

# A paradigm linking herpesvirus immediate-early gene expression apoptosis and myalgic encephalomyelitis chronic fatigue syndrome

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**Abstract:** There is no accepted science to relate herpesviruses (Epstein–Barr virus [EBV], human cytomegalovirus [HCMV], and human herpesvirus 6 [HHV6]) as causes of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). ME/CFS patients have elevated serum immunoglobulin (Ig)G serum antibody titers to EBV, HCMV, and HHV6, but there is no herpesvirus DNA-emia, herpesvirus antigenemia, or uniformly elevated IgM serum antibody titers to the complete virions. We propose that herpesvirus EBV, HCMV, and HHV6 immediate-early gene expression in ME/CFS patients leads to host cell dysregulation and host cell apoptosis without lytic herpesvirus replication. Specific antiviral nucleosides, which alleviate ME/CFS, namely valacyclovir for EBV ME/CFS and valganciclovir for HCMV/HHV6 ME/CFS, inhibit herpesvirus DNA polymerases and/or thymidine kinase functions, thus inhibiting lytic virus replication. New host cell recruitment thus ceases. In the absence of new herpesvirus, nonpermissive herpesvirus replication stops, and ME/CFS recovery ensues.

**Keywords:** ME/CFS, Epstein–Barr virus (EBV), human cytomegalovirus (HCMV), HHV6, abortive replication

The gamma herpesvirus Epstein–Barr virus (EBV) and both beta herpesviruses human cytomegalovirus (HCMV) and human herpesvirus 6 (HHV6) have biphasic life-cycles of replication and latency during which these large virus genomes are expanded or maintained, respectively.<sup>1</sup> During virus latency, both EBV and HCMV are closed, circular, nonintegrated intranuclear episomes; however, HHV6 is integrated into host cell DNA.<sup>2</sup> EBV has a malignant potential and is associated with nasopharyngeal carcinoma, Burkitt's lymphoma, and AIDS-related lymphoproliferative disorder. Previous research has suggested and denied that herpesviruses are associated with myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS).<sup>3–6</sup> ME/CFS illness, like herpesviruses, is experienced worldwide, with over one million CFS sufferers in the US alone.<sup>5</sup>

Canonical evidence for herpesvirus not being the cause of ME/CFS is that there is no herpesvirus DNA-emia, herpesvirus antigenemia, or uniform serum immunoglobulin (Ig)M antibody increase to complete herpesvirus virion or increasing herpesvirus IgG serum antibody titers (Table 1). Nevertheless, we have developed a successful specific serum–cardiac biomarker diagnostic panel for herpesvirus subset-directed treatment of CFS.<sup>6</sup> Using this diagnostic panel, a systemic review of 142 CFS patients completing  $\geq 6$  months of herpesvirus subset-directed antiviral therapy at a single treatment center from 2001 to 2007, including over 7000 patient visits and capturing over 35,000 fields of information, was analyzed. This study distinguished for

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**Table 1** Comparative herpesvirus permissive and nonpermissive replication

Result	Replication	
	Permissive	Nonpermissive
1. Pathogenic process	Necrosis of host cell and new infectious virus	Apoptosis of host cell, no new infectious virus
2. Circulation (blood and lymphatics)	EBV (memory B-cell), HCMV (macrophage, monocyte), HHV6 (T-cell)	None
3. DNA-emia	Yes	No
4. Antigenemia	Yes	No
5. IgM antibody to complete virus	Yes	No
6. IgM antibody to nonstructural gene products	No	Yes
7. Serum IgG antibody titer to complete virus	Yes, increasing	Yes, no increase in IgG titer
8. Immediate-early virus gene products	Yes	Yes
9. Activation of late viral gene products	Yes	Uncommon
10. Therapeutic effect of specific EBV, HCMV, HHV6 DNA polymerase inhibitors	Yes (rapid)	Yes (slow), prevents new host cell recruitment (see Figure 1)
11. Proposed therapeutic effect of specific EBV, HCMV, HHV6 inhibitors of immediate-early gene products	Yes (rapid)	Yes (rapid)
12. Clinical entities	Infectious mononucleosis, myocarditis, meningoencephalitis, polyneuropathy, thyroiditis; enteritis, pneumonia, retinitis	ME/CFS, retinitis, interstitial pneumonia

**Abbreviations:** CFS, chronic fatigue syndrome; EBV, Epstein–Barr virus; HCMV, human cytomegalovirus; HHV6, human herpesvirus 6; Ig, immunoglobulin.

the first time two clinically identical ME/CFS groups, which we designate group A and group B. Among the 142 ME/CFS patients, 106 were group A patients and 36 were group B patients. Each of the 142 ME/CFS patients had elevated serum IgG antibody titers to EBV, HCMV, and/or HHV6 in single or multiple infections. The 106 group A ME/CFS patients had no co-infections, but group B CFS patients had co-infections with tick-borne *Borrelia burgdorferi*, *Babesia microti*, or *Anaplasma (Ehrlichia) phagocytophila*. Adult rheumatic fever was also an indistinguishable co-infection. After analysis of the 142 ME/CFS patients was completed, *Mycoplasma pneumoniae* was added to possible group B co-infections.<sup>6</sup>

A specific ME/CFS designed and validated Energy Index Point Score (EIPS<sup>®</sup>) monitored severity of ME/CFS illnesses every 3 months over the 72 months of the study.<sup>7</sup> Group A ME/CFS patients were treated with long-term valacyclovir for EBV ME/CFS subsets, or long-term valganciclovir for HCMV or HHV6 ME/CFS subsets. ME/CFS patients with both EBV and HCMV/HHV6 subsets were given both nucleosides. With the specific diagnostic panel determining antiviral therapy for the ME/CFS group and subset, 79 of the 106 group A ME/CFS patients (74.5%) now continue normal lives ( $P < 0.0001$ ).<sup>6</sup> This is an unprecedented result.

Initially, ME/CFS patients had abnormal 24-h electrocardiography (ECG) recordings with resting tachycardias and abnormal left ventricular T-wave repolarizations, abnormal myocardial dynamics, and decreased left ventricular ejection fractions.<sup>8–10</sup> Accompanying symptoms were a pervasive life-altering fatigue, vasodepressive syncope, chest pains, fever, cervical lymphadenopathy, and muscle aches or joint pain.<sup>3</sup> All of these findings improved or disappeared with long-term antiviral nucleosides.<sup>6</sup> Resting standard 12-lead ECGs did not detect these cardiac abnormalities, which only became apparent with tachycardia. With antiviral therapy, elevated EBV, HCMV, HHV6 herpesvirus serum antibody titers fell.<sup>11–15</sup> The mean EIPS of the 106 group A ME/CFS patients increased from baseline  $<4$  to final  $>6.5$ , with a mean duration of antiviral treatment of 2.4 years. A former CFS patient (EIPS 4) with an EIPS of 6.5 can now fully participate in activities of normal living.

Surprisingly, after beginning valacyclovir/valganciclovir, the earliest time at which clinical improvement began was 6 months, which is far beyond what might customarily be expected. We offer a paradigm to explain both the absence of DNA-emia, antigenemia, and IgM antibody to complete virus and the long-time interval before ME/CFS patients begin recovery.

Evidence that in the EBV subset, ME/CFS patients treated with long-term elevated EBVEA(D) and/or EBV, VCA IgM serum antibody titers valacyclovir decrease is shown in Table 2.<sup>10</sup> Elevated EBVEA(D) serum antibody titers in ME/CFS patients 1, 4, and 5 decreased with long-term valacyclovir. Similarly, in ME/CFS patients, 2, 3, and 6 with baseline elevated EBV, VCA IgM serum titers decreased. Elevated EBV, VCA IgM serum antibody titers are present in approximately 15% of EBV subset ME/CFS patients, and elevated EBV early antigen (EA)(D) serum titers are regularly present in EBV subset patients.<sup>14</sup> Simultaneous myocardial dynamic studies of left ventricular ejection fractions showed a co-occurring increase in left ventricular ejection fractions with a mean value of +10.8 units (+18.9%),  $P = 0.007$ . The EIPS for these same six EBV ME/CFS patients improved from 3.7 to 6.5,  $P = 0.003$ . Tachycardias at rest, abnormal oscillating T-wave flattenings and inversions with 24-h ECG monitoring, and multiple symptoms improved with long-term valacyclovir.<sup>10–14</sup> Among the 106 group A ME/CFS patients followed for at least 6 months in 2001–2007, there were 42.5% with single herpesvirus EBV, HCMV, or HHV6 subsets and 57.5% with multiple herpesvirus ME/CFS.<sup>6</sup> Single and multiple ME/CFS patients responded equally.

Valacyclovir and valganciclovir inhibit viral EBV, HCMV, or HHV6 replication by inhibiting the core proteins, DNA polymerase, and thymidine kinase, which occupy approximately the 50th gene of the early, middle, and late sequential cascade of the several hundred herpesvirus genes in each of the three genomes. The murine retrovirus XMRV may compromise immune function in ME/CFS patients, facilitating nonpermissive herpesvirus replication.<sup>16,17</sup> We suggest that in ME/CFS patients, valacyclovir and valganciclovir inhibit the herpesvirus lytic replication cycle and thus prevent “recruitment of new host cells to ME/CFS

patients” and indirectly inhibit nonpermissive virus replication, thereby facilitating recovery from ME/CFS illness<sup>18</sup> (Table 1, Figure 1).

We propose that ME/CFS patients have nonpermissive herpesvirus (EBV, HCMV, HHV6) replication, expressing immediate-early (IE) gene products, which induce host cell dysregulation and host cell apoptosis.<sup>19,20</sup> At biopsy in ME/CFS patients, cardiac muscle fiber apoptosis is present, but EBV and HCMV polymerase chain reactions for complete virus are negative.<sup>21</sup>

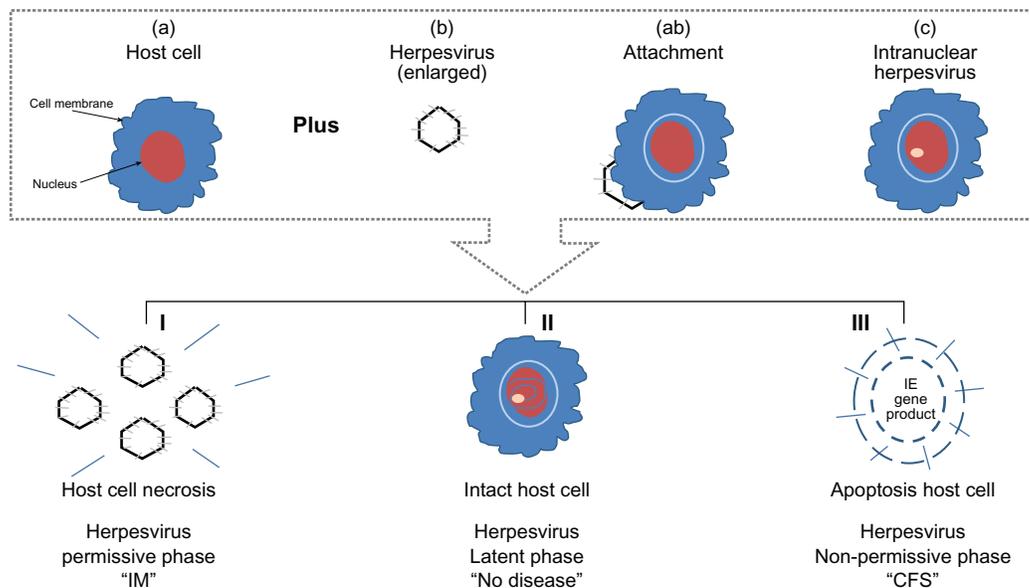
The three earliest genes expressed during initiation of the EBV lytic cycle are the IE genes zta (BZLF1 and EB1), Rta (R and BRLF1), and Mta (SM, BMLF1, and EB2). These early genes and their proteins Z (ZEBA, Zta, EB1) are essential for EBV lytic replication. The EBNA-2 gene is anti-apoptotic, favoring progression of the lytic cycle; therefore, serum assays for this late gene product are not included in the ME/CFS diagnostic profile.<sup>6,14,22</sup> The Zta IE gene product induces apoptosis with activation of many cellular proteolytic enzymes. Zta binds with high affinity to cellular AP-1 sites, altering host cell signaling and inducing IL-6, IL-10, TGF $\beta$ , the tyrosine kinase TKT, matrix metalloproteinases (MMP1 and MMP-9) c-Fos, and the early growth response (EGR-1). IL-10 and TGF $\beta$  suppress host immune responses. In infected and uninfected cells, EBV Zta is taken up and directed to the nucleus, activating apoptosis. Zta inhibits IL-10, decreasing macrophage and NK cell functions, NK and T-cell mediated cytotoxic responses, MHC class I molecules and immune presentations of lytic viral antigens, and major tumor necrosis factor alpha receptor (TNF-R1). Zta minimizes responses to TNF-receptor-mediated apoptosis signaling interferons. Zta mitigates the innate adaptive immune responses to EBV reactivation. Zta mediates these signaling events without EBV gene progression to the lytic

**Table 2** Phase II: valacyclovir treatment in six CFS patients with single-virus EBV infections (EBV antibody titers in serum)

Patient	Left ventricular ejection fraction (units)				Viral capsid antigen, IgM		Early antigen		Energy index point score		
	Pre	Post*	Change*	%*	Pre	Post*	Pre	Post*	Pre	Post	Change
1	59	67	+8	+13.6	Neg	Neg	>320	320	5	8	+3
2	59	76	+17	+29	142	<10	Neg	Neg	1	3	+2
3	70	75	+5	+7	228	39	40	80	3	7	+4
4	56	76	+20	+36	Neg	Neg	20	Neg	5	8	+3
5	51	59	+8	+16	Neg	Neg	320	40	4	5	+1
6	58	65	+7	+12	110	<10	Neg	Neg	4	8	+4
Mean	59	70	+10.8	18.9					3.7	6.5	+2.8
									$P = 0.003$		

**Notes:** \*Studies performed after 6 months of valacyclovir treatment. Copyright © 2002, Drugs Today. Reprinted with permission from Lerner AM, Beqaj SH, Deeter HJ, et al. A six-month trial of valacyclovir in the Epstein-Barr virus subset of chronic fatigue syndrome: improvement in left ventricular function. *Drugs Today*. 2002;38:549–561.

**Abbreviations:** CFS, chronic fatigue syndrome; EBV, Epstein–Barr virus; Ig, immunoglobulin.



**Figure 1** During the proposed three phases of herpesvirus replication (a) host cell and (b) herpesvirus bind at the cytoplasmic membrane (ab) and (c) herpesvirus transits intranuclearly. Permissive herpesvirus replication yields I) new virus and host cell necrosis infectious mononucleosis; II) the latent herpesvirus phase preserves both the virus genome and the healthy host cell; III) nonpermissive herpesvirus replication yields host cell apoptosis no new virus and ME/CFS.

**Abbreviations:** CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis.

cascade.<sup>23–31</sup> ME/CFS illness may require herpesvirus IE gene product-induced apoptosis with associated cellular dysregulation and proteolysis without virus lytic cycle completion and new infectious herpesvirus. Herpesvirus nonpermissive replication may also be a pathogenic mechanism in HCMV interstitial pneumonia where virus recovery in the lung does not correlate with virus titers in affected tissues.<sup>32–34</sup>

In the ME/CFS patient, EBV, HCMV, and HHV6 herpesviruses may enter host cells and initiate IE gene products, host cell dysregulation, cellular proteolysis, and inhibition of the immune response and apoptosis. No infectious new virus results. ME/CFS illness is consistent with herpesvirus IE gene product nonlytic-induced apoptosis. Valacyclovir and valganciclovir inhibit new host cell herpesvirus recruitment and, ultimately, herpesvirus IE-induced host cell apoptosis. ME/CFS clinical recovery follows.<sup>6,14</sup> Direct anti-ME/CFS therapy may be inhibition of EBV, HCMV, and HHV6 IE gene expression with drugs such as the antisense oligonucleotide ISIS 2922.<sup>35,36</sup> Kogelnik et al have described the therapeutic effect of valganciclovir in ME/CFS patients with HHV6 subset CFS, and Klimas and O'Brien have summarized inflammatory immune functions in ME/CFS that are compatible with the host cell dysregulation we propose.<sup>37–39</sup>

Further evidence for IE-induced pathology and nonpermissive replication in the EBV subset ME/CFS parallel to that in the HCMV subset ME/CFS (eg, p52 and CM<sub>2</sub>) is the work of Glaser, Williams, and colleagues.<sup>11,12,40–44</sup> EBV ME/CFS subset patients also have

uniquely elevated serum antibody titers to the nonstructural gene products EBV-specific DNase and DNA polymerase. These elevated EBV-specific serum antibody titers are also present in patients with EBV-related malignancies, Burkitt's lymphoma, and nasopharyngeal carcinoma, but are not present in patients with infectious mononucleosis or in healthy individuals. The EBV-EA(D) encodes for at least six different virus enzymes, including deoxyuridine triphosphate nucleotidohydroxylase (dUTPase). This early gene product, like HCMV, IE, and IE<sub>2</sub>, induces activation of proinflammatory cytokines through NK-K6, demonstrating that EBV dUTPase is a pathogen-associated molecule and that it has immunomodulator functions. Direction of antiviral therapy toward inhibition of IE genes of EBV, HCMV, and HHV6 may well shorten the time for ME/CFS recovery using the nucleosides valacyclovir and valganciclovir, which inhibit only the DNA polymerases and thymidine kinases of these herpesviruses that are present at a relatively mid-gene location in these large genomes.

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