

Valacyclovir Treatment in Epstein-Barr Virus Subset Chronic Fatigue Syndrome: Thirty-six Months Follow-up*

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Abstract. *Background:* We hypothesized that subset classification of Epstein-Barr virus (EBV) in chronic fatigue syndrome (CFS) is required. At first, a blinded-random placebo-controlled trial of valacyclovir in EBV CFS subset was performed (Group 1), and this EBV subset was followed for thirty-six months (Group 2). Patients were given valacyclovir at 14.3 mg/kg every 6 hours. The validated Energy Index (EI) point score assessing physical functional capacity, Holter monitor, multigated (radionuclide) MUGA rest/stress ventriculographic examination, EBV serum IgM viral capsid antibodies (VCA), and EBV early antigen diffuse (EA) were followed. After six-months, Group 1 CFS patients receiving valacyclovir experienced an increased mean least square EI point score +1.12 units (122 kcal/day), while the placebo cohort increased +0.42 EI units (65 kcal/day). EI point scores at Group 2 increased progressively. Sinus tachycardias decreased and abnormal cardiac wall motion improved. Serum antibody titers to EBV VCA IgM decreased. Patients resumed normal activities.

The cause of chronic fatigue syndrome (CFS) is unknown (1-3).

Epstein-Barr virus (EBV), cytomegalovirus (HCMV) and Human Herpesviruses, type 6 (HHV-6) establish "latent" infection in B-lymphocytes, monocyte-macrophage precursors,

or T-lymphocytes respectively (4). Virus reactivation and both abortive and complete virus multiplication occur. CFS subsets, (Group 1) EBV ($p < 0.001$) (5-6), and (Group 2) HCMV ($p < 0.05$) (7), and HHV-6 (5, 8) have been described with continuing primary or reactivated infection.

The physical activity of CDC-defined (9) CFS patients is measured here by < 5 validated Energy Index (EI) point score units per day. In a pilot study, 19 EBV CFS subset patients (no HCMV serum antibodies) improved after six months of valacyclovir, but nine CFS patients with EBV-HCMV subset co-infection did not improve. The initial mean EI of patients with EBV single virus, no HCMV serum antibodies, was 4.1 EI units/day (1960 kcal), and that of CFS patients with EBV-HCMV subset (EBV active infection and positive serum IgG antibody titer to HCMV viral capsid antigen) was also 4.1 units/day. After six months of valacyclovir, EBV CFS subset cohort improved a mean 2.9 EI units/day to an EI point score of 7 units/day, 2205 kcal/day, while the EBV-HCMV CFS subset cohort improved only 0.5 units/day to an EI of 4.6 EI units/day, 1967 kcal/day (10). Therefore, there are at least three CFS groups: an EBV subset, an HCMV subset, and an EBV-HCMV co-infection subset.

Acyclovir has limited gastrointestinal absorption. Valacyclovir (11, 12) and famciclovir (13-16), are well absorbed from the gastrointestinal tract. Valacyclovir is a valine derivative of acyclovir which inhibits EBV thymidine kinase and is absorbed efficiently from the gastrointestinal tract as acyclovir. Valacyclovir achieves serum acyclovir anti-EBV concentrations, and inhibits formation of EBV viral capsid antigen, but does not inhibit formation of early gene products of EBV early antigen (D) complex. The 50% inhibitory concentration (IC_{50}) of acyclovir versus EBV is 4.4-13.3 $\mu\text{m}/\text{mL}$ ($\mu\text{m}/\text{ml}$ acyclovir divided by 4 equals $\mu\text{g}/\text{mL}$) (15-17). Valacyclovir in 1 g doses to a 70 kg patient reaches peak levels of 22-38 $\mu\text{g}/\text{ml}$ (10). Famciclovir, an acyclic guanine, pro-drug, is equally effective versus EBV *in vitro*, is

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Table I. Physical assessment of Energy Index (EI) point score and Stanford heart disease prevention program for CFS and its graded recovery.

EI point score [†]	Stanford Heart Disease Prevention Program (kcal/day) [†]	Activity end-points
0 CFS	1715	Bedridden, up to bathroom only
1 CFS	1750	Out of bed sitting, 30-60 minutes/day
2 CFS	1785	Sitting, standing, walking 1-2 hours/day
3 CFS	1855	Out of bed sitting, standing, walking 2-4 hours/day
4 CFS	1925	Out of bed sitting, standing, walking 4-6 hours/day
5 CFS	1995	Perform with difficulty sedentary job 40 hours/week
6 Recovery	2083	Perform sedentary 40-hour work/week, has limited housekeeping/social activities, daily rests, lying supine up to one-hour necessary
7 Recovery	2205	Up 7 a.m. to 7 p.m., sedentary 40-hour work/week, plus light housekeeping. No supine rests (naps) necessary
8 Recovery	2240	Full work week, no naps, some social activities and light exercise.
9 Recovery	2450	All of above plus exercise 1/2 to 2/3 normal without excessive fatigue, awakens next morning refreshed.
10 Normal	>2500	Normal

This table appears in part (reproduced with permission) (Ref. 10). [†]kcal/day is calculated for a 70 kg CFS patient.

absorbed as well as penciclovir (18). Here, several patients developed valacyclovir diarrheas, and famciclovir was substituted. In group one, with a placebo-controlled 6-month trial, we test the benefit of valacyclovir in 27 EBV subset CFS patients. In group two, 27 similar EBV subset CFS patients received valacyclovir in an open 36-month trial. Seven CFS patients from Group 1 continued in Group 2.

Patients and Methods

Study design. The EI assesses physical activity of a CFS patient (US Copyright, 1999 Lerner, AM and Deeter RG) (10). Physical activity was also expressed by the methodology of the Stanford Heart Disease Prevention Program (19). With a standard question series, we determined the EI and calculated kcal/day every 30 days. Symptoms (syncope, muscle aches, chest ache, palpitations) were assessed. If patients had intercurrent infections, EI evaluations were delayed by two weeks (Table I).

Patients were 18 to 56 years old with a diagnosis of CFS by CDC criteria (9). Twenty-four hours ECG monitoring and symptoms were recorded (syncope, chest pain, palpitations, muscle aches). Patients had an EI ≤ 5 (1995 kcal/day for 70 kg patient), abnormal oscillating (flat or inverted) T-waves at Holter monitor (2, 20) and elevated EBV serum IgM antibodies (EBV viral capsid antigen (VCA) and/or EBV early antigen (EA, diffuse) (6). Infection with HCMV, rheumatic fever, Lyme disease, and Babesiosis were excluded by an absence of ELISA IgG and IgM serum antibodies to viral capsid, strain 169 HCMV, anti-streptolysin 0 titer <400 units, negative ELISA and Western blot (IgM and IgG) to *Borrelia burgdorferi* (IgM and IgG) (Lab Corp, Dublin, OH, USA). Serum assays for EBV, VCA IgM, EBV EA, HCMV(V) IgM and HCMV (V) IgG were repeated every 3 months. Erythrocyte sedimentation rate was not increased. EBV and HCMV antigens were prepared by Diasorin, Inc., Stillwater, MN. Patients had creatinine clearance >60

ml/min by Cockcroft and Gault equation (21). Patients received no other therapy for CFS, did not use alcohol and agreed not to become pregnant. This protocol was approved by the USFDA, and the Human Investigation Committee of William Beaumont Hospital. After possible toxicities of antiviral medicines were explained, informed consent was obtained from each patient. Patients were enrolled in Group 1, 2000-2003, and in Group 2, 1988-2004.

Group 1. CFS patients were otherwise healthy and taking no other medicines. Patients were randomized into one of two treatment arms and received in double blinded method: i) valacyclovir 1.0 g (14.3 mg/kg as 2x500 mg tablets) every 6 hours, or ii) placebo, two tablets every 6 hours with food. Patients were instructed to drink at least six, 8-ounce glasses of water daily to avoid valacyclovir-induced renal stones, and to avoid alcoholic beverages. Exercise was prohibited until the EI point score was >7.0 units/day, when exercise was encouraged, as tolerated without subsequent ill effect. Thirty-three patients were entered into Group 1: five patients did not complete the study and 27 patients completed Group 1; 27 patients comprised Group 2. Seven patients from Group 1 continued valacyclovir in the Group 2 protocol. Four continuing Group 1 patients received placebo.

Group 2. After three months of valacyclovir, if the EI point score had not improved, oral cimetidine (500 mg bid) or probenecid (500 mg bid) were added to valacyclovir (11). Cimetidine and probenecid inhibit excretion of acyclovir and, thus, potentiate antiviral concentrations of serum acyclovir. Three patients experienced valacyclovir-associated diarrheas. They then received famciclovir at 14.3 mg/kg every six hours. When EI reached 8 units/day (Table I), valacyclovir, or famciclovir frequency was decreased to every 12 hours. After one month, if the EI remained unchanged, or improved valacyclovir or famciclovir was discontinued. If the EI again decreased >1.5 units, antiviral therapy was continued at full dosage. When resting tachycardias

Table II. Demographics of EBV subset CFS receiving antiviral therapy.

	Group 1		Group 2	p-value
	Pilot, blinded, random control		Long-term open	
	Valacyclovir	Placebo	Valacyclovir/ Famvir	
Number of patients	14	13	27	0.33
Female	10 (71.4%)	12 (92.3%)	18 (67%)	0.33
Male	4 (28.6%)	1 (7.7%)	9 (33%)	
Age, years*	39.4±2.7	38.3±2.7	39.9±2.4	0.77
Weight, kg*	72.3±2.9	65.0±3.0	77.2±3.0	-
Body mass index kg/m ² *	24.5±0.6	23.2±1.1	26.4±0.9	0.3
Duration of CFS prior to study, years	3.0±0.7	3.1±0.9	3.4±0.4	0.93
Duration of follow-up months	6	6	36	-
Current valacyclovir, famvir, patients	-	-	20 (<i>p</i> =0.74)	

*Standard error of mean.

(group 1 or group 2) were present, atenolol (12.5-50 mg q24 hours) was given orally to control tachycardia. Holter monitors were repeated one week after beginning atenolol to be certain that resting tachycardia was improved. When tachycardia was no longer present and the EI reached 7, atenolol was tapered and stopped.

Measurement. The EI measures the CFS patient physical ability in activities of daily life documenting limitations (Table I) (10). Complete history, physical examination, chest X-ray, electrocardiogram, complete blood count, urinalysis, serum aspartate and aminotransferases (AST, ALT), glucose, thyroid stimulating hormone, sodium, potassium, uric acid and creatinine measurements were performed. Physical examinations and physical activity assessments were carried out at baseline and every 4-6 weeks by the Functional Activity Appraisal [EI score, Health Care Worker Assessment, 14 standard questions, US copyright 1999, Lerner, AM, Deeter RJ (Table I)]. At entry and at 6 months (Group 1), standard 12-lead resting electrocardiogram, 2-D echocardiogram, 24-hour Holter monitor, rest/stress myocardial perfusion study (thallium 201 or Tc-99 sestamibi) and multigated (radionuclide) MUGA rest/stress ventriculographic examinations were carried out (22, 23). Repetitive T-wave flattenings accompany CFS. The absence of abnormal T-waves makes diagnosis of CFS unlikely (statistical sensitivity, 0.96). The combination (*e.g.* the presence of both oscillating T-wave flattenings plus T-wave inversions) is a usual finding in CFS. Right ventricular endomyocardial biopsies in CFS patients show cardiomyopathy (20, 22, 23).

Table III. Serum EBV antibody titers.

	Group 1		Group 2/ Antiviral therapy
	EBV VCA IgM, mean of positive titers*		
	Valacyclovir	Placebo	
Baseline	41 (4/14 pts)	110 (3/13 pts)	31 (8 pts)
Three months	25 (3/14 pts)	108 (3/13 pts)	27 (8 pts)
Six months	26 (3/14 pts)	88 (3/13 pts)	23 (7 pts)
Twelve months	-	-	22 (8 pts)
EBV, EA (diffuse), mean positive titer*			
EBV VCA IgM – negative cohorts			
Baseline	68 (14 pts)	40 (13 pts)	60 (19 pts)
Three months	110 (14 pts)	61 (13 pts)	66 (17 pts)
Six months	65 (13/14 pts)	66 (13 pts)	60 (18 pts)
Twelve months	-	-	60 (16 pts)
Eighteen months	-	-	60 (16 pts)
Twenty-four months	-	-	62 (13 pts)
Thirty months	-	-	61 (12 pts)
Thirty-six months	-	-	59 (9 pts)

* Values >20 are positive.

Toxicity adverse effects were recorded. Complete blood counts, sodium, potassium, AST, ALT, alkaline phosphatase, creatinine and urinalysis were made every 4-6 weeks.

Statistical analyses. Multivariate analysis of variance for repeated measures was used to examine differences between the placebo and valacyclovir groups in this Phase 1 trial.

Results

Demographics. Demographics of the 54 CFS patients of the study are shown in Table II. They are mainly women (70%), approximately 39 years old who had been suffering from CFS for 3-3.4 years. There are no differences between Group 1 and Group 2 characteristics [gender (*p*=0.33), age (*p*=0.77), BMI (*p*=0.30) or duration of CFS at baseline (*p*=0.93)].

Epstein-Barr virus serum antibody titers. Seven patients (Group 1) and eight patients (Group 2) had elevated EBV VCA IgM serum antibody titers indicating active EBV virus multiplication (Table III) (6, 10, 23). Mean EBV VCA IgM serum titers decreased (Group 1, from 41 to 26, negative, <20; Group 2, 31 to 22, negative, <20). The EBV VCA IgM serum antibody titers decreased less in group 1 placebo-cohort, *e.g.* mean titer baseline 110U, six months 88U (negative, <20) (Table III). Twenty patients (group 1) and 19 patients (group 2) had negative EBV VCA IgM serum antibody titers at baseline, but had positive EBV EA

Table IV. Qualitative analysis of resting heart rate variability and abnormal T-wave repolarizations before and after antiviral treatment (Group 2).

Category	Baseline	Post-antiviral treatment (≥6 months)
A) Cardiac rate/minute		
1) ≥100	53.6% (25)†	34.4% (14)*
2) ≥110	32.1% (25)*	13.1% (14)*
3) ≥120	20% (25)*	7% (14)*
B) Isoelectric T-waves		
1) With cardiac rate/mm <100	77.8% (21 of 27 pts)*	85.7% (18 of 21 pts)
2) With cardiac rate/mm >100	96% (24 of 25 pts)	83.3% (15 of 18 pts)
3) > 25% all cardiac contractions	66.7% (18 of 27 pts)	45% (9 of 20 pts)
C) T-wave inversions		
1) With cardiac rate <100/min	44.4% (12 of 27 pts)	30% (6 of 20 pts)
2) With cardiac rate >100/min	50% (13 of 26 pts)	35% (7 of 20 pts)
3) >25% "all"	18.5% (5 of 27 pts)	0% (none of 20 pts)
D) Deep ischemic T-waves	11% (13 of 27 pts)	0% (none of 20 pts)

*This percentage is the number of hours/24 hours with category listed. †Number in parentheses is the number of patients in this group.

serum antibody titers. With valacyclovir therapy serum EBV EA antibody titers did not significantly change. Valacyclovir inhibits formation of EBV late gene product, viral capsid antigen, but does not inhibit formation of at least 12 "early" polymeric nonstructural gene products of EA (24, 25). Serum HCMV serum antibody titers remained negative in all patients.

Cardiac studies. Standard 12-lead resting ECGs, 2-D echocardiograms and myocardial perfusion studies were normal (1) except when abnormal cardiac wall motion (ACWN) at MUGA study was present (22, 23). When ACWM was present at MUGA, T-wave flattenings in standard precordial leads V3-V6 were present. Twenty-four-hour-Holter monitors showed abnormal oscillating T-wave flattenings and/or inversions initially in all patients (2, 20). Continuing tachycardias at rest, sometimes severe with cardiac rates 110-120/minute, were frequent, occurring in 53.6% of the h/day (Table IV). In 20% of CFS patients in group 2 (baseline), heart rates were ≥120/min at rest. Abnormal flat or inverted T-waves increased in frequency with the presence and severity of tachycardias.

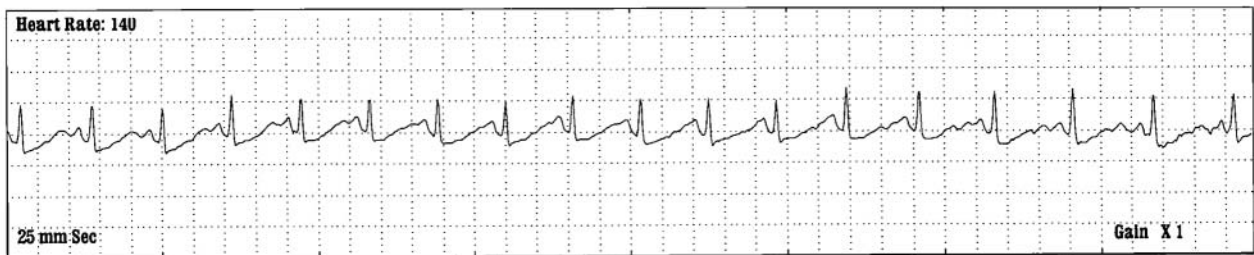
Abnormal flat T-waves were present in 66.7% of CFS patients of group 2 in >25% of the total 24-h cardiac contractions (Table IV). Myocardial perfusion studies were normal excluding coronary artery disease. Deep ischemic "appearing" T-waves were present in 13 of the 27 patients in group 2. These striking T-waves in a 45-year-old woman at baseline and 6 months later after valacyclovir show their evident disappearance (Figure 1).

Rest/stress radionuclide (Tc-99 sodium pertechnetate) ventriculograms were carried out at baseline and after at least six months of antiviral therapy. In group 1, studies were normal except for one valacyclovir-receiving, 20-year-old female college student whose ejection fraction (EF) was 74% (stress, 400 kiloponimeters), falling to 68% with stress (600 kiloponimeters) and, with stress, there was left ventricular dilatation. This decreased EF with stress and cardiac dilatation was not present six months later. Abnormal cardiac wall motion was also present in three patients from group 2. Two of these latter three patients at repeat MUGA testing had normal cardiac wall motion (22, 23).

Assessment of physical activity (Figure 2). Energy Index point scores kcal/day increased +1.12 units (122 kcal/day) at six months in group 1, valacyclovir cohort, but increased 0.42 units, 65 kcal/day for the placebo cohort. In the thirty-six-month open trial (group 2), EI units increased 1.6 EI units/day (+166 kcal/day) at 6 months; 2.6 EI units/day (+187 kcal/day) at 1 year; 3.0 EI units (+307 kcal/day) at 2 years; 3.2 EI units (+159 kcal/day) at 3 years. The sustained increase in physical activity of CFS is unique. To our knowledge this has not previously been reported. Symptoms (syncope, chest pain, palpitations, muscle aches) decreased or disappeared with increasing EI scores.

Toxicity. There was no significant toxicity. Three patients were given famciclovir because of valacyclovir-induced diarrheas. Serum creatinines remained negative, and no patient experienced acyclovir renal calculi. After receiving valacyclovir for a mean of 5.9 months, 67% of patients

T-wave Configurations in EBV-Subset of CFS



I Sinus tachycardia at rest with isoelectric T-waves in a 34-year-old female (#26)



IV Normal sinus rhythm with inverted T-waves and deep inverted T-waves in a 36-year-old female (#5)

Figure 1. Patient #26, a 34-year-old female (upper row) with a sinus tachycardia of 140/min at rest associated with syncope. T-waves are flat. In patient #5, a 36-year-old female (lower row), at a heart rate of 93/min T-waves are inverted, to suddenly become more deeply inverted.

showed an increased mean corpuscular volume ≥ 97 fl. There was no anemia or thrombocytopenia.

Discussion

Epstein-Barr virus subset CFS patients in groups 1 and 2 improved remarkably and maintained their well-being, no longer meeting criteria for CFS. These data confirm our earlier hypothesis (5) and report (10). Seven CFS patients from group 1 continued in group 2, and each patient achieved EI point scores of ≥ 7 (Tables I, V). The EI unit physical activity assessment is a primary end-point: (i) placebo-group at six months +0.42 (+66 kcal/day), (ii) valacyclovir group at six months +1.12 (+122 kcal/day), (iii) valacyclovir group at thirty-six months +3.2 (+159 kcal/day). Secondary end-points are: a) decreased serum IgM antibody titer to viral capsid antigen of EBV; b) improved or disappearance of abnormal cardiac wall motion; c) decreased resting tachycardias; and d) decrease/absence of symptoms, palpitations, muscle aches, chest pain, syncope, tender lymph nodes, sore throat, fever *etc*. The data indicate sustained improvement of EBV subset CFS patients with valacyclovir as outlined here.

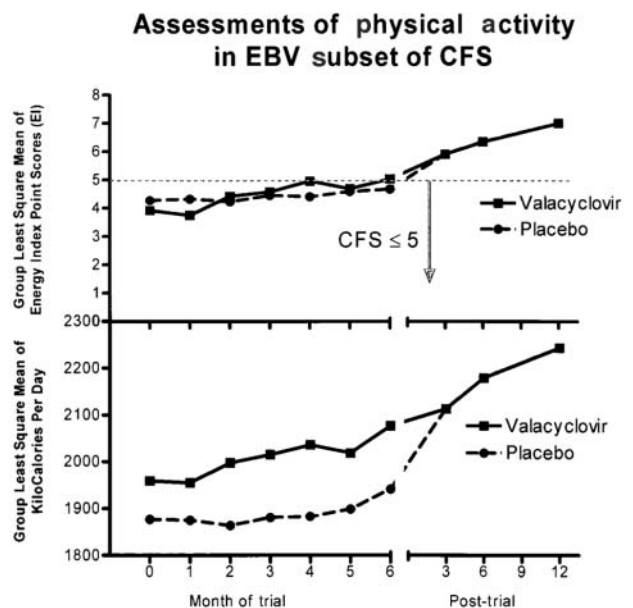


Figure 2. Assessment of physical activity with long-term antiviral therapy (Group 2). These 27 patients had EBV-subset CFS for a mean of three years prior to entering this study. Long-term recovery is evident.

Table V. Assessment of physical activity in EBV subset CFS receiving antiviral therapy.

Month of study	Group I		Month of study	Group II	
	Valacyclovir*	Placebo**		Long-term open Valacyclovir/Famvir***	
	Energy Index point score* kcal/day			Energy Index point score kcal/day	
Baseline	3.92 Φ (1955) Φ	4.27 Φ (1877) Φ	Baseline	4.4 \pm 0.18 ⁺ (2164 \pm 83)	
1	3.75 (1955)	4.32 (1875)	3	5.3 \pm 0.22 (2266 \pm 94)	
2	4.42 (1998)	4.23 (1864)	6	6.2 \pm 0.26 (2330 \pm 92)	
3	4.58 (2015)	4.45 (1881)	9	6.9 \pm 0.18 (2355 \pm 96)	
4	4.96 (2036)	4.41 (1883)	12	7.0 \pm 0.16 (2351 \pm 93)	
5	4.69 (2019)	4.59 (1899)	15	7.1 \pm 0.20 (2383 \pm 107)	
6	5.04 (2077)	4.68 (1942)	18	7.1 \pm 0.24 (2342 \pm 102)	
			21	7.5 \pm 0.16 (2334 \pm 102)	
			24	7.4 \pm 0.20 (2471 \pm 134)	
			27	7.5 \pm 0.14 (2471 \pm 145)	
			30	7.7 \pm 0.19 (2408 \pm 133)	
			33	7.5 \pm 0.17 (2295 \pm 182)	
			36	7.6 \pm 0.24 (2323 \pm 206)	
Change	+1.12 (+122)	+0.42 (+65)		+3.2	+159

Φ Mean of least squares; ⁺Standard error of the mean; *12 patients in group; **11 patients in group; ***27 patients in group.

These data indicate that (i) subset classification of CFS patients is necessary for evaluation of any therapeutic modality. The multiple subsets of CFS and possible co-infections make appropriate subset diagnosis critical before any treatment is begun. Furthermore, (ii) 6-12 months of antiviral therapy (with pacing of patient physical activities and avoidance of alcoholic beverages) is necessary for recovery. Finally, (iii) as with HCMV subset CFS patients with IgM serum antibodies to HCMV mid-gene nonstructural products (HCMV IgM, p52 and CM₂), abortive herpes virus infection is a prominent mechanism of the herpesvirus infection in CFS patients. For the EBV subset patient with negative VCA IgM serum antibody titers, and positive serum EBV, EA(D) antibody titers, these CFS patients are producing EBV gene products parallel to the mid-sequence to HCMV, p52 and CM₂ gene products. Such EBV assays are not yet commercially available. The EBV, EA(D) positive healthy patient, we postulate, is producing "early" EBV gene-products, but "not" mid or late gene products of the abortive infection we postulate to be critical in CFS patients. The results in this 54 patient study support the thesis that herpesvirus latency is not achieved in CFS patients. These data may qualify as a premature discovery according to the definitions of Kuhn, Stent and Hook (26-28).

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