positive men who have

KEY WORDS: CMV DNA; EBV DNA; saliva; HIV RNA; high EBV viral load

Accepted Manuscript Posted Online

JVI Accepted Manuscript Posted Online 3 February 2016
J. Virol. doi:10.1128/JVI.02638-15
Copyright © 2016, American Society for Microbiology. All Rights Reserved.

Replication of Human Herpes Viruses is Associated with Greater HIV DNA Levels during Antiretroviral Therapy Started during Early HIV Infection

Sara Gianella[1], Christy Anderson[1], Susanna R. Var[1], Michelli F. Oliveira[1], Steven Lada[1], Milenka Vargas[1], Marta Massanella[1], Susan Little[1], Douglas Richman[1,2], Matt Strain[1], Josué Pérez-Santiago*[1] and Davey Smith*[1,2]

[1]University of California, San Diego, La Jolla, CA, USA, [2]Veterans Affairs San Diego Healthcare System, San Diego, CA, USA,

*These authors contributed equally to the study

Table 2. Predictors of HIV DNA decay

Fixed Effects (No. TP=515, No. Subjects = 107*)	Individual Models± Unadjusted Effect	P-value	Multivariable Model Adjusted Effect	P-value
Time (log_2 months)	-0.20 (-0.23 to -0.17)	**<0.001**	-0.23 (-0.32 to -0.13)	**<0.001**
Intermittent CMV replication	-0.40 (-0.86 to 0.07)	0.095	-0.41 (-0.87 to 0.04)	0.074
Intermittent CMV replication x time	0.13 (0.03 to 0.22)	**0.008**	0.12 (0.03 to 0.21)	**0.011**
Pre-ART detectable CMV DNA (N = 92)	0.29 (-0.05 to 0.62)	0.091		
EBV DNA (log_{10} copies/millions cells)	0.24 (0.17 to 0.32)	**<0.001**	0.23 (0.14 to 0.32)	**<0.001**
High CD4:CD8 ratio ($\geq$ 1)	-0.54 (-0.69 to -0.40)	**<0.001**	0.06 (-0.15 to 0.27)	0.586
Interaction of EBV and low CD4:CD8 ratio			-0.17 (-0.29 to -0.05)	**0.006**
Early ART initiation (< 3 months)	0.16 (-0.21 to 0.53)	0.403	0.25 (-0.11 to 0.62)	0.175
Early ART x time	-0.05 (-0.11 to 0.005)	0.071	-0.08 (-0.14 to -0.02)	**0.012**
Lengthy time to suppression (> 3.6 mos)	0.17 (-0.14 to 0.48)	0.284		
High peak HIV RNA (> 5.7 log_{10} copies/ml)	0.02 (-0.29 to 0.34)	0.879		
Low nadir CD4 (< 405 cells/µl)	-0.26 (-0.57 to 0.05)	0.1000		
Older in age (> 35 years)	-0.01 (-0.32 to 0.31)	0.964		
Detectable level of CMV IgG (N=102)	0.49 (-0.52 to 1.50)	0.329		

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

- in untreated HIV patients, CMV is associated with a wide range of **serious clinical diseases**, such as retinitis, pneumonitis, colitis, and other end organ diseases

- CMV is also associated with **more rapid HIV disease progression** and increased occurrence of AIDS-related events

- ART decreases dramatically the incidence of such complications, as the consequence of restoration of CMV-specific immune responses and diminished CMV expression and viremia

Ocular immune reconstitution inflammatory syndromes

Juliet Otiti-Sengeri[a], Christina Meenken[b], Gerardus J. van den Horn[c] and John H. Kempen[d]

[a]Department of Ophthalmology, Makerere University and Mulago Hospital, Kampala, Uganda, [b]Department of Ophthalmology, VU Medical Centre, [c]Department of Ophthalmology, Medical Center Jan van Goyen, Amsterdam, The Netherlands and [d]Departments of Ophthalmology and Epidemiology, and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Correspondence to Dr Juliet Otiti-Sengeri, MBCh, B, M.Med Ophthalmology, Department of Ophthalmology, Makerere University and Mulago Hospital, P. O. Box 7072, Kampala, Uganda
Tel: +256 77 381162; fax: +256 41 255962; e-mail: ojsjuliet@hotmail.com

Current Opinion in HIV and AIDS 2008, 3:432–437

Purpose of review

The aim of this article is to review the current literature concerning immune reconstitution inflammatory syndrome in relation to the eye. The definition, epidemiology, pathophysiology, risk factors, clinical features, diagnosis and treatment are discussed.

Recent findings

Immune reconstitution inflammatory syndrome affecting the eye has been documented in association with cytomegalovirus retinitis following the introduction of highly active antiretroviral therapy in a large number of patients. This syndrome is referred to as immune recovery uveitis, which is presumed to be mediated by recovery of immune responses specific to residual cytomegalovirus antigen located in the eye. In addition to improved immunity itself, risk factors include a low $CD4^+$ T count at the time of initiation of highly active antiretroviral therapy and involvement of a larger proportion of retina. Immune recovery uveitis is a major cause of visual loss and morbidity among patients with AIDS who are receiving highly active antiretroviral therapy.

Summary

Immune recovery uveitis is the most common form of immune reconstitution inflammatory syndrome in HIV-infected patients with cytomegalovirus retinitis who are receiving highly active antiretroviral therapy. Clear clinical definitions are required for ocular immune reconstitution inflammatory syndromes to avoid misclassification of other inflammatory conditions. A multidisciplinary approach is important in the diagnosis and management of immune recovery uveitis.

Keywords

cytomegalovirus retinitis, HAART, HIV, immune recovery uveitis, ocular diseases

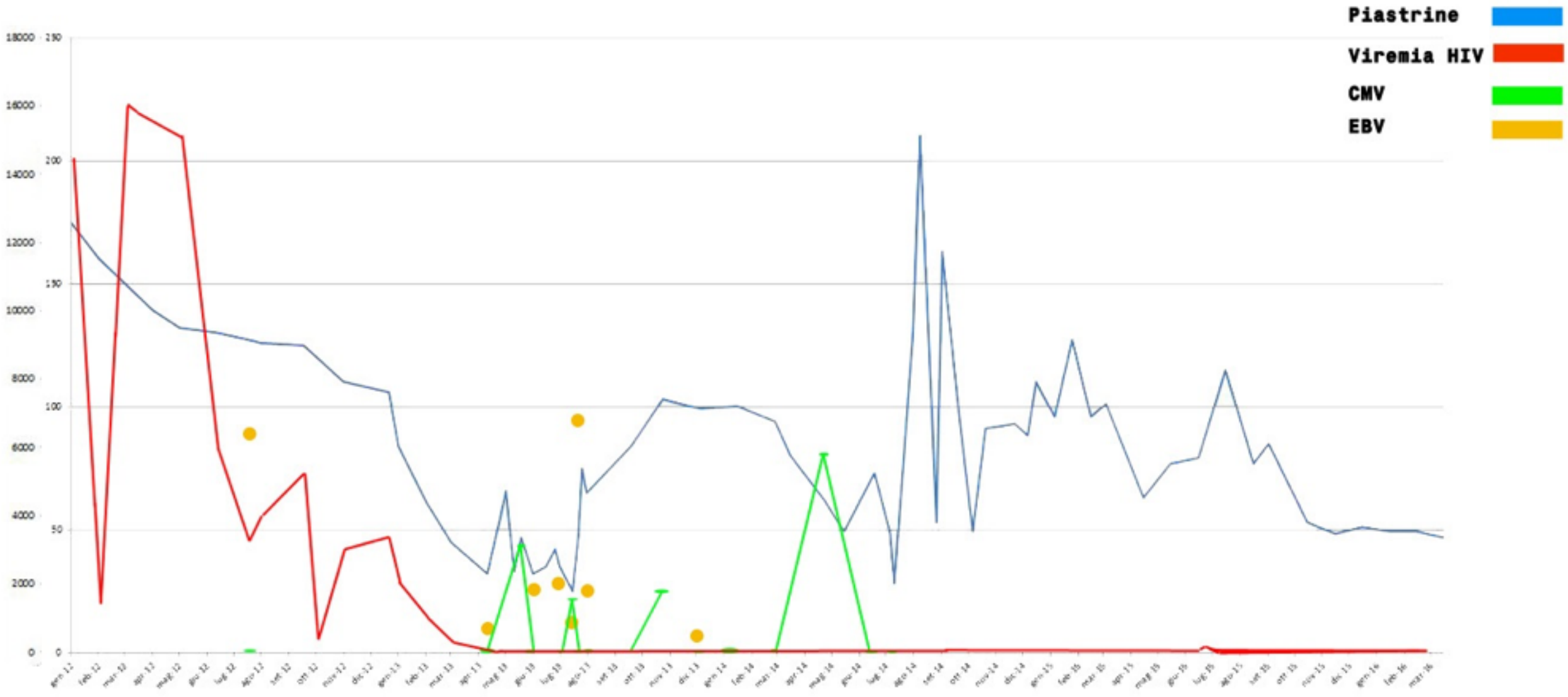
Curr Opin HIV AIDS 3:432–437
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
1746-630X

Mediterranean Journal of Hematology and Infectious Diseases

Case Report

Refractory Immune Thrombocytopenic Purpura and Cytomegalovirus Infection: A Call for a Change in the Current Guidelines

Alexei Shimanovsky[1], Devbala Patel[2] and Jeffrey Wasser[1]



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

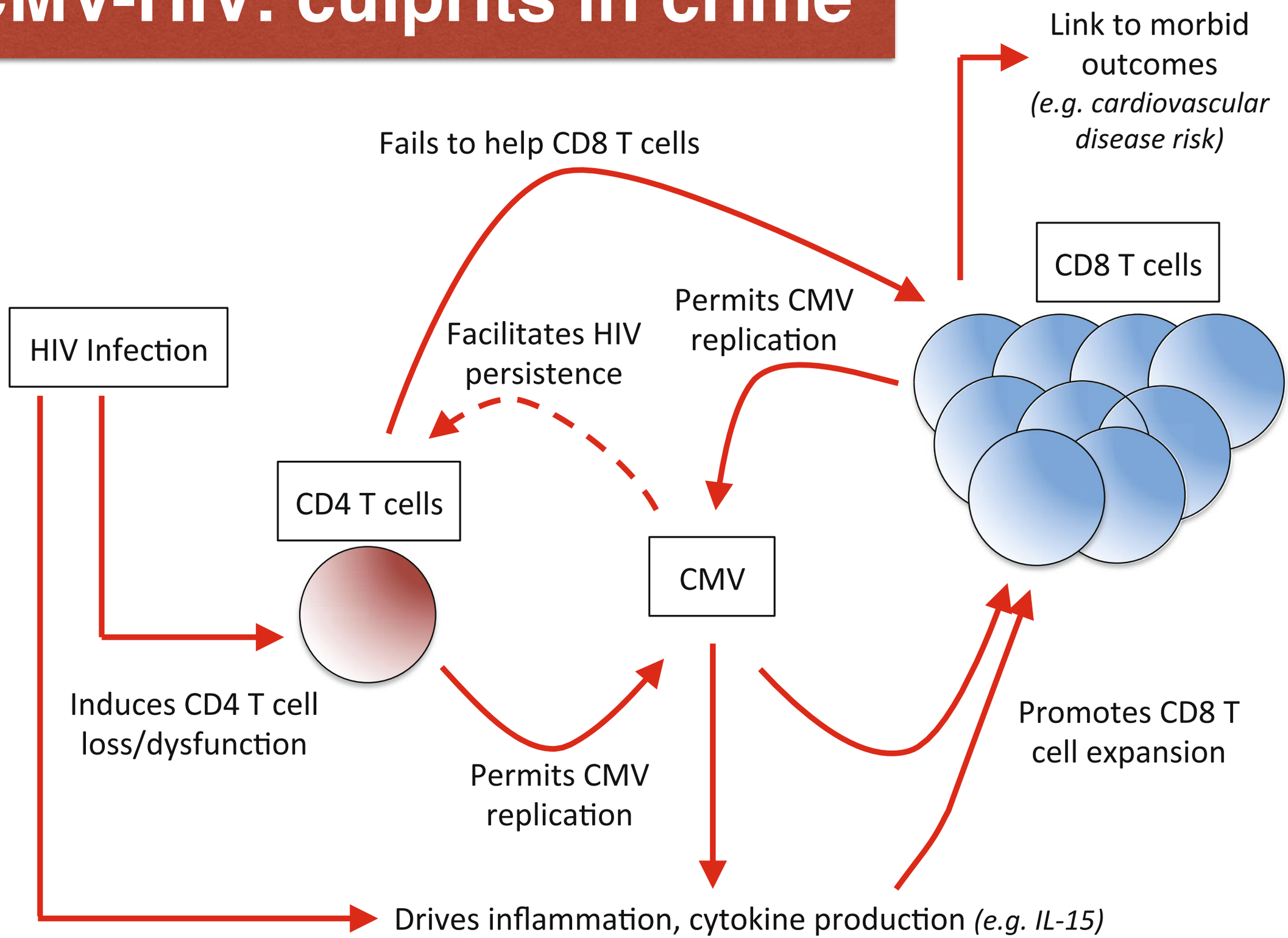
- in treated HIV patients CMV co-infection is linked to a **more inflammatory profile**

- increased circulating levels of Interferon gamma-**induced protein (IP)-10 and D-dimer** have been systematically documented in CMV-HIV coinfection

- robust evidence indicates a profound **expansion of circulating CD8 T cells and a reduced CD4/CD8 ratio**

- this is linked to an increased morbidity and mortality

CMV-HIV: culprits in crime



Clinical Infectious Diseases

MAJOR ARTICLE

HIV/AIDS

CD8 T-Cell Expansion and Inflammation Linked to CMV Coinfection in ART-treated HIV Infection

Michael L. Freeman,[1,a] Joseph C. Mudd,[1,ab] Carey L. Shive,[1,2] Souheil-Antoine Younes,[1] Soumya Panigrahi,[1] Scott F. Sieg,[1] Sulggi A. Lee,[3] Peter W. Hunt,[3] Leonard H. Calabrese,[4] Sara Gianella,[5] Benigno Rodriguez,[1] and Michael M. Lederman[1]

[1]Center for AIDS Research, Division of Infectious Diseases and HIV Medicine, Department of Medicine, Case Western Reserve University/University Hospitals Case Medical Center, and [2]Veterans Administration Medical Center, Cleveland, Ohio; [3]Department of Medicine, University of California San Francisco; [4]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation, Ohio; and [5]Division of Infectious Diseases, University of California San Diego, La Jolla

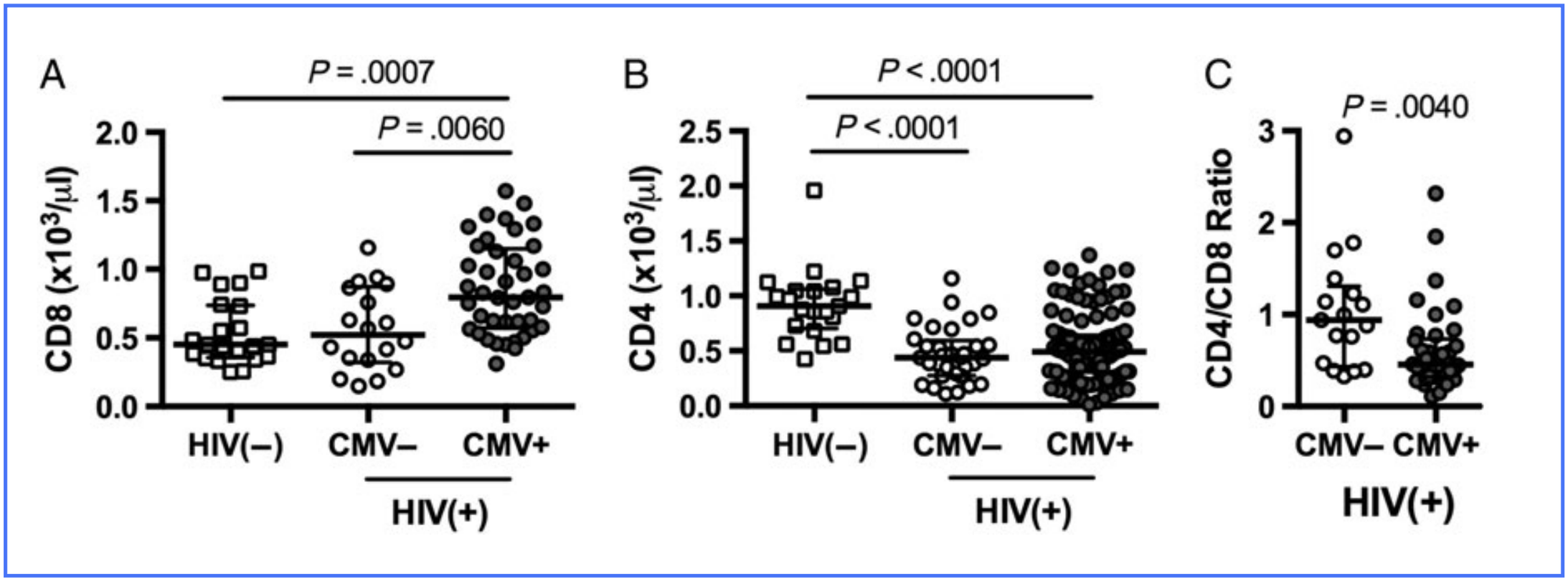
Background. Persistent CD8 T-cell expansion, low CD4/CD8 T-cell ratios, and heightened inflammation persist in antiretroviral therapy (ART)-treated human immunodeficiency virus (HIV) infection and are associated with increased risk of morbid outcomes. We explored the role of cytomegalovirus (CMV) infection in CD8 lymphocytosis and inflammation in ART-treated HIV infection.

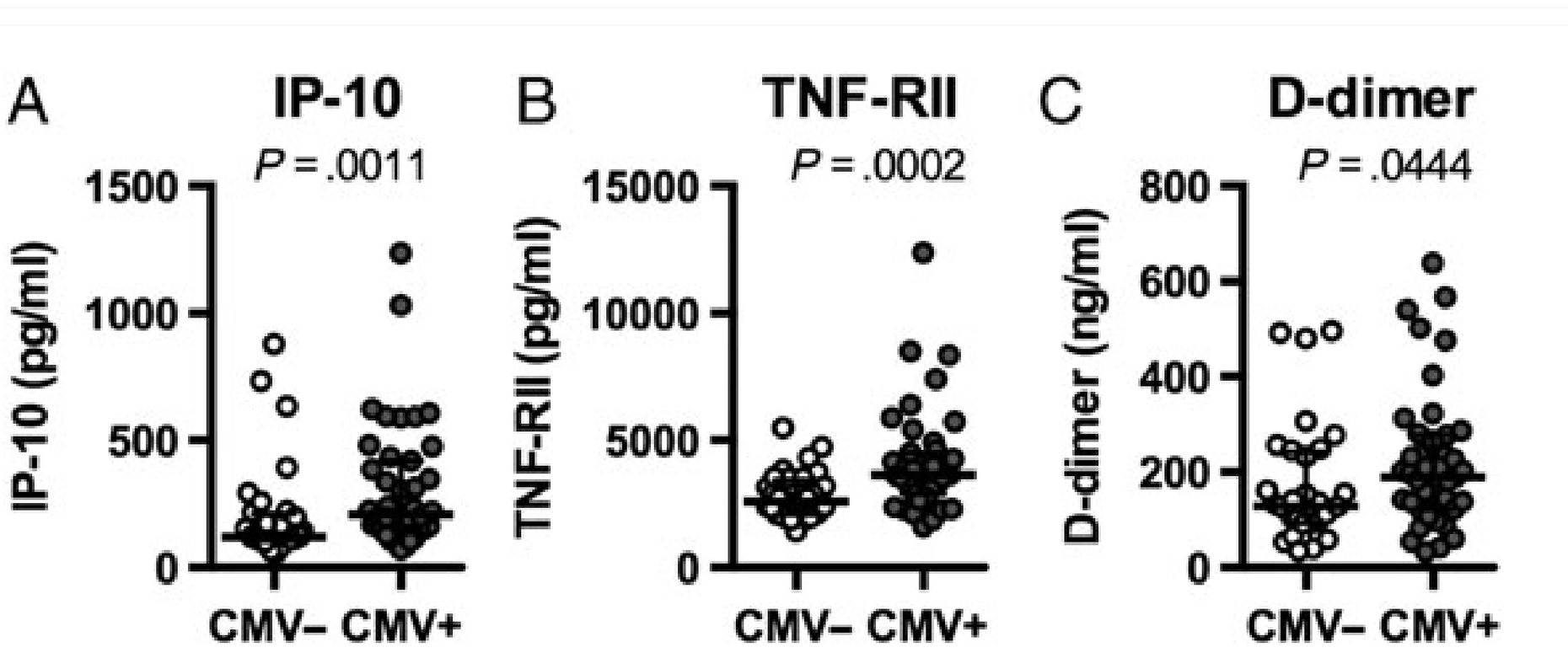
Methods. Absolute CD4 and CD8 T-cell counts were abstracted from clinical records and compared among 32 HIV-infected CMV-seronegative subjects, 126 age, CD4 and gender-matched HIV-infected CMV-seropositive subjects, and among 21 HIV-uninfected controls (9 CMV-negative, 12 CMV-positive). Plasma inflammatory indices were measured in a subset by ELISA.

Results. Median CD8 counts/μL were higher in HIV-positive/CMV-positive patients (795) than in HIV-positive/CMV-negative subjects (522, $P = .006$) or in healthy controls (451, $P = .0007$), whereas CD8 T-cell counts were similar to controls' levels in HIV-positive/CMV-negative subjects. Higher plasma levels of IP-10 ($P = .0011$), TNF-RII ($P = .0002$), and D-dimer ($P = .0444$) were also found in coinfected patients than in HIV-positive/CMV-negative subjects.

Conclusions. CMV infection is associated with higher CD8 T-cell counts, resultant lower CD4/CD8 ratios, and increased systemic inflammation in ART-treated HIV infection. CMV infection may contribute to risk for morbid outcomes in treated HIV infection.

Keywords. HIV; CMV; coinfection; CD8 T-cell expansion; inflammation.


A
P = .0007
P = .0060
CD8 (x10³/μl)
2.0
1.5
1.0
0.5
0.0
HIV(–)
CMV–
CMV+
HIV(+)
B
P < .0001
P < .0001
CD4 (x10³/μl)
2.5
2.0
1.5
1.0
0.5
0.0
HIV(–)
CMV–
CMV+
HIV(+)
C
P = .0040
CD4/CD8 Ratio
3
2
1
0
CMV–
CMV+
HIV(+)


A
IP-10
P = .0011
IP-10 (pg/ml)
1500
1000
500
0
CMV–
CMV+
B
TNF-RII
P = .0002
TNF-RII (pg/ml)
15000
10000
5000
0
CMV–
CMV+
C
D-dimer
P = .0444
D-dimer (ng/ml)
800
600
400
200
0
CMV–
CMV+

Impact of CMV HIV Co-infection in african children

- in treated and untreated HIV infected children in Africa, the deleterious effect of CMV co-infection is well established

- many cofactors, including malnutrition and early transmission, may well contribute

TABLE 1 | Association between CMV infection and disease progression and mortality in HIV infection in African children.

Author	Publication Year	Study Location	Population Studied	Findings
Vilioen	2015	South Africa	124 HIV-infected mothers and their babies	CMV is associated with increased HIV shedding in breast milk
Gumbo	2014	Zimbabwe	257 ART-naïve HIV-positive infants	79% CMV IgG positive by age 6 weeks. No increase in mortality associated with CMV
Tembo	2015	Zambia	303 pediatric inpatients, age 3 weeks to 2 years	CMV viraemia in 41%, associated with being underweight, HIV-positive, or suspected meningitis
Schaftenaar	2014	South Africa	405 ART-naïve HIV-positive children	CMV IgG in 100%, higher titres associated with lower CD4+ T cell count
Manicklal	2014	South Africa	748 neonates born to HIV-infected mothers	Congenital CMV in 2.9%, associated with maternal CD4 count <200 cells/mm3
Mwaanza	2014	Zambia	395 neonates	Congenital CMV in 3.8%, maternal HIV associated with increased congenital CMV infection
Hsiao	2013	South Africa	425 HIV exposed infants	CMV viraemia is associated with pneumonia in HIV exposed infants
Zampoli	2011	South Africa	202 children with suspected PCP	CMV associated pneumonia more common in HIV infected children
Goussard	2010	South Africa	25 HIV-positive children with suspected PJP	CMV most likely cause of pneumonia and is associated with low CD4 counts and mortality
Slyker	2009	Kenya	64 infants born to HIV-positive mothers	Maternal CMV DNAemia is a significant factor for mortality in HIV infected infants
Roxby	2014	Kenya	141 infants born to HIV-positive mothers	66% acquired CMV by 1 year of age
Slyker	2012	Kenya	474 infants born to HIV-positive mothers	CMV induced T cell activation contributes to rapid disease progression in coinfected infants

The studies summarized are conducted solely in African children and published between 2009 and 2015.

Cytomegalovirus Infection in Human Immunodeficiency Virus (HIV)–Exposed and HIV-Infected Infants: A Systematic Review

Sascha R. Ellington, Kristie E. N. Clarke, and Athena P. Kourtis

Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Table 2. Studies Evaluating the Effect of Early Cytomegalovirus (CMV) Infection on Human Immunodeficiency Virus (HIV) Disease Progression Among Infants Perinatally Infected With HIV

Reference, Publication Year	Study Site, Period, Design	No. of HIV-Infected Infants Followed	Statistical Method(s)	Disease Progression Result(s)	Strength(s)	Weakness(es)
Frenkel et al [31], 1990	United States, 1983–1990, retrospective cohort study	24 HIV-infected infants aged 0–39 mo at the time of referral	None described; Fisher exact test[a] was used to compare proportions of infants who died, by CMV status	11 HIV-infected children (46%) were coinfected with CMV; 7 of 11 CMV-coinfected children (64%) died as compared to 3 of 13 CMV-negative children (23%); authors reported that the difference was statistically significant ($P < .05$), but $P = .095$ by the Fisher exact test	Longitudinal study among HIV-infected children	Small sample of HIV-positive infants with CMV results; not all children were followed from birth; included CMV infections acquired after age 1 y
Cooper et al [27], 1992	United States, retrospective cohort study	39 HIV-infected infants (38 infected perinatally and 1 child infected via blood transfusion in the first week of life)	Fisher exact test was used to compare proportions of infants who died, by CMV status	25 (64%) HIV-infected children were coinfected with CMV; CMV disease was identified in 5 children all of whom acquired CMV in the first year of life; 6 of 25 coinfected children (24%) died as compared to 1 of 14 children (7.1%) infected with HIV alone ($P = .39$)	Longitudinal study design	Small sample of HIV-positive infants with CMV results (n = 39); timing of CMV infection was unknown; 60% of CMV-coinfected infants (15) were CMV positive within first y of life, but results were not stratified by age at CMV infection
Chandwani et al [26], 1996	United States, 1989–1993, prospective cohort study	37 HIV-infected infants tested for CMV infection by age 6 mo	Analysis of covariance was used to evaluate age-adjusted differences in quantitative variables	11 HIV-infected infants (30%) were coinfected with CMV in the first 6 mo of life, of whom 5 (45%) developed symptomatic disease, with 4 of these 5 dying within 10 mo of diagnosis; mean p24 antigen concentrations were higher in CMV-coinfected infants as compared to CMV uninfected infants (313 pg/mL vs 212 pg/mL; $P = .04$) at age 6 mo; mean $CD8^+$ T-lymphocyte proportion was significantly higher among CMV-coinfected infants as compared to CMV-uninfected infants (34% vs 24%; $P = .03$) at age 6 mo; mean $CD4^+$ T-lymphocyte proportion was not different by CMV status (30% vs 31%; $P = .85$) at age 6 mo	Longitudinal study	Small sample of HIV-positive infants with CMV results within first year of life (n = 37); survival data were not provided for CMV-negative infants; incident CMV could not be assessed
Doyle et al [21], 1996	United States, 1988–1995, retrospective cohort study	24 HIV-infected infants tested for CMV during age ≤2 mo	Student *t* test was used to analyze quantitative variables; Kaplan–Meier method was used to compare survival, by CMV status	6 HIV-infected infants (25%) acquired CMV infection during age ≤2 mo; mean absolute $CD4^+$ T-lymphocyte count was significantly lower for CMV-coinfected infants as compared to CMV-negative infants (643 vs 1590 cells/m^3; $P = .004$) at age 6 mo; mean $CD4^+$ T-lymphocytes proportion was significantly lower for CMV-coinfected infants as compared to CMV-negative infants (16 vs 30%; $P = .04$) at age 6 mo; mean ratios of $CD4^+$ to $CD8^+$ T lymphocytes were significantly lower for CMV-coinfected infants as compared to CMV-negative infants (0.48 vs 1.26; $P = .04$) at age 6 mo; mean survival time for HIV-positive infants coinfected with CMV was 25 mo, while mean survival time for CMV-negative was 39 mo ($P = .088$)	Longitudinal study focused on congenital CMV infection	Small sample of HIV-positive infants with CMV results

CMV Co-infection and cardiovascular disease

- A highly relevant finding is the consistent association between **unfavorable glucose and lipid profiles** with the accumulation of late stage CD8 T cells in a large cohort (n=400) of CMV+ individuals, as compared to uninfected controls matched for age, sex, sociodemographics and lifestyle

- Both CMV replication itself and the immune response against CMV can promote **changes in endothelial cells**

  - secretion of pro-angiogenic factors as IL-6, GM-CSF

  - direct endothelial damage through CMV-induced inflammation and **fractalkine-fractalkine receptor (CX3CR1) interactions**

CMV Co-infection and CX3CR1

- **fractalkine** is a **key marker of inflammation** in human endothelial cells

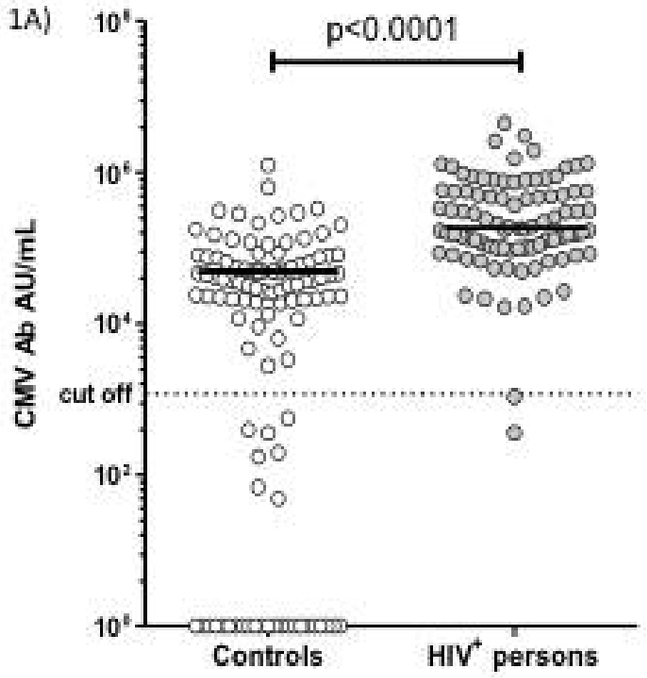
- its expression is **strongly upregulated in the presence** of PBMCs from donors with a high frequency of **CMV-specific T cells**

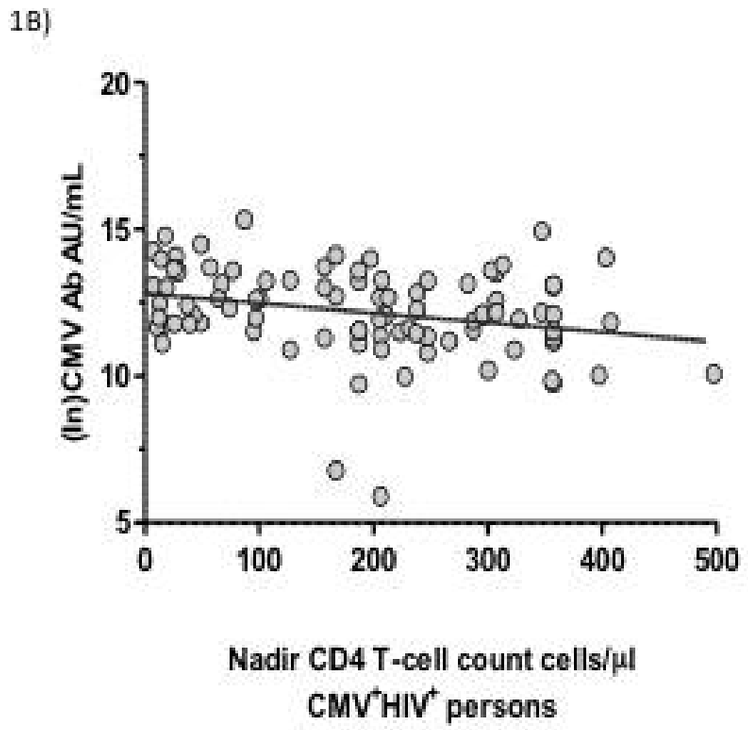
- the fractalkine-CX3CR1 interaction results in **recruitment of natural killer cells, monocytes and possibly also CX3CR1+ CD8+ T** cells driving vascular inflammation, coagulation, and the formation of **atheromas**

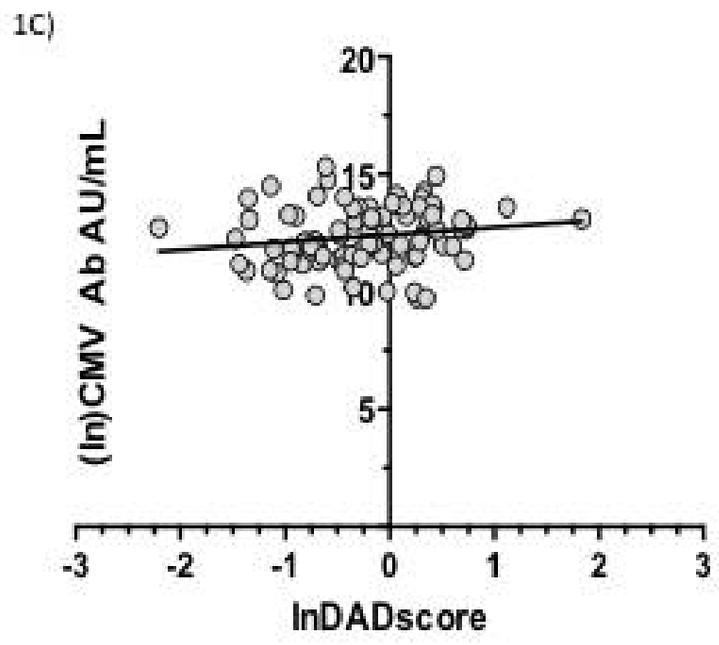
Do CMV antibody levels associate with age-related syndromes in HIV patients stable on ART?

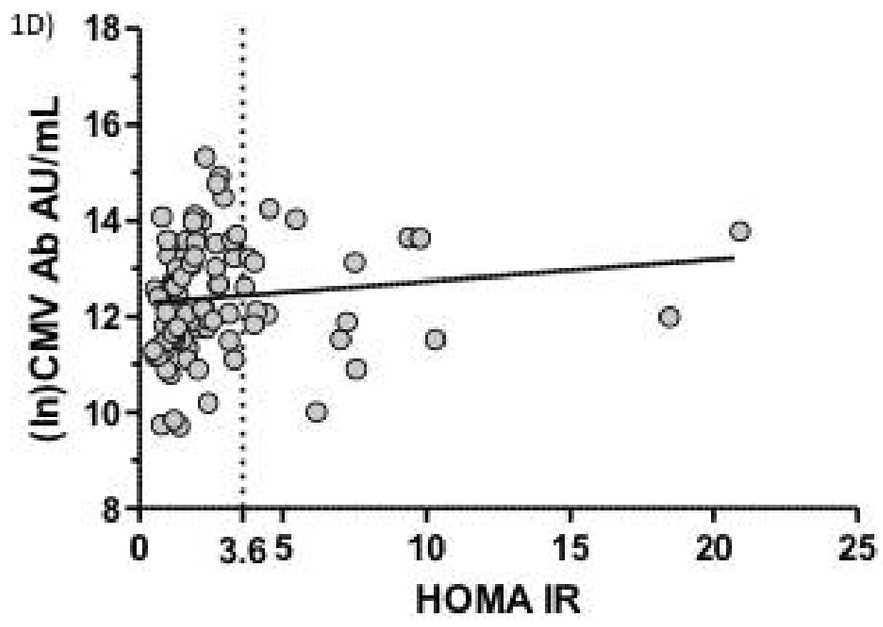
Samantha J. BRUNT[1*], Lucette A. CYSIQUE[2,3,4*], Silvia LEE[5,6], Sally BURROWS[7], Bruce J. BREW[2,4,8], Patricia PRICE [6,7].

1. Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Australia
2. Peter Duncan Neurosciences Unit, St. Vincent's Applied Medical Research Centre, Sydney, Australia
3. Neuroscience Research Australia, Sydney, Australia
4. University of New South Wales, Sydney, Australia
5. Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Australia
6. School of Biomedical Science, Curtin University of Technology, Perth, Australia
7. Medicine and Pharmacology, University of Western Australia, Nedlands, Australia
8. Neurology Department, St Vincent's Hospital, Sydney, Australia


1A)
p<0.0001
CMV Ab AU/mL
cut off
Controls
HIV+ persons


1B)
(ln)CMV Ab AU/mL
Nadir CD4 T-cell count cells/µl
CMV+HIV+ persons


1C)
(ln)CMV Ab AU/mL
lnDADscore


1D)
(ln)CMV Ab AU/mL
HOMA IR

Clinical Infectious Diseases 2013;57(9):1331–8
© The Author 2013. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/cit539

A Randomized Controlled Pilot Trial of Valacyclovir for Attenuating Inflammation and Immune Activation in HIV/Herpes Simplex Virus 2–Coinfected Adults on Suppressive Antiretroviral Therapy

Tae Joon Yi,[1] Sharon Walmsley,[1,2] Leah Szadkowski,[3] Janet Raboud,[3,4] Nimerta Rajwans,[5] Brett Shannon,[1] Sachin Kumar,[1] Kevin C. Kain,[1,2,5] Rupert Kaul,[1,2] and Darrell H. S. Tan[1,2,6]

[1]Department of Medicine, University of Toronto; [2]Division of Infectious Diseases and [3]Toronto General Research Institute, University Health Network; [4]Dalla Lana School of Public Health, University of Toronto; [5]SAR Labs, Sandra Rotman Centre for Global Health, University Health Network; and [6]Division of Infectious Diseases, St Michael's Hospital, Toronto, Canada

Background. Human immunodeficiency virus (HIV) is associated with increased systemic inflammation and immune activation that persist despite suppressive antiretroviral therapy (ART). Herpes simplex virus type 2 (HSV-2) is a common coinfection that may contribute to this inflammation.

Methods. Sixty HIV type 1 (HIV-1)/HSV-2–coinfected adults on suppressive ART were randomized 1:1:1 to 12 weeks of placebo, low-dose valacyclovir (500 mg twice daily), or high-dose valacyclovir (1 g twice daily) in this 18-week trial. Co–primary outcome measures were the percentage of activated ($CD38^+HLA\text{-}DR^+$) CD8 T cells in blood, and highly sensitive C-reactive protein, interleukin 6, and soluble intercellular adhesion molecule 1 in plasma. Secondary outcomes included additional immune, inflammatory cytokine, and endothelial activation markers. The impact of valacyclovir (both groups combined) on each outcome was estimated using treatment × time interaction terms in generalized estimating equation regression models.

Results. Participants were mostly white (75%) men who have sex with men (80%). Median age was 51 (interquartile range [IQR], 47–56) years, median duration of HIV infection was 15 (IQR, 8–21) years, median CD4 count at enrollment was 520 (IQR, 392–719) cells/μL, and median nadir CD4 count was 142 (IQR, 42–240) cells/μL. Valacyclovir was not associated with significant changes in any primary or secondary immunological outcomes in bivariate or multivariable models. Medication adherence was 97% by self-report, 96% by pill count, and 84% by urine monitoring. Eight patients had adverse events deemed possibly related to the study drug (5 placebo, 1 low-dose, 2 high-dose), and 6 patients reported at least 1 HSV outbreak (3 placebo, 3 low-dose, 0 high-dose).

Conclusions. Valacyclovir did not decrease systemic immune activation or inflammatory biomarkers in HIV-1/HSV-2–coinfected adults on suppressive ART.

Clinical Trials Registration. NCT01176409.

is there any room for prevention now?

- newer **less toxic** drugs with activity against CMV as **Brincidofovir** and **Letermovir** might be applied in clinical trials to evaluate the effects of CMV suppression on immune activation and inflammation

- as these agents will not eradicate CMV, **prolonged courses of therapy will be needed** to gauge their effects on clinical endpoints and outcomes

- it remains to be seen if attenuation of CMV expression will be sufficient to reverse the inflammatory process initiated by CMV infection in great advance


©Roberto Cilli

final remarks

- through millions of years of co-existence, CMV has developed a number of strategies to adapt and **synergistically co-exist** with the human immune system

- **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 - **vaccine prevention unlikely for both viruses**

- we are in **urgent need** to develop new strategies to prevent the premature occurrence of end-organ diseases that may be linked to CMV infection both in HIV infected and uninfected individuals - **further research warranted**

Curr HIV/AIDS Rep
DOI 10.1007/s11904-016-0297-9

HIV PATHOGENESIS AND TREATMENT (AL LANDAY, SECTION EDITOR)

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

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

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

The silent war of CMV in aging and HIV infection

Rita B. Effros*

Department of Pathology & Laboratory Medicine and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 30 August 2015
Received in revised form 9 September 2015
Accepted 10 September 2015
Available online xxx

Keywords:
CMV
Aging
HIV
CD8T cell
Replicative senescence

ABSTRACT

Human cytomegalovirus (CMV), the prototypical β-herpervirus, is a widespread pathogen tha
lishes a lifelong latent infection in myeloid progenitor, and possibly other cells as well. Al
immunocompetent individuals show mild or no symptoms despite periodic reactivation during r
cell differentiation, CMV is responsible for considerable morbidity and mortality in older adults
persons chronically infected with HIV. Indeed, in these individuals, reactivation of CMV can cause
complications. This review will focus of the effects of CMV during aging and HIV/AIDS, with pa
attention to the cellular immunity and age-related pathology outcomes from this persistent in
The impact of the long-term chronic exposure to CMV antigens on the expansion of CD8 T ce
features of replicative senescence will be highlighted.

© 2015 Elsevier Ireland Ltd. All rights re

Contents