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Herpes simplex virus 1 infection and valacyclovir treatment in schizophrenia: Results from the VISTA study

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ABSTRACT

Background: Several studies have implicated herpes simplex virus-type 1 (HSV-1) in the pathophysiology of schizophrenia. A recent trial demonstrated that the anti-viral medication valacylovir, which prevents replication of activated HSV-1, improved selected cognitive deficits in people with schizophrenia. In this study, we examined demographic and illness related differences between HSV-1 positive versus HSV-1 negative subjects with early phase schizophrenia and attempted to replicate the previous valacyclovir treatment results in this population.
Methods: 170 subjects with schizophrenia (HSV-1 positive N = 70; HSV-1 negative N = 96) from 12 US sites participated in the HSV-1 positive versus negative comparisons, and were randomized 1:1 to valacyclovir (1.5 g BID) or placebo for a 16-week, double-blind efficacy trial. The primary endpoints were working and verbal memory.
Results: The HSV-1 positive group, as compared to the HSV-1 negative group, were older ($p < 0.001$) with fewer males ($p = 0.003$), and had a longer duration of illness ($p = 0.008$), more positive symptoms ($p = 0.013$), poorer quality of life ($p = 0.034$) and more impairment on the letter-number sequencing test, which is a measure of working memory ($p = 0.045$). Valacyclovir failed to significantly improve any of the cognitive indices, symptom or functioning measures.
Conclusions: HSV-1 sero-positivity appears to be a marker of a subgroup with a more severe form of schizophrenia. Valacyclovir was not efficacious in the study, perhaps because the herpes virus was in the dormant, non-activated state and therefore non-responsive to valacyclovir effects.
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1. Introduction

The viral hypothesis of schizophrenia posits that infection by neurotrophic viruses, either in utero through maternal transmission or exposure later in life, results in persistent low level neuro-inflammation leading to cortical circuit damage and the symptoms and cognitive impairments of this illness (Bechter, 2013; Brown, 2011; Ellman et al.,

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2010). A faulty immune system is proposed to account for the aberrant inflammatory response (Bechter, 2013). Numerous studies have provide evidence of immunological abnormalities in schizophrenia (Drago et al., 2014; Laskaris et al., 2016; Muller et al., 2015; Potvin et al., 2008; Watkins and Andrews, 2016), including whole genome wide analyses that identified genes in the MHC region (Sekar, et al., 2016). Several viruses have been associated with the pathophysiology of schizophrenia with a growing number of studies suggesting that the herpes simplex virus 1 (HSV-1) may be particularly relevant to cortical circuit damage and cognitive impairment.

Herpes viruses are enveloped viruses with double stranded DNA genome (Steiner et al., 2007). The "family" of herpes viruses includes HSV-1, HSV-2, HSV-6, HSV-7, HSV-8, cytomegalovirus (CMV), Epstein-Barr (EBV) and varicella zoster (VZV). Recent evidence has convincingly implicated HSV-1 (Harris and Harris, 2018), HSV-6 and HSV-7 (Eimer et al., 2018; Readhead et al., 2018) in the pathogenesis of Alzheimer's disease. Approximately, 40% to 60% of the general population (Bradley et al., 2014) and individuals with schizophrenia (Prasad et al., 2013; Shirts et al., 2008; Yolken et al., 2011) test positive for exposure to HSV-1 infection. HSV-1 is primarily transmitted person to person through oral and nasal secretions during coughing and close facial contact. Most individuals have no or mild symptoms of HSV-1 infection and may be unaware they have been infected. The classical clinical manifestations of activated HSV-1 infection are ulcerative lesions known as "cold sores". However, serious consequences of HSV-1 infection may also occur (Steiner et al., 2007; Whitley and Lakeman, 1995). HSV-1 is the most common causes of sporadic encephalitis (Bradshaw and Venkatesan, 2016) with significant morbidity including psychosis and cognitive impairment, and mortality (Schlitt et al., 1985; Steiner et al., 2007; Whitley and Lakeman, 1995).

HSV-1 viruses penetrate mucosal membranes and reside in the trigeminal and olfactory ganglia located inside the blood-brain barrier (Jennische et al., 2015; Mori et al., 2005; Shukla et al., 2012; Spivack and Fraser, 1988). There, they follow cycles of dormancy and activation throughout the life span of infected individuals (Steiner et al., 2007). When activated, viral replication occurs and HSV-1 gains access to the brain through retrograde transport via trigeminal and olfactory nerves to frontal and temporal lobes (Jennische et al., 2015; Mori et al., 2005; Shukla et al., 2012), and then may spread to other brain regions including the contralateral lobes through the anterior commissure (Jennische et al., 2015). Post mortem studies have shown significant correlations between levels of HSV-1 transcripts in trigeminal ganglia and blood levels of HSV-1 antibodies (Lapaglia et al., 2018), as well as HSV-1 particles in fronto-temporal brain regions in non-encephalitic individuals. HSV-1 infections trigger a response from both the innate and adaptive immune systems. Repeated inflammatory responses, particularly through recruitment of activated leukocytes, may cause brain tissue damage and related neurological and psychiatric sequelae (Lundberg et al., 2008; Marques et al., 2008).

There is compelling evidence to implicate HSV-1 infection in the pathophysiology of schizophrenia. Dickerson et al. reported a significant relationship between HSV-1 seropositive status and cognitive impairment in schizophrenia (F. B. Dickerson et al., 2003). In that study, other neuro-viruses, including HSV-2, HSV-6, CMV, EBV and VZV, were not associated with cognitive impairment, which suggests specificity for HSV-1 infection. Similarly, Yolken et al. (Yolken et al., 2011) reported a significant relationship between cognitive impairment and seropositive HSV-1 status, but not with HSV-2, CMV, or *Toxoplasma gondii* exposures, in a large sample from the CATIE study. Numerous additional studies have convincingly confirmed the link between HSV-1 exposure and cognitive impairment in schizophrenia (F. Dickerson et al., 2008; Dickerson et al., 2003; Prasad et al., 2012; Schretlen et al., 2010; Shirts et al., 2008; Thomas et al., 2013; Watson et al., 2013). Although several cognitive domains were linked to HSV-1 infection suggesting widespread cortical effects (Prasad et al., 2012; Thomas et al., 2013), working memory and executive function impairment were among the most commonly reported (Dickerson et al., 2003; Schretlen et al., 2010; Shirts et al., 2008; Thomas et al., 2013; Watson et al., 2013; Yolken et al., 2011). Also, HSV-1 exposure has been linked to negative symptoms in schizophrenia (Bolu et al., 2016). HSV-1 infection has also been associated with cognitive impairment in bipolar disorder (Dickerson et al., 2004) and in elderly populations (Nimgaonkar et al., 2016; Strandberg et al., 2003; Tarter et al., 2014).

Structural and functional brain changes are associated with HSV-1 infections in schizophrenia. In three studies of early phase schizophrenia, HSV-1 infection was associated with fronto-temporal volume reductions (Pandurangi et al., 1994; Prasad et al., 2007; Schretlen et al., 2010). In addition, HSV-1 exposure was associated with progressive decrements in gray matter volume and related decline in working memory in early phase schizophrenia (Prasad et al., 2011). Whitford TJ and associates found reductions in gray matter volumes in the cuneus in HSV-1 positive ultra-high risk individuals compared to HSV-1 negative ultra-high risk individuals and healthy controls (Whitford et al., 2012). In an fMRI study, HSV-1 exposure was related to altered blood oxygen level dependent (BOLD) signal responses during a working memory task (D'Aiuto et al., 2015). Furthermore, HSV-1 infection induced lytic changes in iPSC-derived glutamatergic neurons and neuroprogenitor cells (D'Aiuto et al., 2015). Taken together, these studies strongly support a link between HSV-1 infection and cognitive impairment and related brain changes and suggests the possibility that the presence of HSV-1 infection may identify a subgroup of people with schizophrenia with neuro-immune based etiopathophysiology.

The above data makes a strong case for the consideration of antiviral medication trials in schizophrenia. Valacyclovir is a highly effective and relatively safe treatment for HSV-1 infection (Acosta and Fletcher, 1997; Alrabiah and Sacks, 1996). It is rapidly metabolized to acyclovir which is a nucleic acid homolog that is incorporated into DNA in place of guanosine in its phosphorylated form, but is only phosphorylated in the presence of herpes viral thymidine kinase. This insertion blocks virus replication. Consequently, valacyclovir is only effective during the activated stage of viral replication, not for dormant infections. Prasad and colleagues (Prasad et al., 2013) conducted a clinical trial of valacylovir focused on cognitive impairment in a small sample of individuals with schizophrenia ($N = 24$) who were HSV-1 seropositive. The sample was within 10 years of illness onset with a mean 3.5 years of illness. They reported that valacylovir, in comparison to placebo, was associated with improvement in visual learning, and working and verbal memory. Effects sizes were moderate to high. Given the small sample size, a replication study was warranted.

The purpose of this study was to: a) further characterize the clinical profile of HSV-1 positive versus HSV-1 negative individuals with schizophrenia; and b) attempt to replicate the valacyclovir treatment results of Prasad et al. (2012) with a larger sample and include both HSV-1 positive and negative randomized subjects. A HSV-1 negative cohort was included to reduce bias in subject selection, insure the study blind was maintained and to assess the possibility of off-target treatment effects. This study, hereafter referred to as the VISTA trial, was a multi-site US based clinical trial. Baseline data from the clinical trial was used to address the first aim. The clinical trial design mirrored many features of the Prasad trial including similar valacylovir dose (1.5 g BID), treatment duration (16 weeks at full dose), duration since psychosis onset (Prasad 10 years; VISTA 8 years), intent to treat data analytic plan and primary cognitive endpoints of working and visuospatial memory. An upper age of 40 years, illness duration of no >8 years and clinical stability requirements were inclusion criteria aimed at recruiting a cohort that was not subject to the confounding effects of chronic illness.

2. Experimental/materials and methods

2.1. Investigative sites

The VISTA study was conducted at 12 US sites with extensive clinical trial experience with subjects with early phase psychosis. Indiana University School of Medicine (IUSM) was the coordinating center and responsible for study oversight, rater training and ongoing reliability, and data processing.

2.2. Subjects

Subjects were consented with the "teach back" method to an IRB approved protocol. Subjects were serotyped as HSV-1 positive or HSV-1 negative during screening and all subjects who met inclusion/exclusion criteria were randomized 1:1 to valacyclovir (1.5 g, BID) or placebo.

2.3. Inclusion/exclusion criteria

Subjects were between 18 and 40 years of age, male or female and had a DSM IV-TR Diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder. The Structured Clinical Interview for DSM-IV-TR (SCID-I/P Patient Edition) (First, MB 2002) was used to confirm the diagnosis of each psychotic disorder and/or rule out other diagnoses. The SCID-IP is a semi-structured interview designed to evaluate DSM-IV-TR Axis I diagnoses.

Onset of these disorders was within 8 years, which was confirmed with medical records and subject and family interviews. Subjects met the following clinical stability criteria: Clinical Global Impression – Severity scale (CGI-S) (Guy, 1976) score of 4 or less at randomization; absence of an illness exacerbation within 4 weeks of randomization which required intensification of psychiatric care; and no changes in antipsychotic medications 4 weeks prior to randomization.

Exclusion criteria included: DSM-IV-TR diagnosis of substance dependence within 3 months of study entry (with the exception of nicotine or caffeine dependence); high risk for suicidal acts; any serious active medical condition that affects brain or cognitive functioning (e.g. epilepsy, serious head injury, brain tumor or other neurological disorders); IQ < 70 as determined by medical history; and current acute, serious, or unstable medical conditions.

2.4. Serological testing

Serological assessment of HSV-1 antibodies to group subjects into HSV-1 positive and negative categories was conducted at Mayo Clinic Mayo Medical Laboratories during the screening phase; HSV-1 status was also used to stratify randomization. The Bio-Rad BioPLex HSV assay that detects the presence of IgG-class antibodies to HSV-1 was used. This assay was validated with a comparison to the HerpesSelect HSV-1 EIA with sensitivity of 99.2% and specificity of 96.8%. Sites were blinded to the HSV status of their subjects. In addition, secondary analyses were conducted with individual HSV-1 antibody levels that were determined in the Stanley Neurovirology Laboratory, Johns Hopkins University using an assay that has been previously described (Yolken et al., 2011).

2.5. Assessments

Measurement and Treatment Research to Improve Cognition in Psychosis (MATRICS) Consensus Cognitive Battery (MCCB) (Kern et al., 2008; Nuechterlein et al., 2008) was used to assess cognitive function. Each of the individual test raw scores is standardized to age- and gender corrected t-scores (mean = 50, standard deviation = 10). The visual and working memory components of the MCCB were administered first because they represented the primary aims of the study. The MCCB was completed by (a minimum of) master's level trained clinical raters, who underwent an extensive training and certification process, and who also were re-certified annually to ensure reliability of MATRICS administration across sites. Negative Symptom Assessment Scale – 16-item (NSA-16) was used to assess negative symptoms (Alphs et al., 1989). The Positive and Negative Syndrome Scale (PANSS) was used for general symptoms assessment (Kay et al., 1987). CGI-S was used to assess illness severity. Functioning and quality of life were assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) (Endicott et al., 1993), Personal and Social Performance Scale (PSP) (Morosini et al., 2000), UCSD Performance-Based Skills Assessment-B (UPSA-B) (Mausbach et al., 2013).

2.6. Study medication

Valacyclovir hydrochloride and matching placebo capsules were used as the study medication for this study. Placebo capsules were matched on shape, taste and color to the valacyclovir capsules. Subjects who met all criteria for enrollment were 1:1 randomized in a double-blind fashion to adjunctive treatment with valacyclovir or placebo. Assignment to treatment groups was determined by a computer-generated random sequence provided to sites by the biostatistics team at the IUSM. To minimize potential imbalance among treatment groups of factors that may influence efficacy outcomes, a stratified random assignment of subjects to therapy was used to insure equal representation of HSV-1 positive and negative subjects in the valacyclovir and placebo arms. The stratification factors used for this study also included the investigative site. Study medications were sent to the study sites at regular intervals from the University of Iowa, which was contracted by the IUSM for preparation and shipping study medication for this study. The dosing used in this study was 3 capsules of either valacyclovir or placebo by mouth twice per day, given without regard to meals. Each valacyclovir capsule contained 500 mg of active ingredient for a total daily dose of 3 g per day.

2.7. Statistical analysis

The effect sizes observed in the completed Prasad et al. (2013) study were used to estimate the sample size necessary for adequate power to detect differences in cognitive variables for this clinical trial. The earlier study, which enrolled 12 patients in each group, saw changes in cognitive function with effect sizes on some tests that ranged from small (d = 0.25) to quite large (d = 1.21). Prasad reported effect sizes of Cohen's d = 0.79 for working memory and d = 0.97 for visual object learning on the Penn Computerized Neurocognitive Battery when comparing valacyclovir to placebo in HSV-1 seropositive subjects. With 70 HSV-1 positive subjects enrolled (35 per treatment group), we would be able to detect a minimum effect size of d = 0.63 (a conservative estimate based on the Prasad study) for each of the two primary outcome measures at significance level alpha = 0.05 using two-sided *t*-tests.

An intent-to-treat (ITT) analysis was adopted, which includes all randomized subjects. We used two cognitive domains from the MATRICS battery: the working memory composite score and visual memory score as the primary clinical trial outcome variables. The cognitive and functioning measures were assessed at baseline, week 8 and 16; symptom measures were assessed at baseline, week 4, week 8, week 12 and week 16. To analyze these measures, we employed a mixed model for repeated measures analysis of covariance (ANCOVA), of the general form for each measure: score at visit i = treatment + visit + HSV-1 status + interactions among treatment, visit, and HSV-1 status + other baseline covariates, where visit is a categorical measure. Within-subject correlations were modeled with the random intercept. In this model, interactions involving treatment, HSV-1 and visit estimate how the magnitude of treatment differences in the change score from baseline, on average at week 8 versus 16, was altered by HSV-1 status. The 3-way interactions were tested and F test statistics

along with p-values were presented. The change score contrasts, baseline value – post-baseline values, for valacyclovir and placebo were analyzed with t-tests. All missing scores were imputed by the predicted values from model: for each outcome, we fit a repeated measures ANCOVA model mentioned above and that model was applied to the observations with missing data, which generated a predicted outcome that was used in place of the missing observations.

Baseline analyses were conducted to summarize subject characteristics for four groups: HSV-1 positive valacyclovir and placebo groups, and HSV-1 negative valacyclovir and placebo groups. Demographics and relevant baseline clinical variables, including cognition scores and symptom severity, were compared between groups using two-sample *t*-tests and one-way ANOVAs (for continuous variables) and chi-square tests (for categorical variables).

3. Results

As shown in Fig. 1, 170 subjects were randomized in the study: a total of 74 were HSV-1 positive and 96 were HSV-1 negative. As displayed in Table 1, The HSV-1 positive group, as compared to the HSV-1 negative group, were significantly: older ($p < 0.001$), had a longer durations of illness ($p = 0.009$), fewer males ($p = 0.003$), more impairment on the letter-number sequencing test (a measure of working memory; $p = 0.046$), more positive symptoms ($p = 0.016$) and poorer quality of life ($p = 0.035$).

Table 2 contains baseline characteristics for HSV-1 status and treatment assignment (valacyclovir and placebo). Consistent with the HSV-1 sero-status data above, the groups differed on age, gender, working memory scores, positive symptoms and quality of life. Baseline age and gender were used as covariates in all outcome analyses.

Table 3 shows the treatment data for the MCCB working memory composite and visuospatial memory test scores (primary aims), and the two working memory test scores that compromise the composite, and the MCCB overall composite score. The HSV status x treatment x time interaction was significant for the working memory composite ($p = 0.032$), but change score analyses in the HSV-1 positive groups

Table 1
Baseline HSV1 positive versus HSV1 negative comparisons.

	HSV1(+) N = 74 Mean (SD)	HSV1(−) N = 96 Mean (SD)	P
Age (years)	30.0 (6.1)	26.4 (5.6)	<**0.001**
Duration of illness (years)	4.3 (2.5)	3.4 (2.0)	**0.009**
Lifetime antipsychotic log (gm)	428.1 (410.2)	3314.5 (18,272.0)	0.195
Gender, N (%)			
Female	28 (37.8%)	17 (17.7%)	**0.003**
Male	46 (62.2%)	79 (82.3%)	
Race, N (%)			
African American	43 (58.1%)	52 (54.2%)	0.290
Other	12 (16.2%)	10 (10.4%)	
White Caucasian	19 (25.7%)	34 (35.4%)	
Education, N (%)			
HS degree/GED	24 (32.4%)	37 (38.5%)	0.385
Some college	27 (36.5%)	38 (39.6%)	
Some HS	23 (31.1%)	21 (21.9%)	
Current employment, N (%)			
Employed (full and part time)	15 (20.3%)	26 (27.1%)	0.303
Unemployed	59 (79.7%)	70 (72.9%)	
MATRICS working memory	33.1 (10.1)	35.9 (13.1)	0.141
MATRICS brief visuospatial memory	35.4 (13.0)	35.6 (13.3)	0.950
MATRICS letter-number sequencing	35.1 (9.0)	38.3 (11.0)	**0.046**
MATRICS spatial span	37.0 (10.6)	38.3 (12.9)	0.501
MATRICS overall composite	28.4 (12.2)	30.0 (14.4)	0.466
PANSS total score	64.9 (16.7)	61.9 (15.3)	0.229
PANSS positive symptom factor (MARDER)	20.3 (6.3)	18.0 (6.0)	**0.016**
PANSS negative symptom factor (MARDER)	16.1 (6.3)	16.4 (6.5)	0.783
PANSS cognitive/disorganized factor (MARDER)	13.8 (4.1)	13.3 (4.0)	0.433
Q-LES-Q-SF total score	48.6 (11.0)	51.9 (8.8)	**0.035**
CGI-S	3.6 (0.6)	3.6 (0.8)	0.494
PSP adjusted score (1–99)	55.9 (12.9)	58.7 (12.5)	0.165
NSA-16 total score	43.1 (13.3)	44.0 (14.3)	0.690
UPSA-B total score	72.5 (15.0)	69.4 (16.8)	0.215

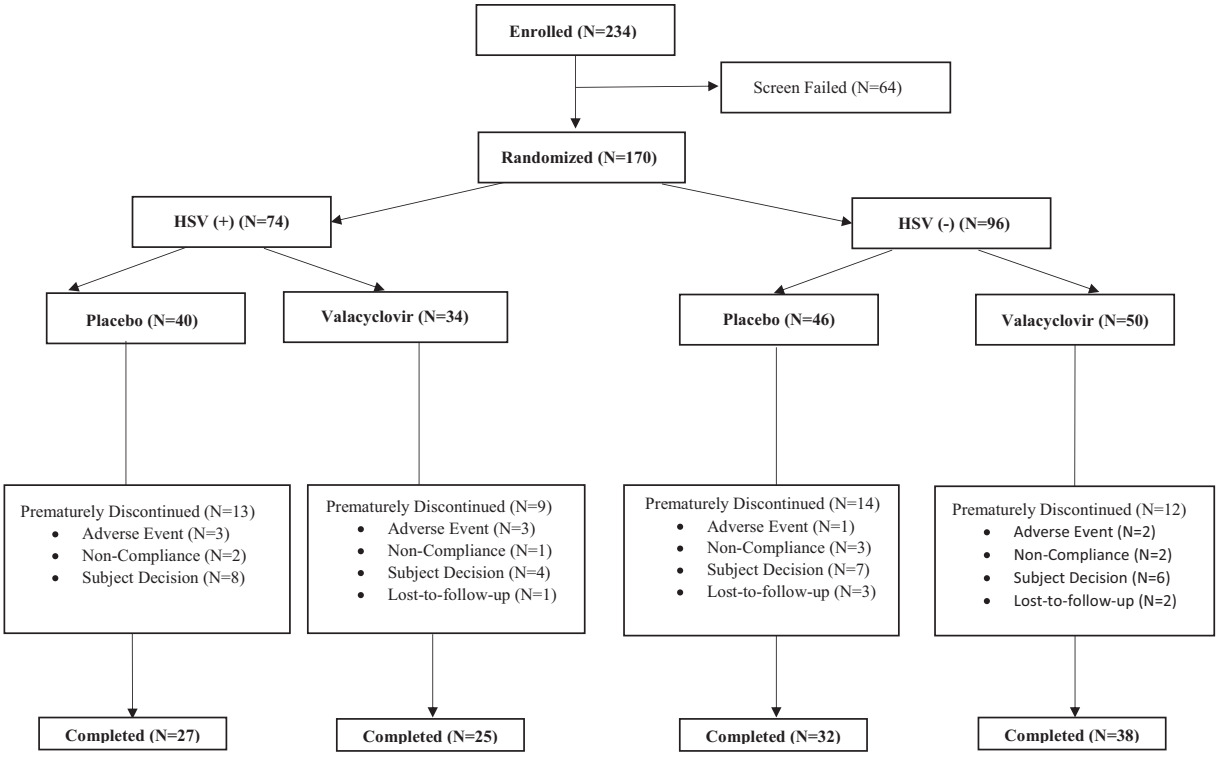

Fig. 1. CONSORT subject flow diagram.

Table 2
Baseline characteristics.

	VAL(+) N = 34 Mean (SD)	Placebo(+) N = 40 Mean (SD)	VAL(−) N = 50 Mean (SD)	Placebo(−) N = 46 Mean (SD)	P
Age (years)	29.9 (6.1)	30.0 (6.2)	27.4 (6.0)	25.4 (4.9)	<**0.001**
Duration of illness (years)	4.2 (2.7)	4.4 (2.3)	3.3 (1.9)	3.6 (2.1)	0.062
Lifetime antipsychotic log (gm)	305.9 (289.0)	536.6 (471.6)	601.1 (749.6)	6217.1 (26,119.7)	0.146
Gender, N (%)					
Female	14 (41.2%)	14 (35.0%)	12 (24.0%)	5 (10.9%)	**0.011**
Male	20 (58.8%)	26 (65.0%)	38 (76.0%)	41 (89.1%)	
Race, N (%)					
African American	23 (67.6%)	20 (50.0%)	29 (58.0%)	23 (50.0%)	0.446
Other	4 (11.8%)	8 (20.0%)	4 (8.0%)	6 (13.0%)	
White Caucasian	7 (20.6%)	12 (30.0%)	17 (34.0%)	17 (37.0%)	
Education, N (%)					
Some college	15 (44.1%)	12 (30.0%)	24 (48.0%)	14 (30.4%)	0.169
HS degree/GED	7 (20.6%)	17 (42.5%)	16 (32.0%)	21 (45.7%)	
Some HS	12 (35.3%)	11 (27.5%)	10 (20.0%)	11 (23.9%)	
Current employment, N (%)					
Employed (full and part time)	7 (20.6%)	8 (20.0%)	17 (34.0%)	9 (19.6%)	0.285
Unemployed	27 (79.4%)	32 (80.0%)	33 (66.0%)	37 (80.4%)	
MATRICS working memory	32.1 (9.8)	34.1 (10.5)	39.0 (11.1)	32.4 (14.4)	**0.017**
MATRICS brief visuospatial memory	37.3 (11.9)	33.9 (13.9)	38.6 (12.3)	32.3 (13.7)	0.083
MATRICS letter-number sequencing	34.5 (8.7)	35.7 (9.2)	40.6 (9.9)	35.8 (11.8)	**0.023**
MATRICS spatial span	35.9 (10.0)	37.9 (11.2)	41.2 (10.7)	35.1 (14.4)	0.063
MATRICS overall composite	27.8 (11.9)	29.0 (12.5)	32.9 (13.9)	26.8 (14.3)	0.130
PANSS total score	67.7 (15.3)	62.6 (17.6)	59.6 (14.4)	64.5 (16.1)	0.134
PANSS positive symptom factor (MARDER)	20.9 (6.1)	19.8 (6.5)	17.2 (5.4)	19.0 (6.4)	**0.037**
PANSS negative symptom factor (MARDER)	17.6 (6.1)	14.9 (6.2)	16.2 (5.9)	16.6 (7.1)	0.328
PANSS cognitive/disorganized Factor (MARDER)	13.8 (3.6)	13.8 (4.5)	12.9 (3.9)	13.7 (4.1)	0.636
Q-LES-Q-SF total score	47.0 (10.0)	50.0 (11.8)	53.2 (7.7)	50.4 (9.8)	**0.044**
CGI-severity	3.7 (0.6)	3.6 (0.5)	3.5 (0.8)	3.6 (0.7)	0.779
PSP adjusted score (1–99)	54.6 (12.4)	57.1 (13.3)	59.0 (12.5)	58.3 (12.6)	0.437
NSA-16 total score	45.2 (13.3)	41.3 (13.2)	44.0 (14.0)	43.9 (14.7)	0.652
UPSA-B total score	73.1 (14.4)	71.9 (15.7)	69.7 (16.2)	69.0 (17.7)	0.643

failed to demonstrate a positive treatment effect of valacylovir. Similarly, the letter-number sequencing test demonstrated a significant 3-way interaction ($p = 0.007$) but change score analyses failed to show a positive valacyclovir treatment effect. Visuospatial memory, MCCB overall composite and the remaining MCCB individual test scores did not have significant 3-way interactions. The HSV-1 negative cohort change from baseline score comparisons in Table 3 revealed no significant effects favoring valacylovir treatment, however, there were tests with findings favoring placebo. In Table 4, only the PANSS Cognitive/Disorganization factor showed a significant 3-way interaction ($p = 0.018$) with significant change scores at weeks 8 and 16 indicating greater decreases in the placebo condition. Adjustments for multiple comparison were not conducted for the analyses in Tables 3 and 4. We re-analyzed all outcome data with Bonferoni corrections and found that no comparisons were then significant, suggesting comparisons favoring placebo were likely chance effects. A completor analysis was conducted on all outcome variables contained in Tables 3 and 4 and no significant drug effects were found. Lastly, there were no significant relationships between individual HSV-1 antibody titer values and outcome measures in the HSV-1 positive participants.

4. Discussion

The results of this study indicated that subjects with schizophrenia who were HSV-1 positive were older, had a longer duration of illness, fewer males, more working memory impairment, more positive symptoms, and poorer quality of life than those who were HSV-1 negative suggesting HSV-1 infection may be associated with a more severe variant of schizophrenia. Valacyclovir failed to demonstrate significant treatment effects on the two primary cognitive outcome measures: the MCCB working memory composite and visuospatial memory scores; therefore, this study did not replicate the findings of Prasad et al. (Prasad et al., 2013). Other cognitive, symptom and functional measures were not improved by valacyclovir.

The results from this study comparing HSV-1 positive and negative subjects is consistent with previous studies that have reported greater cognitive impairment in HSV-1 positive people with schizophrenia (F. Dickerson et al., 2012; Dickerson et al., 2008; Dickerson et al., 2003; Prasad et al., 2012; Schretlen et al., 2010; Shirts et al., 2008; Thomas et al., 2013; Watson et al., 2013; Yolken et al., 2011). The relationship between working memory impairment and HSV-1 infection was found in several previous studies (D'Aiuto et al., 2015; Prasad et al., 2011; Schretlen et al., 2010; Thomas et al., 2013). Not all previous studies have found demographic, symptom and functioning differences between HSV-1 positive and negative subjects (Dickerson et al., 2003). Our sample was relatively earlier in their illness course (mean duration of psychosis: HSV-1+: 4.3 years; HSV-1−: 3.4 years), which may explain this discrepancy. The results that HSV-1 + subjects were older, had longer illness durations, more positive symptoms, lower working memory scores and poorer quality of life suggest the possibility the HSV-1 antibodies identify a more severely ill subgroup of schizophrenia. The exception is the finding of fewer males as male gender has been associated with poor prognosis schizophrenia (Davidson and McGlashan, 1997; Lieberman et al., 1996). The hypothesis that HSV-1 infection is associated with greater illness severity is consistent with previous brain imaging studies that reported a link between HSV-1 infection and cortical mass loss (Pandurangi et al., 1994; Prasad et al., 2011; Prasad et al., 2007; Schretlen et al., 2010; Whitford et al., 2012), progressive cortical decrements (Prasad et al., 2011) and a relationship between brain morphological and cognitive deficits (Prasad et al., 2011; Schretlen et al., 2010).

The failure of valacyclovir to improve working memory and visuospatial memory is inconsistent with the findings of Prasad et al. (Prasad et al., 2013). The failure to replicate these findings was despite many similar methodological features including the valacyclovir dose,

Table 3
Valacyclovir effects on cognitive outcomes.

	Time	4 treatment groups, LSM (SEM)				Time × HSV1× treatment	Change score comparisons			
							HSV1 (+): VAL – placebo		HSV1 (−): VAL – placebo	
		VAL(+) N = 34	Placebo(+) N = 40	VAL(−) N = 50	Placebo(−) N = 46	F (P)[a]	LSM (SEM)[b]	T (P)[c]	LSM (SEM)[b]	T (P)[c]
MATRICS working memory	Baseline	31.8 (1.9)	34.1 (1.8)	40.7 (1.6)	35.5 (1.8)					
	W8	34.4 (1.9)	34.7 (1.8)	41.6 (1.6)	39.5 (1.8)		2.0 (1.5)	1.4 (0.177)	−3.1 (1.3)	−2.4 (0.015)
	W16	34.7 (1.9)	36.4 (1.8)	42.6 (1.6)	39.0 (1.8)	3.47 (0.032)	0.6 (1.5)	0.4 (0.664)	−1.5 (1.3)	−1.2 (0.231)
MATRICS brief visuospatial memory	Baseline	37.1 (2.1)	33.9 (1.9)	39.6 (1.7)	34.2 (1.9)					
	W8	38.2 (2.1)	34.6 (1.9)	39.4 (1.7)	38.0 (1.9)		0.4 (2.1)	0.2 (0.841)	−3.9 (1.8)	−2.1 (0.035)
	W16	39.6 (2.1)	37.3 (1.9)	42.2 (1.7)	41.3 (1.9)	1.35 (0.260)	−0.9 (2.1)	−0.5 (0.652)	−4.4 (1.8)	−2.4 (0.016)
MATRICS letter-number sequencing	Baseline	34.2 (1.7)	35.6 (1.6)	42.0 (1.5)	38.6 (1.6)					
	W8	37.0 (1.7)	35.8 (1.6)	43.1 (1.5)	42.2 (1.6)		2.6 (1.4)	1.9 (0.056)	−2.6 (1.2)	−2.1 (0.034)
	W16	37.5 (1.7)	39.5 (1.6)	43.7 (1.5)	41.3 (1.6)	4.98 (0.007)	−0.6 (1.4)	−0.4 (0.676)	−1.0 (1.2)	−0.8 (0.402)
MATRICS spatial span	Baseline	35.9 (1.8)	38.1 (1.7)	42.5 (1.5)	37.5 (1.7)					
	W8	37.1 (1.8)	39.3 (1.7)	42.9 (1.5)	40.0 (1.7)		0.1 (1.8)	0.1 (0.936)	−2.1 (1.6)	−1.3 (0.182)
	W16	37.3 (1.8)	38.1 (1.7)	44.1 (1.5)	40.8 (1.7)	0.99 (0.373)	1.5 (1.8)	0.8 (0.399)	−1.8 (1.6)	−1.1 (0.261)
MATRICS overall composite	Baseline	27.8 (2.3)	29.4 (2.1)	34.8 (1.9)	30.2 (2.2)					
	W8	27.8 (2.3)	30.0 (2.1)	35.6 (1.9)	33.3 (2.2)		−0.7 (1.3)	−0.5 (0.614)	−2.3 (1.1)	−2.0 (0.042)
	W16	29.6 (2.3)	32.6 (2.1)	39.2 (1.9)	36.4 (2.2)	0.49 (0.613)	−1.4 (1.3)	−1.0 (0.298)	−1.9 (1.1)	−1.6 (0.104)

[a] F (ANOVA) 3-way interaction: time (study visit) × HSV1 sero-status × treatment (valacyclovir vs. placebo); DF = 2, 332.
[b] Post hoc change score contrast: (Val baseline value − post-baseline values) − (placebo baseline value − post-baseline values).
[c] T for change score contrast between HSV1 positive valacyclovir vs. placebo; DF = 332.

treatment duration and sample characteristics. The mean age of valacyclovir HSV-1 positive treated subjects were nearly identical (VISTA: 29.6 years; Prasad: 29.5 years) and mean duration of psychosis was similar (VISTA: 4.2 years; Prasad: 3.5 years). Differences between the studies include the cognitive battery (VISTA used the MCCB; Prasad used the Penn Computerized Neurocognitive Battery) even though the tests from each battery assessed similar neurocognitive functions. While the Penn Computerized Neurocognitive Battery includes additional speed measures than are not present in the MCCB, the positive Prasad et al. (2013) cognitive results involved predominantly accuracy measures that are also present in the MCCB. Furthermore, the MCCB has been found to have very high test-retest reliability (Nuechterlein et al., 2008) and has been shown to be sensitive to cognitive interventions (Green et al., 2014). Our study, but not the Prasad trial, randomized both HSV-1 positive and negative subjects, which may have strengthened the study blind as well as tested for potential effects other than those on HSV-1 replication (which were not found when only HSV-1 negative subjects were analyzed separately). At the same time our study was being conducted, another replication trial was initiated by the Prasad investigators in India (Bhatia et al., 2018). In this follow-up study, valacyclovir failed to improve working and visuospatial memory in HSV-1 positive subjects, which is consistent with the findings of our study. However, they reported improvement in accuracy scores of emotional identification and discrimination, which is a finding requiring replication (Bhatia et al., 2018).

The failure to find efficacy of valacyclovir may be because this medication is only effective when the virus is in the activated state. It is possible that in our trial, HSV-1 viruses may have been in the predominately dormant state and therefore resistant to the therapeutic actions of valacyclovir. It may be important to conduct future valacyclovir trials in subjects with clinical signs of activated virus and perhaps those with very high HSV-1 antibody titers. It is also possible that irreversible damage to key cortical networks occurred earlier in the illness course prior to study enrollment and therefore the related cognitive deficits could not be ameliorated by antiviral therapies once this damage had occurred. It may be important to enroll a much earlier stage cohort, such as prodromal and high-risk individuals.

In summary, people with schizophrenia who were HSV-1 positive were older, had a longer duration of illness, fewer males, more working memory impairment, more severe positive symptoms, and poorer quality of life than patients who were HSV-1 negative suggesting that HSV-1 infection may represent a subgroup of greater illness severity. Valacyclovir failed to demonstrate significant treatment effects on the two cognitive primary aims of the working composite score and visuospatial memory and therefore this study did not replicate the findings of Prasad et al. (Prasad et al., 2013). Future clinical trials in individuals with known activated HSV-1 replication are needed.

CRediT authorship contribution statement

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Table 4
Valacyclovir effects on symptoms and functioning.

	Time	4 treatment groups, LSM (SEM)				Time × HSV1 × treatment	Change score comparisons			
							HSV1 (+): VAL – placebo		HSV1 (−): VAL – placebo	
		VAL(+) N = 34	Placebo(+) N = 40	VAL(−) N = 50	Placebo(−) N = 46	F (P)	LSM (SEM)[c]	T (P)	LSM (SEM)[c]	T (P)
PANSS total score[a]	Baseline	66.4 (2.7)	61.1 (2.5)	58.9 (2.3)	64.2 (2.6)					
	W4	64.8 (2.7)	60.5 (2.5)	58.0 (2.3)	62.1 (2.6)		−1.1 (1.7)	−0.6 (0.524)	1.2 (1.4)	0.8 (0.404)
	W8	64.0 (2.7)	59.5 (2.5)	57.3 (2.3)	63.5 (2.6)		−0.9 (1.7)	−0.5 (0.600)	−0.9 (1.4)	−0.6 (0.550)
	W12	62.6 (2.7)	59.3 (2.5)	56.0 (2.3)	61.1 (2.6)		−2.1 (1.7)	−1.3 (0.196)	0.3 (1.4)	0.2 (0.861)
	W16	65.1 (2.7)	57.9 (2.5)	56.0 (2.3)	58.9 (2.6)	0.60 (0.665)	1.9 (1.7)	1.1 (0.259)	2.4 (1.4)	1.6 (0.101)
PANSS positive symptom factor (MARDER)[a]	Baseline	20.5 (1.0)	19.3 (1.0)	17.2 (0.9)	19.3 (1.0)					
	W4	20.7 (1.0)	18.8 (1.0)	17.1 (0.9)	18.7 (1.0)		0.6 (0.7)	0.9 (0.390)	0.5 (0.6)	0.8 (0.403)
	W8	20.1 (1.0)	18.4 (1.0)	16.8 (0.9)	18.7 (1.0)		0.5 (0.7)	0.7 (0.456)	0.4 (0.6)	0.6 (0.568)
	W12	19.2 (1.0)	18.0 (1.0)	16.0 (0.9)	18.3 (1.0)		0.0 (0.7)	0.0 (0.981)	−0.2 (0.6)	−0.3 (0.743)
	W16	19.1 (1.0)	17.1 (1.0)	16.1 (0.9)	17.2 (1.0)	0.06 (0.994)	0.8 (0.7)	1.2 (0.244)	1.0 (0.6)	1.7 (0.097)
PANSS negative symptom factor (MARDER)[a]	Baseline	17.1 (1.1)	14.2 (1.0)	15.6 (0.9)	16.0 (1.0)					
	W4	16.8 (1.1)	15.0 (1.0)	15.4 (0.9)	15.5 (1.0)		−1.1 (0.7)	−1.4 (0.150)	0.3 (0.6)	0.4 (0.665)
	W8	16.5 (1.1)	15.3 (1.0)	14.9 (0.9)	16.0 (1.0)		−1.7 (0.7)	−2.3 (0.024)	−0.8 (0.6)	−1.2 (0.219)
	W12	16.6 (1.1)	14.7 (1.0)	14.7 (0.9)	16.0 (1.0)		−0.9 (0.7)	−1.3 (0.206)	−0.9 (0.6)	−1.4 (0.157)
	W16	17.5 (1.1)	14.8 (1.0)	14.9 (0.9)	14.8 (1.0)	0.69 (0.597)	−0.2 (0.7)	−0.3 (0.761)	0.4 (0.6)	0.7 (0.487)
PANSS cognitive/disorganized factor (MARDER)[a]	Baseline	13.7 (0.7)	13.5 (0.6)	12.5 (0.6)	13.2 (0.6)					
	W4	14.0 (0.7)	12.7 (0.6)	12.3 (0.6)	13.0 (0.6)		1.1 (0.5)	2.3 (0.022)	−0.1 (0.4)	−0.2 (0.816)
	W8	14.0 (0.7)	12.8 (0.6)	11.9 (0.6)	13.7 (0.6)		1.1 (0.5)	2.2 (0.028)	−1.1 (0.4)	−2.5 (0.014)
	W12	13.6 (0.7)	12.7 (0.6)	12.2 (0.6)	13.0 (0.6)		0.8 (0.5)	1.6 (0.121)	−0.2 (0.4)	−0.5 (0.626)
	W16	14.6 (0.7)	12.5 (0.6)	12.1 (0.6)	12.4 (0.6)	3.00 (0.018)	2.0 (0.5)	4.1 (<0.001)	0.4 (0.4)	0.9 (0.367)
Q-LES-Q-SF total score[b]	Baseline	47.8 (1.6)	50.8 (1.5)	53.0 (1.3)	49.4 (1.5)					
	W8	50.9 (1.6)	51.4 (1.5)	52.6 (1.3)	50.7 (1.5)		2.5 (1.6)	1.6 (0.106)	−1.6 (1.4)	−1.2 (0.231)
	W16	49.3 (1.6)	53.7 (1.5)	54.0 (1.3)	52.7 (1.5)	2.25 (0.107)	−1.3 (1.6)	−0.9 (0.390)	−2.2 (1.4)	−1.6 (0.106)
CGI-S[a]	Baseline	3.6 (0.1)	3.6 (0.1)	3.5 (0.1)	3.6 (0.1)					
	W4	3.6 (0.1)	3.5 (0.1)	3.5 (0.1)	3.5 (0.1)		0.1 (0.1)	0.6 (0.519)	0.0 (0.1)	0.3 (0.736)
	W8	3.5 (0.1)	3.3 (0.1)	3.4 (0.1)	3.5 (0.1)		0.1 (0.1)	1.2 (0.235)	−0.0 (0.1)	−0.4 (0.714)
	W12	3.5 (0.1)	3.5 (0.1)	3.4 (0.1)	3.5 (0.1)		0.0 (0.1)	−0.2 (0.866)	0.0 (0.1)	0.03 (0.977)
	W16	3.5 (0.1)	3.4 (0.1)	3.3 (0.1)	3.5 (0.1)	0.49 (0.744)	0.0 (0.1)	0.2 (0.838)	−0.0 (0.1)	−0.2 (0.872)
PSP adjusted score (1–99)[b]	Baseline	55.4 (2.1)	58.2 (2.0)	59.9 (1.8)	59.2 (2.0)					
	W8	55.6 (2.1)	60.5 (2.0)	61.7 (1.8)	61.4 (2.0)		−2.1 (1.7)	−1.2 (0.219)	−0.4 (1.5)	−0.3 (0.784)
	W16	58.3 (2.1)	60.8 (2.0)	61.3 (1.8)	61.5 (2.0)	0.78 (0.459)	0.2 (1.7)	0.1 (0.895)	−0.9 (1.5)	−0.6 (0.548)
NSA-16 total score[a]	Baseline	44.5 (2.3)	40.2 (2.2)	42.5 (2.0)	41.7 (2.2)					
	W4	43.3 (2.3)	40.2 (2.2)	42.7 (2.0)	41.1 (2.2)		−1.3 (1.6)	−0.8 (0.408)	0.8 (1.4)	0.6 (0.548)
	W8	44.4 (2.3)	39.9 (2.2)	41.5 (2.0)	41.5 (2.2)		0.1 (1.6)	0.1 (0.927)	−0.8 (1.4)	−0.6 (0.575)
	W12	43.7 (2.3)	40.6 (2.2)	41.0 (2.0)	42.1 (2.2)		−1.2 (1.6)	−0.8 (0.442)	−1.8 (1.4)	−1.3 (0.183)
	W16	46.5 (2.3)	39.9 (2.2)	41.5 (2.0)	41.1 (2.2)	1.37 (0.241)	2.3 (1.6)	1.5 (0.145)	−0.4 (1.4)	−0.3 (0.788)
UPSA-B total score[b]	Baseline	72.6 (2.5)	71.8 (2.4)	71.9 (2.2)	73.4 (2.4)					
	W8	73.4 (2.5)	74.5 (2.4)	75.3 (2.2)	78.6 (2.4)		−1.9 (2.4)	−0.8 (0.423)	−1.8 (2.1)	−0.9 (0.391)
	W16	76.7 (2.5)	75.6 (2.4)	77.5 (2.2)	78.8 (2.4)	0.00 (0.996)	0.3 (2.4)	0.1 (0.897)	0.1 (2.1)	0.06 (0.950)

[a] F (ANOVA) 3-way interaction: time (study visit) × HSV1 sero-status × treatment (valacyclovir vs. placebo); DF = 4, 664. T for change score contrast between HSV1 positive valacyclovir vs. placebo; DF = 664.
[b] F (ANOVA) 3-way interaction: time (study visit) × HSV1 sero-status × treatment (valacyclovir vs. placebo); DF = 2, 332. T for change score contrast between HSV1 positive valacyclovir vs. placebo; DF = 332.
[c] Post hoc change score: (Val baseline value − post-baseline values) − (placebo baseline value − post-baseline values).

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Contributions

AB, AR, MF provided medical over-site, and developed and designed the study; JH conducted the symptom and cognitive assessments; NM, AV, EM coordinated study procedures; ZY, YZ conducted statistical analyses.

Conflicts of interest

The authors had no competing financial interests.

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