

# Subset-directed antiviral treatment of 142 herpesvirus patients with chronic fatigue syndrome

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**Purpose:** We hypothesized that chronic fatigue syndrome (CFS) may be caused by single or multiple Epstein–Barr virus (EBV), cytomegalovirus (HCMV), or human herpesvirus 6 (HHV6) infection. To determine if CFS life-altering fatigue and associated findings including muscle aches, tachycardia at rest, chest aches, left ventricular dysfunction, syncope, and elevated herpesvirus serum antibody titers are reversed by long-term subset-directed valacyclovir and/or valganciclovir.

**Patients and methods:** Data were collected at physician visits every 4–6 weeks from 142 CFS patients at one clinic from 2001 to 2007. To be included in this study, patients had to be followed for at least six months. The data captured included over 7000 patient visits and over 35,000 fields of information. Severity of fatigue was monitored by a validated Energy Index Point Score® (EIPS®). Baseline and follow-up serum antibody titers to EBV, HCMV, and HHV6, as well as coinfections with *Borrelia burgdorferi*, *Anaplasma phagocytophila*, *Babesia microti*, and antistreptolysin O, 24-hour ECG Holter monitors, 2D echocardiograms, cardiac dynamic studies, symptoms, and toxicity were captured and monitored. International criteria for CFS plus a specifically designed CFS diagnostic panel were used.

**Results and conclusions:** The Group A herpesvirus CFS patients (no coinfections) returned to a near-normal to normal life ( $P = 0.0001$ ). The long-term EIPS value increased (primary endpoint,  $P < 0.0001$ ) with subset-directed long-term valacyclovir and/or valganciclovir therapy. Secondary endpoints (cardiac, immunologic, and neurocognitive abnormalities) improved or disappeared. Group B CFS patients (herpesvirus plus coinfections) continued to have CFS.

**Keywords:** valacyclovir, valganciclovir, treatment, chronic fatigue syndrome, CFS, Energy Index Point Score®, EIPS®

## Introduction

Chronic fatigue syndrome (CFS) is a life-altering illness affecting women to men in a ratio of 4:1,<sup>1–3</sup> for which there is no evidence-based etiology or treatment.<sup>4–7</sup> An association of CFS with an infectious gamma retrovirus XMRV, previously found in high-grade malignant prostate cancers, has been reported.<sup>8</sup> This xenotropic virus is similar to Maloney murine leukemia and the sarcoma virus in rodent, feline, and primate species. XMRV possesses a slow mechanism for oncogenesis, and its course does not always lead to cancer.<sup>8,9</sup> However, the XMRV report requires confirmation.<sup>10</sup>

Cardiac, immunologic, radiographic, and genetic abnormalities are present in CFS patients.<sup>11–21</sup> We hypothesized that CFS is caused by Epstein–Barr virus (EBV), cytomegalovirus (HCMV), and human herpesvirus 6 (HHV6) in single or multiple virus infection.<sup>22</sup> This suggests CFS patients continue EBV, HCMV, and HHV6 herpesvirus replication, and do not achieve the viral latency necessary for

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recovery.<sup>23–25</sup> We propose that early and middle herpesvirus (EBV, HCMV, HHV6) gene products to about the fiftieth gene of these complex viruses, containing over 200 open-reading frames, are synthesized without achieving complete virus formation.<sup>26</sup> We now test this hypothesis with the nucleosides valacyclovir for a suspected EBV CFS subset and valganciclovir for suspected HCMV or HHV6 CFS subsets. We report long-term benefit, assessed by the validated severity of an illness metric, the Energy Index Point Score® (EIPS®).<sup>27</sup> Seventy-nine of 106 (74.5%) CFS patients returned to a near-normal to normal life (primary endpoint). Secondary endpoints of cardiac, immunologic, and neurocognitive abnormalities improved or disappeared. The data support the paradigm that CFS illness is a herpesvirus infection.

Group A CFS patients have EBV, HCMV, and HHV6 in single or multiple infection without coinfection. Group B CFS patients are similar to Group A, but with coinfections, tick-borne *Borrelia burgdorferi*, *Babesia microti*, *Anaplasma phagocytophila*, and/or adult rheumatic fever. Our research questions were whether subset-directed antiviral therapy to single and multiple herpesvirus CFS patient groups causes a significant change in EIPS; what percentages of groups A and B CFS patients have EBV, HCMV, and/or HHV6 infection; whether long-term valacyclovir (for EBV) and valganciclovir (for HCMV, HHV6) treatment can cause lasting improvement in EIPS values for CFS patients; if long-term valacyclovir and/or valganciclovir are free of deleterious effects to complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine; whether single and coinfection CFS subsets respond similarly; and if there are identifiable demographics of Group A CFS patients who are “responders” and “non-responders” to antiviral therapy?

## Methods

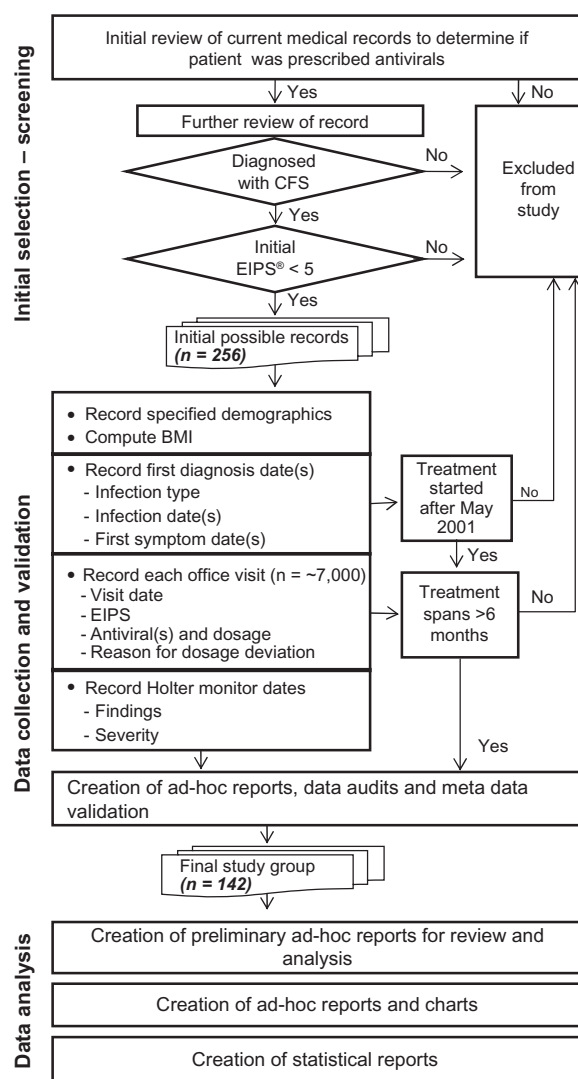
### Data collection process

The work process flow for this systematic review included initial selection screening, data collection and validation, and data analysis (Figure 1). Patient data were captured using a pre-defined set of data points. Demographics and each office visit were recorded by date, including presence of positive EBV, HCMV, and HHV6 serum antibody titers, specific antiviral therapy with dosage, change in antiviral treatment and reason for change, EIPS, 24-hour ECG Holter monitoring (HM), and toxicities. Serum antibody titers to *B. burgdorferi*, *B. microti*, *A. phagocytophila*, and antistreptolysin O were assessed. Each patient was assigned a blinded numerical number, and data

were entered into a Microsoft Office Access 2007 database that had been specifically designed for this study. A 100% audit was performed (>7000 office visits and >35,000 fields of data). Data were collected and analyzed by nonphysician, information-experienced professionals. Microsoft Office Access 2007 was used for data entry, validation, and storage. The blinded patient number was maintained throughout the study. This study was approved by the Human Investigation Committee at William Beaumont Hospital.

### Study selection

International criteria for diagnosis of CFS were used.<sup>2</sup> Intravenous ganciclovir (1997) and oral valacyclovir (2002, 2007) had been explored in earlier small clinical trials.<sup>28–30</sup>



A. Martin Lerner –Chart Study –Process Flow Chart

**Figure 1** Work process flow systematic review of herpesvirus in CFS patients, 2001–2007.

**Abbreviations:** BMI, body mass index; CFS, chronic fatigue syndrome; EIPS, Energy Index Point Score.

Oral valganciclovir became available for clinical use in 2000, and was then used in place of intravenous ganciclovir. The Dr A Martin Lerner Chronic Fatigue Syndrome Foundation was organized in 2007 to support research determining the possible value of specific subset-directed antiviral treatment of CFS.

Active charts of CFS patients (EIPS  $\leq 5$ ) who began and continued antiviral medications at this clinic from 01 May 2001 to December 2007 for at least six months were randomly selected for inclusion in this study.<sup>27</sup> Serologic evidence for EBV, HCMV, and HHV6 were identified. CFS patients were considered to have active EBV infection if there were elevated enzyme-linked immunosorbent assay (ELISA) serum antibodies to EBV IgM viral capsid recombinant peptide antigen VCA p18 (Diasorin, Stillwater, MN) and/or EBV early antigen EA-D, a 47 kDa recombinant polypeptide.<sup>23,29,30</sup> HCMV infection was identified by elevated serum antibody titers to human fibroblast lysate HCMV strain AD69, IgM, or IgG by ELISA tests and elevated Copalis light-scatter HCMV IgM p52 recombinant protein, UL44, and HCMV CM2, UL44, and part UL57 recombinant protein.<sup>24,25</sup> HHV6 infection was identified by elevated IgM and IgG serum antibody titers  $\geq 160$  (LabCorp, Dublin, OH).<sup>31</sup> CFS patients had abnormal 24-hour HM recordings.<sup>12,15,16</sup> When baseline abnormal resting standard ECG and abnormal recurrent oscillating T-waves (flat, inverted) on HM recordings were present, myocardial perfusion studies to exclude coronary artery disease and radionuclide ventriculography (MUGA) by bicycle protocol stress studies were performed.<sup>14,16</sup> Seven randomly selected CFS patients had cardiac muscle biopsies.<sup>15</sup> Two patients had postcardiac biopsy bleeding.

There were 106 CFS patients who had negative IgM and IgG serum antibody titers to *B. burgdorferi* by Western blot and ELISA test, with antistreptolysin O titers  $<400$  units, and negative serum IgM and IgG antibody titers to *B. microti* and *A. phagocytophila*. These patients were categorized as Group A CFS. An additional 36 CFS patients had elevated serum antibody titers to *B. burgdorferi*, *B. microti*, *A. phagocytophila*, or antistreptolysin O  $> 400$ , and comprised Group B CFS.

## Severity of fatigue

The EIPS is a validated metric determining severity of CFS illness.<sup>27</sup> Patients were evaluated by EIPS with consensus of physician and patient. An EIPS of 0–5 is diagnostic of CFS. At EIPS values 6–10, patients no longer have CFS. An effect size of 0.8 is significant. A CFS patient was considered a “responder” to antiviral treatment if the change in EIPS effect

|                 |   |
|-----------------|---|
| 0               | Bedridden, up to bathroom only  |
| 1               | Out of bed 30–60 minutes a day (sitting in chair is out of bed)   |
| 2               | Out of bed sitting, standing, walking 1–2 hours per day   |
| 3               | Out of bed sitting, standing, walking 2–4 hours per day   |
| 4               | Out of bed sitting, standing, walking 4–6 hours per day   |
| 5               | Perform with difficulty sedentary job 40 hours a week, daily naps   |
| <b>Recovery</b> |   |
| 6               | Daily naps in bed, may maintain a 40-hour sedentary work week plus light, limited housekeeping and/or social activities |
| 7               | No naps in bed. Up 7:00 am to 9:00 pm. Able to work a sedentary job plus light housekeeping                             |
| 8               | Full sedentary workweek, no naps, some social activities plus light exercise  |
| 9               | Same as 8 above plus exercise approximately 1/2 to 2/3 normal without excessive fatigue, awakens next morning refreshed |
| 10              | Normal  |

**Figure 2** Energy Index Point Score®: A functional capacity measurement tool for CFS patients. The Energy Index Point Score® (EIPS®) chart provides the severity of patient fatigue. A change in EIPS level of 1 is a large significant change. The EIPS level is determined by agreement of physician and patient with the EIPS chart easily available for viewing at outpatient visits. As the EIPS level increases, CFS symptoms lessen and disappear. The EIPS system can be used in four easy steps: post the EIPS chart in examining room; ask the patient to evaluate his/her level of activity based on the prior two weeks; question the patient's EIPS evaluation; record and track the EIPS level; report every 6–12 weeks. Copyright © 2002 Prous Science, S.A. All rights reserved. Adapted with permission from Lerner AM, Beqaj SH, Deeter RG, et al. A six-month trial of valacyclovir in the Epstein-Barr virus subset of chronic fatigue syndrome: Improvement in left ventricular function. *Drugs of Today*. 2002; 38(8):549–561.

size was  $\geq 1$ . A CFS patient was considered a “nonresponder” to antiviral treatment if the effect size was  $<1$  (Figure 2).

## Valacyclovir (or famciclovir) for EBV infection

Valacyclovir and famciclovir are oral prodrugs which are absorbed as acyclovir and penciclovir, respectively, and effectively inhibit EBV thymidine kinase.<sup>32,33</sup> The EBV ID<sub>50</sub> for valacyclovir is 1.1–4.4  $\mu\text{g/L}$ . Its bioavailability is increased by food. Valacyclovir may cause diarrhea, so famciclovir was then substituted if necessary. Both valacyclovir and

famciclovir were given as 1 gm (14.3 mg/kg) every six hours. When the patient weighed  $\geq 79.5$  kg, 1500 mg valacyclovir (or famciclovir) was given every six hours. Maximum acyclovir levels are present after 90–120 minutes (7.9–21  $\mu\text{g/mL}$ ).<sup>29</sup> Valacyclovir is excreted by renal glomerular filtration and tubular secretion. The elimination half-lives of acyclovir and penciclovir are in the range of 1.5–6 hours. Patients were instructed to drink at least 1500 mL of water daily to avoid valacyclovir-induced renal calculi. At the physician's discretion, cimetidine (400 mg every 12 hours) and/or probenecid (500 mg every 12 hours) which inhibit(s) acyclovir tubular secretion were given to increase acyclovir serum levels.<sup>32,34</sup> Valacyclovir and famciclovir do not effectively inhibit HCMV or HHV6 multiplication. In order to continue therapy, normal CBC, platelet count, aminotransferases, and urinalysis were required at physician visits every 4–6 weeks.

## Valganciclovir for HCMV and/or HHV6 infection

The valganciclovir  $\text{ID}_{50}$  for HCMV and HHV6 is 0.2–2.8  $\mu\text{g/mL}$ . The  $\text{ID}_{50}$  for ganciclovir versus EBV is 0.5  $\mu\text{g/mL}$ .<sup>35</sup> In this study valganciclovir was used for CFS patients with suspected HCMV or HHV6 infections. Valganciclovir is efficiently absorbed as ganciclovir, inhibiting human bone marrow progenitor cells and lymphocyte blastogenesis. After 0.5–1.0 gm doses, the average peak valganciclovir concentration ( $C_{\text{max}}$ ) is 6.1  $\mu\text{g/mL}$ . Valganciclovir was also given after meals, thereby increasing its bioavailability. Valganciclovir was started at 450 mg once daily in the morning after food for three days, and then continued as two in the morning for three days; and finally given, two in the morning followed by 450 mg 12 hours later as a continuing dose. If elevated aminotransferase(s) occurred, valganciclovir was withheld for 1–2 weeks until serum transaminases were normal. Valganciclovir was then continued 900 mg once daily. If the patient weighed  $>91$  kg, 900 mg valganciclovir was given every 12 hours.

## Atenolol and fludrocortisone acetate

Resting tachycardia with orthostatic hypotensive syncope were treated with atenolol 12.5–50 mg every 12 to 24 hours.<sup>11,12,14,15</sup> After beginning atenolol, the 24-hour HM recording was repeated seven days later to confirm that tachycardia had decreased. When needed, digoxin was also used to decrease tachycardia. For associated orthostatic hypotension, 0.1 mg fludrocortisone acetate every 12 to 24 hours was administered. As the EIPS value rose and symptoms diminished, atenolol, digoxin, and fludrocortisone were discontinued.

## Treatment of coinfections

Patients with elevated serum antibody titers to *B. burgdorferi*, anaplasmosis, babesiosis, or adult rheumatic fever were treated according to the clinical practice guidelines of the Infectious Diseases Society of America, the American Heart Association, and the World Health Organization.<sup>36,37</sup> Patients with elevated serum antibody titers to *B. burgdorferi* were given ceftriaxone 1–2 gm intravenously every 12 hours. *A. phagocytophila* infection was treated with doxycycline 100 mg every 12 hours orally or intravenously. *B. microti* infection was treated orally with atovaquone 750 mg and azithromycin 500 mg every 12 hours. Coinfections were treated for 30 days and then assessed.

## Toxicity

At 4–6 week visits, recorded entries were made for abnormal white blood cells, platelet counts, aminotransferases, participation in a smaller, randomized, blinded, placebo-controlled trial, weight gain or loss, substitution of famciclovir for valacyclovir, and any changes in dosage of valganciclovir, valacyclovir, or famciclovir.<sup>30</sup>

## Qualitative Holter monitor assessments

Twenty-four hour HM recordings were evaluated qualitatively for simple counts of abnormalities and severity, (mild, 1 point; medium, 2 points; or severe, 3 points). Tachycardia at rest ( $>100$  per minute) was assessed as mild  $<6$  hours/24 hours; medium  $>6$  and  $\leq 10$  hours/24 hours; or severe  $>10$  hours/24 hours). Oscillating abnormal T-wave flattenings and T-wave inversions were evaluated as mild (occasional), medium (intermittent), or severe (frequent) and given severity point scores of 1, 2, or 3, respectively. Deep inverted T-waves, multiple and multifocal ventricular premature contractions, and bigeminal rhythms were evaluated by count and severity. Thus, HM recordings had two numeric evaluations, ie, a simple numeric count of types of abnormality and a severity score. For example, a patient with an HM showing T-wave flattening (severity score 1), mild supraventricular tachycardia (severity score 1), but with no inverted T-waves would equate to a severity score of 2 with an abnormality count of 2. Another patient with an HM and moderate supraventricular tachycardia (severity score 2) “abnormal count 1”, and both moderate numbers of oscillating T-wave flattenings (severity score 2) “abnormal count 1”, multifocal ventricular premature contractions (severity score 2) “abnormal count 1”, and a bigeminal rhythm (severity score 3) “abnormal count 1.” The latter HM would have a total severity score of 9 and an abnormal simple occurrence count of 4.



## Summary measures

For Group A CFS in 106 patients, gender distribution for age, BMI, duration of illness prior to treatment, duration of treatment, baseline EIPS value, last EIPS value, and EIPS delta value were determined by t-tests (two-tailed). Change between overall baseline EIPS value and overall last EIPS value was examined by a paired t-test (two-tailed). Differences in gender distribution by herpesvirus category (single or multiple) were examined by Fisher's exact test (two-tailed). Pearson chi-square analyses were used to examine gender distribution by subset classification within the herpesvirus category. Change in EIPS value was examined by multivariate analysis of variance with repeated measures. CFS patient responder and non-responder differences by gender and by herpesvirus

category were examined by the Fisher's exact test (two-tailed). Differences between responders and nonresponders for age, BMI, CFS duration prior to antiviral therapy, duration of antiviral therapy, initial EIPS value, and last EIPS value were examined by t-tests (two-tailed). Numbers of Group B CFS patients were too small for statistical analysis. Microsoft Office Excel 2007 and SAS Version 8.0.1 were used for reporting and statistical analysis, respectively.

## Results

### Demographics of Group A CFS patients

There were 106 Group A CFS patients treated with antiviral medicines (Table 1), of whom 73% were female and 27% were male. Mean age was 46.2 years and mean BMI was

**Table 1** Demographics of 142 patients with CFS, 2001–2007

| Patients   | Group A patients<br>(n = 106) | P value              | Group B                |                        | Patients without<br>B.b. (n = 10) |
|--|-------------------------------|----------------------|------------------------|------------------------|-----------------------------------|
|  |                               |                      | All patients (n = 36)  | B.b. (n = 26)          |                                   |
| Women  | 77 patients (73%)             |                      | 28 patients (77.8%)    | 23 patients (63.8%)    | 5 patients (13.9%)                |
| Men  | 29 patients (27%)             |                      | 8 patients (22.2%)     | 3 patients (8.3%)      | 5 patients (13.9%)                |
| Age, all patients (mean ± SEM)                                   | 46.2 ± 1.3 years              |                      |                        |                        |                                   |
| Age, women   | 47.1 ± 1.5 years              | 0.309 <sup>1</sup>   | 44.2 years             | 44.5 years             | 43 years                          |
| Age, men   | 44.0 ± 2.8 years              |                      | 40.9 years             | 48.3 years             | 36.4 years                        |
| BMI, all patients (mean ± SEM)                                   | 26.4 ± 0.5 kg/m <sup>2</sup>  |                      | 26.5 kg/m <sup>2</sup> | 26.8 kg/m <sup>2</sup> | 25.7 kg/m <sup>2</sup>            |
| BMI, women   | 26.6 ± 0.6 kg/m <sup>2</sup>  | 0.573 <sup>1</sup>   | 26.4 kg/m <sup>2</sup> | 26.9 kg/m <sup>2</sup> | 24.1 kg/m <sup>2</sup>            |
| BMI, men   | 26.0 ± 0.6 kg/m <sup>2</sup>  |                      | 26.7 kg/m <sup>2</sup> | 26 kg/m <sup>2</sup>   | 27.1 kg/m <sup>2</sup>            |
| All patients duration of illness (mean ± SEM prior to treatment) | 4.8 ± 0.5 years               |                      | 5.9 years              | 4.7 years              | 8.9 years                         |
| Duration of illness prior to 1st antiviral treatment, women      | 4.6 ± 0.6 years               | 0.537 <sup>1</sup>   | 4.5 years              | 4.1 years              | 6.1 years                         |
| Duration of illness prior to 1st antiviral treatment, men        | 5.3 ± 1.2 years               |                      | 10.8 years             | 9.5 years              | 11.6 years                        |
| All patients duration of antiviral treatment (mean ± SEM)        | 2.4 ± 0.2 years               |                      | 2.6 years              | 2.6 years              | 2.4 years                         |
| Duration of antiviral treatment, women                           | 2.5 ± 0.2 years               | 0.416 <sup>1</sup>   |                        |                        |                                   |
| Duration of antiviral treatment, men                             | 2.2 ± 0.3 years               |                      |                        |                        |                                   |
| All patients baseline EIPS, (mean ± SEM)                         | 4.2 ± 0.1                     |                      | 3.8                    | 4.0                    | 3.4                               |
| Baseline, EIPS, women  | 4.2 ± 0.1                     | 0.695 <sup>1</sup>   |                        |                        |                                   |
| Baseline, EIPS, men  | 4.3 ± 0.2                     |                      |                        |                        |                                   |
| All patients last EIPS, patients (mean ± SEM)                    | 6.1 ± 0.2                     |                      | 5.3                    | 5.4                    | 5.0                               |
| Last EIPS, women   | 6.0 ± 0.2                     | 0.329 <sup>1</sup>   |                        |                        |                                   |
| Last EIPS, men   | 6.3 ± 0.3                     |                      |                        |                        |                                   |
| All patients delta*, (mean ± SEM)                                | 1.9 ± 0.2                     | <0.0001 <sup>2</sup> | 1.5                    | 1.5                    | 1.9                               |
| Delta*, women  | 1.8 ± 0.2                     | 0.378 <sup>1</sup>   |                        |                        |                                   |
| Delta*, men  | 2.1 ± 0.3                     |                      |                        |                        |                                   |

**Abbreviations:** B.b., *Borrelia burgdorferi*; EIPS®, Energy Index Point Score®; CFS, chronic fatigue syndrome; SEM, standard error of measurement; BMI, body mass index.

<sup>1</sup>t-test (two-tailed) to determine differences between men and women; <sup>2</sup>paired t-test (two-tailed) to determine difference between baseline and last EIPS; \*last EIPS minus first EIPS. Group B patients have multiple coinfections. Data listed are mean values.

26.4 kg/m<sup>2</sup>. The patients had been ill for a mean of 4.8 years before their first clinic visit. The mean duration of antiviral therapy was 2.4 years. Baseline EIPS value was 4.2. The baseline EIPS value for women was 4.2 and the baseline EIPS value for men was 4.3. The last EIPS value for all patients was 6.1. The women's last EIPS value was 6.0, and the last men's EIPS value was 6.3. This change between baseline and last EIPS is large ( $P < 0.0001$ ). The effect size for the 106 patients was +1.9 (+1.8 for women and +2.1 for men).

## Herpesvirus subset classification, Group A CFS

Among the 106 Group A patients with single herpesvirus subsets, there were 30 (28.3%) EBV patients; 13 (12.3%) HCMV patients, and two (1.9%) HHV6 patients (Table 2). Among multiple herpesvirus CFS patients, there were 30 (28.3%) EBV/HCMV patients, 12 (11.3%) EBV/HCMV/HHV6 patients, 14 (13.2%) EBV/HHV6 patients, and five (4.7%) HCMV/HHV6 patients.

Serial EIPS value changes from baseline and at 24 three-month intervals for Group A CFS are shown in Table 3 and

**Table 2** Single and multiple herpesvirus subsets in 106 Group A CFS patients

|                                   | Women (n) | Men (n) | Total patients |
|-----------------------------------|-----------|---------|----------------|
| <b>Single herpesvirus CFS</b>     |           |         |                |
| EBV                               | 20        | 10      | 30 (28.3%)     |
| HCMV                              | 8         | 5       | 13 (12.3%)     |
| HHV6                              | 2         | 0       | 2 (1.9%)       |
| <b>Total</b>                      | 30        | 15      | 45 (42.5%)     |
| Pearson<br>Chi-square $P = 0.562$ |           |         |                |
| <b>Multiple herpesvirus CFS</b>   |           |         |                |
| EBV/HCMV                          | 24        | 6       | 30 (28.3%)     |
| EBV/HCMV/HHV6                     | 7         | 5       | 12 (11.3%)     |
| EBV/HHV6                          | 11        | 3       | 14 (13.2%)     |
| HCMV/HHV6                         | 5         | 0       | 5 (4.7%)       |
| <b>Total</b>                      | 47        | 14      | 61 (57.5%)     |
| Pearson<br>chi-square $P = 0.258$ |           |         |                |

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

**Table 3** Mean EIPS® at three-month intervals for 106 Group A CFS patients including 79 (74.5%) Group A "responders"\*

| <b>Total Group A (n = 106)</b> |              |             |           | <b>Group A "responders" (n = 79)</b> |              |             |           |
|--------------------------------|--------------|-------------|-----------|--------------------------------------|--------------|-------------|-----------|
| Three-month intervals          | Patients (n) | EIPS (mean) | EIPS (SD) | Three-month intervals                | Patients (n) | EIPS (mean) | EIPS (SD) |
| 0                              | 106          | 4.21        | 0.87      | 0                                    | 79           | 4.36        | 0.80      |
| 1                              | 98           | 4.19        | 0.95      | 1                                    | 75           | 4.29        | 0.93      |
| 2                              | 104          | 4.44        | 1.21      | 2                                    | 77           | 4.70        | 1.19      |
| 3                              | 103          | 4.94        | 1.49      | 3                                    | 76           | 5.30        | 1.47      |
| 4                              | 96           | 5.49        | 1.50      | 4                                    | 73           | 5.84        | 1.40      |
| 5                              | 84           | 5.77        | 1.47      | 5                                    | 68           | 6.03        | 1.37      |
| 6                              | 78           | 6.06        | 1.46      | 6                                    | 65           | 6.44        | 1.24      |
| 7                              | 66           | 6.17        | 1.38      | 7                                    | 57           | 6.37        | 1.25      |
| 8                              | 59           | 6.25        | 1.25      | 8                                    | 53           | 6.35        | 1.20      |
| 9                              | 51           | 6.55        | 1.05      | 9                                    | 46           | 6.71        | 0.82      |
| 10                             | 47           | 6.83        | 1.15      | 10                                   | 44           | 6.94        | 0.98      |
| 11                             | 46           | 6.65        | 1.24      | 11                                   | 42           | 6.84        | 0.97      |
| 12                             | 40           | 6.26        | 1.40      | 12                                   | 37           | 6.35        | 1.33      |
| 13                             | 38           | 6.32        | 1.46      | 13                                   | 35           | 6.44        | 1.39      |
| 14                             | 38           | 6.54        | 1.36      | 14                                   | 36           | 6.63        | 1.32      |
| 15                             | 33           | 6.42        | 1.19      | 15                                   | 31           | 6.45        | 1.18      |
| 16                             | 30           | 6.59        | 1.20      | 16                                   | 28           | 6.70        | 1.03      |
| 17                             | 28           | 6.83        | 1.21      | 17                                   | 26           | 6.94        | 1.10      |
| 18                             | 27           | 6.52        | 1.40      | 18                                   | 25           | 6.64        | 1.34      |
| 19                             | 22           | 6.55        | 1.48      | 19                                   | 20           | 6.74        | 1.31      |
| 20                             | 18           | 6.69        | 1.86      | 20                                   | 16           | 6.89        | 1.74      |
| 21                             | 14           | 6.40        | 1.47      | 21                                   | 12           | 6.64        | 1.40      |
| 22                             | 13           | 6.51        | 0.89      | 22                                   | 12           | 6.47        | 0.92      |
| 23                             | 13           | 6.70        | 0.88      | 23                                   | 12           | 6.72        | 0.92      |
| 24                             | 6            | 6.70        | 1.32      | 24                                   | 5            | 6.75        | 1.49      |

**Notes:** \*CFS "responder" is a CFS patient whose EIPS increases by at least one EIPS unit. All CFS patients included here received  $\geq$  six months of valacyclovir/valganciclovir treatment.

**Abbreviations:** CFS, chronic fatigue syndrome; EIPS, Energy Index Point Score; SD, standard deviation.

Figure 3. In the total group of 106 patients, the baseline EIPS value was  $4.2 \pm 0.87$  (standard deviation) and the last 72-month EIPS value was  $6.7 \pm 1.32$  ( $n = 6$ ). Seventy-nine (74.5%) CFS patients had EIPS increases  $\geq 1.0$ . For the 79 CFS “responders,” the mean baseline EIPS value was  $4.36 \pm 0.8$  ( $n = 79$ ), and the last 72-month mean EIPS was  $6.75 \pm 1.49$  ( $n = 5$ ).

## Demographics of Group A CFS responders and nonresponders

Group A CFS responders and nonresponders were similar for sex, age, BMI, and distributions of single and multiple herpesvirus subsets (Table 4). However, these patients did differ in average duration of CFS illness prior to initiation of antiviral treatment (7.3 years for nonresponders versus 3.9 years for responders,  $P = 0.005$ ). Duration of antiviral therapy for responders averaged 2.70 years, but the nonresponders' duration of therapy was 1.53 years ( $P < 0.0001$ ). Single and multiple herpesvirus CFS subsets responded equally well to antiviral therapy ( $P = 0.825$ ). The delta EIPS for responders was 2.54 ( $P < 0.0001$ ). EIPS improved in both single and multiple herpesvirus CFS patients. Twenty-one Group A single herpesvirus CFS patients had last EIPS values 7–9, and 27 Group A multiple herpesvirus CFS patients had last EIPS values 7–9.

**Table 4** Demographics of 106 Group A herpesvirus CFS patients, 2001–2007

|   | Responders | Non responders | P value              |
|---|------------|----------------|----------------------|
| Number of patients                                      | 79         | 27             |                      |
| Females   | 58         | 19             | 0.805 <sup>1</sup>   |
| Males   | 21         | 8              |                      |
| Age (years)   | 45.5       | 48.4           | 0.347 <sup>2</sup>   |
| BMI (kg/m <sup>2</sup> )                                | 26.1       | 27.2           | 0.353 <sup>2</sup>   |
| Mean duration of CFS prior to antiviral therapy (years) | 3.9        | 7.3            | 0.005 <sup>2</sup>   |
| Single herpesvirus subset (patients)                    | 33 (41.7%) | 12 (44.4%)     | 0.825 <sup>1</sup>   |
| Multiple herpesvirus subset (patients)                  | 46 (58.3%) | 15 (55.6%)     |                      |
| Mean duration of antiviral therapy (years)              | 2.70       | 1.53           | 0.001 <sup>2</sup>   |
| Mean first EIPS   | 4.34       | 3.81           | 0.006 <sup>2</sup>   |
| Mean last EIPS  | 6.88       | 3.73           | <0.001 <sup>2</sup>  |
| Difference, EIPS associated with antiviral therapy      | 2.54       | −0.08          | <0.0001 <sup>3</sup> |

**Abbreviations:** CFS, chronic fatigue syndrome; EIPS®, Energy Index Point Score®.

<sup>1</sup>Fisher's exact test (two-tailed); <sup>2</sup>t-test (two-tailed); <sup>3</sup>multivariate analysis of variance with repeated measures.

## Demographics of Group B CFS patients and changes in EIPS

Of 36 Group B CFS patients, 26 had elevated serum IgM or IgG, Western Blot or ELISA antibody titers to *B. burgdorferi*, with/without elevated serum antibody titers to Babesia or Anaplasma, or antistreptolysin O titers  $> 400$ , and 10 patients did not have elevated Western Blot or ELISA IgM or IgG *B. burgdorferi* serum antibody titers, but did have elevated serum antibody titers to Babesia and/or Anaplasma and/or antistreptolysin O titers  $> 400$ .<sup>37</sup> At first visits, Group B CFS patients were 43–48 years old and their BMI was 25.7–27.1 kg/m<sup>2</sup>. Group B CFS patients had been ill for a mean of 5.9 years; Group B with *B. burgdorferi* had been ill for a mean of 4.7 years and those with no *B. burgdorferi* infection had been ill for 8.9 years. In all CFS patients in the Group B subset, men had been ill for longer than women. Baseline subset EIPS values were 3.1–4.0. After a mean 2.6 years of directed treatment, the last mean EIPS value was 5.3, thereby continuing a CFS diagnosis.

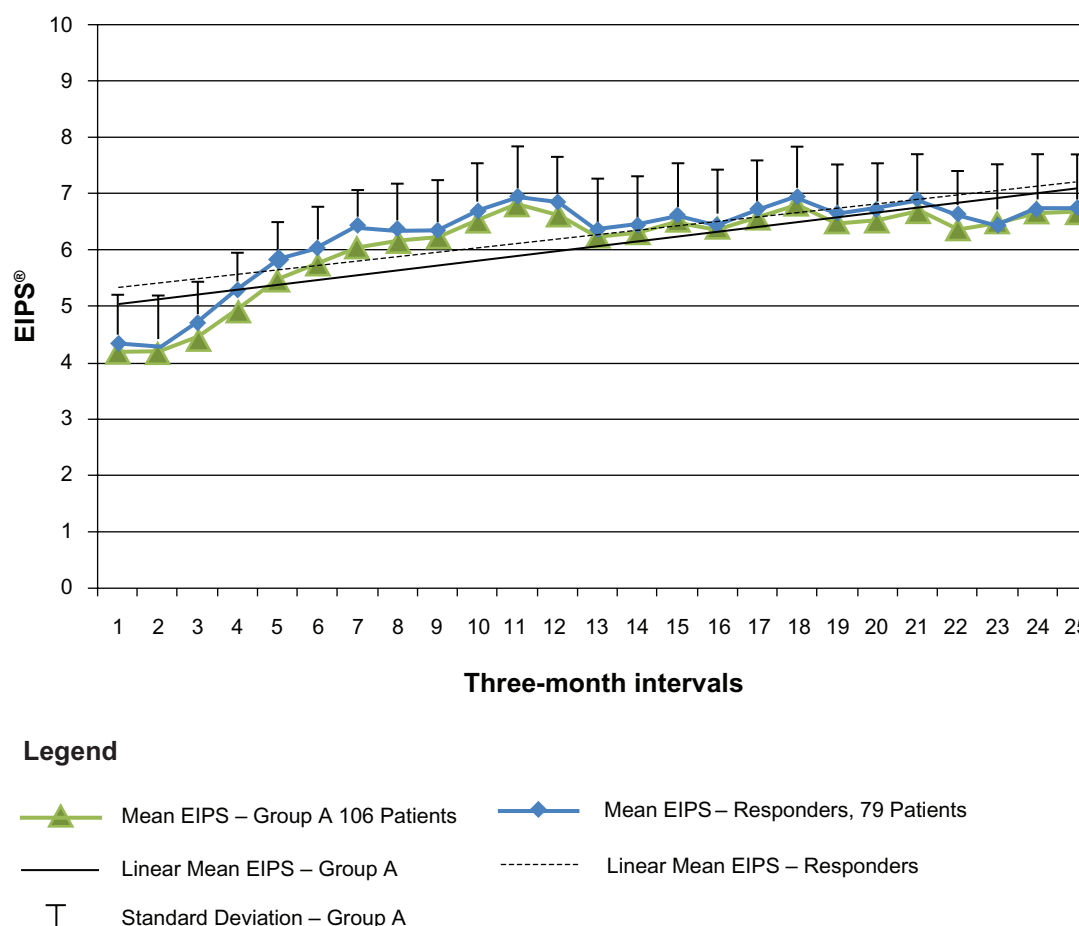
Among the 36 Group B CFS patients, 26 (72.2%) had elevated serum titers to *B. burgdorferi*. There were 22 Group B CFS patients with EBV coinfection, 13 with HCMV coinfections, and 12 with HHV6 coinfections. Ten Group B CFS patients had no coinfecting *B. burgdorferi*, but included five EBV coinfections, seven HCMV coinfections, and five HHV6 coinfections. CFS Group B patients without *B. burgdorferi* included one patient with an elevated serum antibody titer to *B. microti*, two with elevated serum antibody titers to *A. phagocytophila*, and two with antistreptolysin O titers  $> 400$ .

## EIPS changes at baseline and at three-month intervals for Group B CFS patients

Baseline EIPS values for all Group B CFS subsets were similar, ie, 3.78 (for all 36 patients), 3.95 (for 26 patients with *B. burgdorferi* infection), and 3.35 (for 10 patients without *B. burgdorferi* infection). The last mean three-month EIPS values for these three subsets of Group B CFS patients were somewhat increased at 5.28, 5.39, and 4.97, respectively. However, at completion of the study, the three Group B CFS subsets continued to meet criteria for CFS diagnosis. Improvement was small.

## ECG Holter monitor recordings

Of 104 Group A CFS patients with baseline HMs and follow-up HMs  $\geq$  six months later, 92 (88.5%) had abnormal baseline HM recordings.<sup>12,15</sup> There were 77 (74%) with abnormal oscillating T-wave flattening, 46 (44.2%) with



**Figure 3** Mean increase in EIPS<sup>®</sup> of 106 Group A CFS patients treated with subset-directed antiviral nucleosides, 2001–2007 at a single clinic.

abnormal oscillating T-wave inversions, and 47 (44.5%) with resting tachycardia. These abnormal HM findings in CFS patients with no coronary artery disease, hypertension, or abnormal electrolyte abnormalities are a biomarker of CFS cardiomyopathy.<sup>12,15,16</sup> Severity scores and abnormal data counts improved with valacyclovir/valganciclovir, but did not return to normal.

There were 25 Group B CFS patients with baseline and repeat HMs after six months of treatment. All of these patients had baseline abnormal HMs. Of Group B CFS patients, 22 (88%) had abnormal oscillating T-wave flattening and 12 patients each (48%) had abnormal oscillating T-wave inversions and resting tachycardia.

## Toxicity

After beginning valacyclovir (or famciclovir) or valganciclovir there were two to 10 weeks with worsening initial symptoms, decreased EIPS, and increased syncope, palpitations, chest pain, and muscle pain. These transiently worsening symptoms are Jarisch-Herxheimer reactions. At these

times CFS patients were usually afebrile and CBC, AST, ALT, and creatinine remained normal. No patient had serious toxicity. Transient increases in aminotransferases were seen with valganciclovir. Aminotransferase abnormalities resolved with modifications in administration of valganciclovir. There was no serious toxicity among groups A or B CFS patients. Fourteen Group A CFS patients with EBV received famciclovir for a mean of 0.88 years. The mean baseline EIPS value for these patients was 3.9, and the 24 three-month interval EIPS value was 5.89 for the patients, all of whom received valacyclovir for portions of their antiviral treatment. The value of famciclovir in CFS illness cannot be estimated from these data.

## Discussion

We describe a CFS illness exemplifying a conflict between a complex system and attempts at reductionism.<sup>38</sup> CFS illness is divided into Group A herpesvirus (EBV, HCMV, HHV6) without coinfection and Group B herpesvirus CFS with coinfection(s). Coinfections are, remarkably,



tick-borne Lyme disease, babesiosis and anaplasmosis, as well as non-tick-borne adult rheumatic fever. Long-term valacyclovir and/or valganciclovir subset-directed administration improved or eliminated CFS symptoms in Group A CFS patients, allowing them to return to normal life. EBV, HCMV, and HHV6 single and multiple herpesvirus Group A CFS patients were identified and responded equally well. Different patient populations in other CFS clinics may have varying percentages of these three herpesviruses. Valacyclovir and valganciclovir as administered here were safe. Single and multiple infected Group A CFS patients responded. An initial Jarisch-Herxheimer response at the start of antiviral medication initiates successful treatment. The higher the baseline EIPS, the better the prognosis. The long-term recovery of Group A CFS patients reported in this study is unprecedented. These remarkable results are dependent upon the careful diagnostic panel outlined here under Methods. We emphasize that the serologic antigens utilized for antibody assays of *B. burgdorferi* are identical to those used by the US Centers for Disease Control.

It is unclear whether XMRV gamma retrovirus infection initiates the immunosuppression which may be responsible for CFS. Nevertheless, specific herpesvirus antiviral treatment reversed CFS illness in 79 of 106 Group A CFS patients. Earlier studies suggesting a herpesvirus CFS causation had not used either the diagnostic criteria or long-term herpesvirus therapy, nor had previous herpesvirus CFS research separated groups A and B CFS which is critical to these results.<sup>4,5</sup>

Cardiac muscle disease, syncope, chest pain, positive tilt table tests, tachycardias at rest, decreased left ventricular ejection fraction, and left ventricular dilatation improved and/or disappeared with antiviral treatment. The abnormal HM is a reliable biomarker of CFS cardiac disease. The EIPS is integral to follow severity and reversal of CFS illness.

Questions about the pathogenesis of CFS remain. There is a preponderance of tick-borne *B. burgdorferi*, and Anaplasma and Babesia coinfections in Group B CFS patients. Studies of possible antibiotics in patients with suspected chronic Lyme disease need to consider the possibility of an unrecognized presence of Group B herpesvirus CFS. Does herpesvirus CFS inhibit a class-switch transformation from IgM to IgG in *B. burgdorferi* infection? Elevated IgG HCMV titers with no IgM HCMV titers are common in human immunodeficiency virus (HIV)-acquired immunodeficiency syndrome (AIDS) patients, but AIDS patients have HCMV DNA in their blood by polymerase chain reaction. Does nonpermissive latent herpesvirus replication in CFS inhibit classic IgM/IgG

class-switch interchange for the involved CFS herpesvirus? Meta-analysis of multiple randomized CFS therapeutic studies have determined a 17% placebo response.<sup>39</sup> Graded exercise and psychotherapy alleviate some CFS symptoms,<sup>6,7</sup> but neither therapy approaches the results of this report. The data here suggest exercise may be tolerated at EIPS > 7. A CFS patient (EIPS value  $\leq 5$ ) with a posttreatment EIPS value of 6 lives a normal life with only a short midday nap. The present data are remarkable considering that these CFS patients had been ill for a mean of 4.8 years before antiviral therapy was begun. The mean duration of antiviral therapy for Group A CFS patients was 2.4 years. Both valacyclovir and valganciclovir were equally effective in single or multiple herpesvirus CFS subsets.

In these CFS patients, herpesvirus antigenemia, viremia, and polymerase chain reactions in CFS tissues and bloods were negative.<sup>4,15</sup> The CFS nonpermissive abortive herpesvirus paradigm postulates mRNA to middle or late EBV, HCMV, and HHV6 genes is present in the blood macrophages and lymphocytes of CFS patients. The presence of IgM serum antibodies to the nonstructural tegument middle-gene products HCMV p52 and HCMV CM<sub>2</sub> in HCMV CFS is consistent with this hypothesis.<sup>24,25</sup> CFS is a result of persistent single or multiple EBV, HCMV and/or HHV6 infections(s), categorized as a two-group complex illness without coinfection (Group A) or with coinfections (Group B). These data show that 74.5% of 106 Group A CFS patients returned to near-normal to normal lives after long-term herpesvirus subset-directed antiviral therapy.

Finally, the rationale for prolonged antiviral treatment requires discussion. This CFS herpesvirus paradigm is that herpesviruses (EBV, HCMV, HHV6) are constantly attempting to produce virulent complete virus as early, middle, and late gene product in progression, and, ultimately, cytopathic effects, and an inflammatory cytolysis of the affected cells. Progeny-complete herpesvirus then continues to infect new host cells. Similarly, the host-immune system attempts to inhibit herpesvirus replication and induce silent virus latency as intranuclear episomes with no viral gene products. In CFS, we hypothesize there is immediate-early gene and early gene expression, dysregulation of host cell functions, and cell cycle progression leading ultimately to noninflammatory apoptosis, such as that observed at cardiac biopsy.<sup>15</sup> This proposed CFS process produces no viral DNA, no viral antigenemia, and no virion maturation.<sup>40</sup> The CFS patient cannot successfully achieve herpesvirus latency. Valacyclovir (EBV) and valganciclovir (HCMV, HHV6) inhibit viral DNA polymerases. The long duration

of antiviral therapy responds to the ongoing opposing forces, ie, virus induction-infected cellular destruction versus cellular survival by an effective immune response. We continue valacyclovir/valganciclovir until the EIPS is  $\geq 7$ . If no further antiviral therapy is necessary, the CFS patient now independently maintains herpesvirus latency. The biologic parameters to be followed in this ongoing process are critical in our diagnostic panel and are described fully under Methods. These are EBV VCA, IgM (returns to negative), EBV, EA-D (decreases and returns to negative), HCMV IgM p52 and IgM CM<sub>2</sub> (return to normal), and HM abnormalities (eg, T-waves normalize and tachycardias disappear). This thesis predicts that mRNA to intermediate-early herpesvirus genes is circulating in mononuclear cells in the blood of CFS patients, but this mRNA is not present in healthy subjects.

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