

GSK Medicine: Valacyclovir, aciclovir
Study No.: WWE113849/WEUK347
Title: The Safety of Valacyclovir Among Severely Immunocompromised Patients with HIV-1/HSV-2 Co-Infection.
<p>Rationale: Herpes simplex virus (HSV) can cause recurrent infectious outbreaks, often in response to triggers such as immunosuppression. Patients co-infected with human immunodeficiency virus (HIV) and HSV are more likely to have frequent outbreaks with longer duration and greater severity of symptoms, compared to immunocompetent individuals. Although side effects in immunocompetent patients are rare, the potential for adverse events (AEs) in immunocompromised patients, are of concern.</p> <p>To fulfil a phase IV commitment with the US Food and Drug Administration (FDA), GlaxoSmithKline (GSK) agreed to conduct a clinical research study, with the aim of providing safety information on valacyclovir use in HIV-infected patients with CD4+ cell count <100 cells/mm³. An international randomized, double-blind placebo-controlled trial (GSK Study Number HS2100181) of valacyclovir for the suppression and episodic treatment of recurrent genital herpes in HIV-infected patients with CD4+ cell counts <100 cells/mm³ was initiated Apr 2004. This study was terminated with mutual agreement by GSK and the FDA due to substantive barriers in its enrollment. In lieu of completing this study, in Sep 2004 GSK agreed to conduct a retrospective review of historical data from two observational databases [EuroSIDA and Collaborations in HIV Outcomes Research/US (CHORUS)].</p>
<p>Objectives: The purpose of this observational database study was to evaluate whether HIV/HSV-2 co-infected patients with low CD4+ cell counts (<100 cells/mm³) receiving valacyclovir were at greater risk for having adverse events compared to HIV/HSV-2 co-infected patients with low CD4+ cell counts who did not take antiherpetic medications for the treatment of genital herpes.</p>
Indication: Not Applicable
Study Investigators/Centers: GSK Conducted Study
Research Methods:
<p>Database Source(s): CHORUS CHORUS has a substantial population of HIV-1/HSV-2 co-infected patients, with availability of data on treatment, diagnosis, laboratory tests, and sociodemographic factors.</p> <p>EuroSIDA The EuroSIDA database was planned to be used with the CHORUS database to evaluate the safety profile of valacyclovir in HIV-1/HSV-2 co-infected adult patients with CD4+ cell counts less than 100 cells/mm³. EuroSIDA was found to be unsuitable for assessing the safety profile of valacyclovir in this population for three main reasons: 1) Of the 7,062 adult HIV patients, only 9 patients (0.13%) had both a CD4+ cell count of <100 cells/mm³ and exposure to valacyclovir. 2) Diagnoses of genital herpes are not recorded in EuroSIDA. 3) EuroSIDA does not collect data on outcomes that could be classified as potential adverse events. Because of these limitations, the EuroSIDA results were not robust and therefore considered to be supplemental to the CHORUS results.</p>
Study Design: Prospective Observational Cohort Analysis
<p>Study Population: This study population consisted of patients participating in CHORUS who had a diagnosis of genital herpes (type 2 or non-specific) or a laboratory test indicating HSV-2 infection (patients with HSV-1 infection only were excluded from the analysis population), and at least one CD4+ cell count below 100 cells/mm³.</p>
<p>Study Exposures, Outcomes: Study Exposure(s): Exposure was defined as having taken valacyclovir for the treatment or prevention of outbreaks of genital herpes during an interval of low CD4+ cell count. For patients with the exposure of interest, baseline was defined as the later date between their low CD4+ cell count interval and initiation of a qualifying antiherpetic medication</p> <p>Comparator group: The comparison group is comprised of patients with HIV-1 and HSV-2 coinfection with low CD4+ measures, who had never used antiherpetic medications to treat genital herpes</p>

Primary Outcome(s):

Primary outcomes were defined in the following three mutually-exclusive categories

- 1) **Events of Special Interest-** These events have been associated with valacyclovir and are noted in the product insert.
- 2) **Events of Possible Interest-** These events were observed during clinical practice, and occasionally have been observed with the use of valacyclovir as spontaneous reports or reported in the literature.
- 3) **Clinically Significant Laboratory Abnormalities-** The criteria for defining clinically relevant lab abnormalities were provided by FDA.

Secondary Outcomes: all "other diagnoses" not historically associated with herpes or antiherpetic medication.

Outcomes (AEs) of Interest

Events must have occurred during a low CD4+ interval which is defined as the time window between baseline and the earlier of a subsequent CD4+ measurement that was at least 100 cells/mm³ or the last follow-up date. Events occurring after the end of the CD4+ interval were considered if they took place within 30 days of the end of the low CD4+ interval.

Event Type	Definition
Adverse Events of Special interest	Nausea, headache, vomiting, dizziness, abdominal pain, dysmenorrhoea, diarrhoea, loose stools, upper respiratory tract infection, fatigue, influenza-like illness, nasopharyngitis, pyrexia, cough, bronchitis, sinusitis, arthralgia, back pain, depression, facial edema, hypertension, tachycardia, thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) or the discontinuation of valacyclovir due to an adverse event.
Adverse events of Possible Interest	Constipation, appendicitis, pancreatitis, facial edema, hypertension, confusion, dysarthria, auditory or visual hallucinations, visual abnormalities, elevated liver enzymes, elevated serum creatinine, renal failure, leukocytoclastic vasculitis, alopecia, aplastic anemia, decreased consciousness, reduced mental alertness, encephalopathy, mania, psychosis, seizures, tremors, agitation, ataxia, coma, non-viral hepatitis, renal insufficiency, hypersensitivity reaction, anaphylaxis, andioedema, dyspnea, pruritis, rash, urticaria, erythema multiforme, photosensitivity, aggressive behavior, hallucinations, tachycardia, hematuria, bleeding or bruising.
Clinically relevant lab abnormalities	Alkaline phosphatase >1.5 X upper limit of normal (ULN), Aspartate aminotransferase (AST) >2 X ULN, Alanine aminotransferase (ALT) >2 X ULN, Serum creatinine >1.5 X ULN, Hemoglobin <0.8 X lower limit of normal (LLN), Neutrophils <0.8 X LLN, White blood cells <0.75 X LLN, Platelets <100,000/mm ³

Data Analysis Methods:

The distribution of key variables across exposure and outcome groups were examined. Continuous variables such as age and liver function tests were compared using the Wilcoxon Rank Sum test statistics, while categorical variables were compared using Chi-square or Fisher's Exact test where appropriate. Multivariable logistic regression models were used to address the study hypothesis. Covariates were included in the model individually and in combinations to determine if they altered the crude or unadjusted relative risks by at least 10%. Additionally, stepwise regression was performed to identify statistically significant covariates. Variables that are known to be associated with specific adverse

events (e.g. alcohol abuse and elevated liver enzymes), but which do not qualify as confounders by the pre-determined statistical criteria were retained in the model. Multivariate logistic regression models were fit for each event type category: (1) events of special interest (2) events of possible interest (3) or events defined by clinically relevant lab abnormalities. The measures of association were adjusted risk ratios and 95% confidence intervals.

Limitations:

Every effort was made to control for factors known to be associated with adverse events, however, treatment assignment was not randomized. Therefore, it is possible that subtle characteristics determined which patients took antiherpetic medications and which did not. If these characteristics were not taken into consideration during statistical analyses, these results would be biased due to residual confounding. Since the frequency of clinic visits are determined by patients and their physicians and not by study protocols, patients may have chosen not to report events that caused minimum discomfort, such as dizziness or headache. Therefore, there is a potential for underestimating mild events that may occur during the follow-up period.

Patients who took valacyclovir or acyclovir had a significantly higher number of clinic visits during the follow-up period than patients who did not take any antiherpetic medications. It is possible that treated patients had a greater opportunity to report events, including those that qualified as events of interest for this study, and a greater chance of being diagnosed with problems because they were monitored more frequently. Selection bias is likely to favour more events being recorded for patients in the exposed group than for patients in the unexposed group, although the risk of adverse events was comparable across both groups.

Study Results:

Baseline Characteristics for Valacyclovir, CD4+ cell counts <100 cells/ mm³

Numbers in parenthesis indicate column percentage for categorical variables and range of values for continuous measures	Valacyclovir exposure		P- value**
	Yes n=34	No N=56	
Male sex	31 (91.2)	51 (91.1)	1.000*
Median age at baseline	41.2 (22.2, 55.6)	40.4 (31.6, 76.7)	0.668
Race/ethnicity			
Caucasian			0.127*
African American	17 (50.0)	40 (71.4)	
Hispanic	10 (29.4)	10 (17.9)	
Other	6 (17.7)	6 (10.7)	
Had a history of alcohol abuse	1 (2.9)	0 (0.0)	
Hepatitis B Virus at baseline	3 (8.8)	5(8.9)	1.000*
Hepatitis B Virus </during low CD4+ interval§	11(32.4)	17(30.4)	0.843
Hepatitis C Virus at baseline	12(35.3)	20(35.7)	0.968
Hepatitis C Virus </during low CD4+ interval§	2(5.9)	5(8.9)	0.706*
Baseline LFT ¹ ≥ grade 1	2(5.9)	7(12.5)	0.474*
Baseline creatinine ≥ grade 1	4(11.8)	12(21.4)	0.378*
AIDS diagnosis ≤ baseline	1(2.9)	0(0.0)	0.197*
AIDS diagnosis </during low CD4+ interval§	34(100.0)	49(87.5)	0.042*
Median baseline CD4+ cell count	34(100.0)	53(94.6)	0.287*
Median baseline log viral load	78 (2, 98)	62.5 (2, 99)	0.314
ART ² naïve at baseline	4.6 (1.7, 6.3)	4.8 (1.7, 6.5)	0.648
First ART was HAART ³	2 (5.9)	5 (8.9)	0.706*
Took abacavir during interval	11 (32.4)	25 (44.6)	0.249
Took TMA-meds during interval	15 (44.1)	13 (23.2)	0.038
Nephrotoxic meds during interval	22 (64.7)	37 (66.1)	0.895
NNRTI ⁴ during interval	25 (73.5)	47 (83.9)	0.232
Protease inhibitor during interval	27 (79.4)	36 (64.3)	0.129
	28 (82.4)	47 (83.9)	0.232

Median months on interval	6.3 (0.5, 87.5)	5.2 (0.8, 56.6)	0.874
Median months of total follow up	17.1 (0.5, 87.5)	31.4 (2.5, 87.9)	0.034
Median # low CD4+ intervals	1 (1, 5)	1 (1, 6)	0.866

* Fisher's Exact Test

§ Prior to or during low CD4+ interval of interest

¹ LFT – Liver function test

² ART = antiretroviral therapy

³ HAART = highly active antiretroviral therapy

⁴ NNRTI = non-nucleoside reverse transcriptase inhibitor

Adverse Events of Interest for Valacyclovir treated patients with CD4+ cell counts <100 cell/mm³

Primary Outcomes:	Exposure Group	Comparison Group	P-Value
	Valacyclovir treated (n=34)	No anti-herpetic treatment (n=56)	
AEs special interest	13 (38.2)	16 (28.6)	0.342
AEs possible interest	5 (14.7)	5 (8.9)	0.494*
Lab AEs	20 (58.8)	31 (55.4)	0.748

Secondary Outcome:

Other diagnoses	26 (76.5)	35 (62.5)	0.169
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*Fisher's Exact Test

(number in parentheses indicate column percentages)

Risk Ratios (RR) :

[Having an event of interest for patients who took valacyclovir during a low CD4+ interval (<100 cells/mm³) versus patients who did not take any antiherpetic medication and their 95% confidence interval]

Models for Valacyclovir, CD4 <100 cells/mm ³	Unadjusted RR (95% CI)	Adjusted * RR (95% CI)	Adjusted ** RR (95% CI)
AEs of special interest	1.55 (0.63, 3.82)	1.55 (0.63, 3.82) ¹	1.17 (0.43, 3.21) ⁴
AEs of possible interest	Inadequate sample size	Inadequate sample size	Inadequate sample size
Lab AEs	1.15 (0.49, 2.73)	0.83 (0.27, 2.54) ²	0.93 (0.34, 2.57) ⁵
Other diagnoses	1.95 (0.75, 5.09)	1.95 (0.75, 5.09) ³	2.21 (0.49, 9.86) ⁶

* Covariate selection was done based on stepwise regression methods.

** Covariate selection was done based on clinical rather than statistical criteria alone, as with stepwise regression.

^{1,3} No covariate met model inclusion criteria.

² Adjusted for grade 1+ baseline LFT, concurrent use of abacavir, baseline viral load > 20,000 copies/ml

⁴ Adjusted for concurrent use of TMA drugs, hepatotoxic drugs, NNRTIs, abacavir, and concurrent AIDS

⁵ Adjusted for concurrent use of hepatotoxic drugs, nephrotoxic drugs, abacavir, grade 1+ baseline LFT, grade 1+ baseline serum creatinine

⁶ Adjusted for study site, age, race, concurrent AIDS, hepatitis C coinfection, baseline viral load >20,000 copies/ml, first ART was HAART

Note- Reference group are patients with HIV-1/HSV-2 coinfection who had one or more intervals of low CD4 but never took any antiherpetic medication. For adjusted models, RRs reported are for the main effect only.

Summary of Results:

Patients who took valacyclovir were slightly more likely to have AIDS than patients in the unexposed group; the former had a higher median CD4+ cell counts and lower median viral load at baseline, although neither of these differences was statistically significant. The only significant differences were in the concurrent use of abacavir during a low CD4+ interval (patients who took valacyclovir were more likely to have taken abacavir) and median months of follow-up (patients who took antiherpetic medications had a shorter duration of follow-up.) When analyzing the distribution of outcome variables across exposure groups, none of the comparisons were statistically significant, although a greater proportion of patients in the valacyclovir group experienced AEs and other diagnoses.

Multivariable analyses showed a slightly higher risk of AEs of special interest and other diagnoses for patients in the

valacyclovir group, however, none of these risk ratios approached statistical significance.

Multivariable analyses indicated that the most significant predictors of adverse events were high baseline viral load, elevated liver enzymes at baseline, concurrent comorbidities like hepatitis B and C coinfection and the use of drugs that are known to be associated with TMA. The concurrent use of abacavir was significant in some models that had abnormal lab measures as the outcome of interest. This may be due to the fact that abacavir is frequently co-prescribed with zidovudine, which is known to be associated with anemia, one of the end-points of interest for lab abnormalities. The concurrent use of abacavir was also an important covariate in one of the models for AEs of special interest, most likely due to its association with rash.

Conclusions:

Highly immune compromised HIV-1/HSV-2 co-infected patients who take valacyclovir to treat genital herpes do not have an increased risk of adverse events when compared to co-infected and immune compromised patients who do not take antiherpetic medications.

Publications: No publications

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