HERPES SIMPLEX

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 HSV infections present as “grouped vesicles, erythema and related discomfort”, and are spread due to viral shedding which can occur unrelated to absence or presence of symptoms (Dougal & Lee, 2013, p. 713). Diagnosis frequently occurs following first onset of symptoms however patients most likely have had the disease for some time. Reactivation of the virus coincides with emotional and physical stressors, and surfaces as lesions or sores appearing either on the face (herpes labialis) or in the genital area (genital herpes). Since the “the majority of HSV infections are asymptomatic”, transmission rates are negatively affected. (Belshe et al., 2012, p.35). Globally, HSV 2 infects more than 500 million people with 23 million new cases each year. These numbers of infected individuals represent why aggressive treatment of HSV infections are essential until a cure can be established. For this reason research has targeted prevention of infection and management techniques to reduce likelihood of recurrences. “Seroprevalence indicates that 60% - 90% of adults are infected with HSV-1” (Hull et al., 2010) with “labial outbreaks of vesicular herpetic lesions affecting 20-40% of the population” (Khemis et al., 2011). Additionally “only 10 to 25% of patients with HSV2 immunity are aware that they have genital herpes”, further adding to the concern of spread without the knowledge of their disease status (Khemis et al., 2014).

**Method**

A review of the literature was conducted to analyze current treatment modalities and guidelines utilized in provision of care for persons with herpes simplex virus infections. The analysis performed focused on articles with the most up-to-date evidenced-based research. The purpose of the literature review is to demonstrate the current treatment guidelines for herpes simplex virus infections, based on clinical evidence, in effort to help the nurse practitioners and all advanced practice registered nurses (APRNs) make decisions regarding appropriate treatment for that patient population. For the purpose of the literature review, treatment management will only pertain to herpes labialis and genitalis.

 Articles for the review were acquired through PubMed, CINAHL plus full text, Google Scholar, Cochrane Review and Medline. Inclusion criteria of English language, articles published within the last ten years, peer-reviewed and keywords of “herpes”, “herpes labialis”, “genital herpes”, “treatment”, “antivirals”, “cold sores” and “HSV 1 & 2.” A considerable amount of the literature focused on concurrent herpes simplex virus infections with HIV infections as well as complications that arise as a result of infection with herpes simplex virus, such as: neonatal, encephalitis and keratitis. Therefore, those terms were also eliminated from article selection and served as exclusion criteria. Fifteen articles in total were selected (Appendix A) based on their study design and management approaches. Additionally, the subcategories of herpes simplex virus were narrowed down to solely include HSV1 and HSV2 representing herpes labialis and genitalis.

**Review of Literature**

 Belshe et al. (2012) conducted a study to determine the efficacy of a HSV vaccine when given over a course of six months, with numerous end points., primarily prevention of genital herpes from HSV-1 and 2. Previous studies containing similar ingredients showed varying efficacy in different populations for both HSV-1 and 2 (Belshe et al., 2012). Women from America and Canada from ages eighteen to thirty were selected utilizing strict inclusion and exclusion criteria, a total 8323 in number (Belshe et al., 2012). During the six month randomized double-blind study, 4,577 women received a series of three vaccinations and 3,746 received a placebo (Belshe et al., 2012). Viral testing was performed at pre-determined time periods and with onset of symptoms along with a questionnaire to determine sexual-risk behavior (Belshe et al., 2012, p. 35). Results of this study concluded that the vaccine is only effective against HSV-1 genital disease at 58%, with no efficacy observed against HSV-2 infection (Belshe et al., 2012). All data collection took place with the GlaxoSmith-Kline remote data-entry system (Belshe et al., 2012). The weaknesses of this study include evaluation of vaccination in solely one gender and not inclusive for HSV-2 population.

 The focus of treatment for Herpes labialis continues to be symptom management. Carvalho et al. (2010) conducted a randomized clinical trial to determine the effectiveness of phototherapy on herpetic outbreaks (Carvalho et al., 2010). Seventy young adult patients were enrolled in the study and randomly assigned to groups. The control group consisted of thirty patients that used 5% acyclovir cream five times a day while the treatment group, of forty-one patients, underwent phototherapy once a week for ten weeks, if symptoms presented (Carvalho et al., 2010, p.398). Following treatment, measurements of lesion size, edema, pain level, and cycle of recurrence were recorded to determine the interventions effect (Carvalho et al., 2010, p. 399). Findings showed statistical significance in the size (P=0.013) and amount of edema (P=0.031) with no significant reduction in pain (P=0.051) or recurrences (P=0.076) (Carvalho et al., 2010, p. 399). These findings add significance to the variety of treatment options that focus on reduction of symptoms with herpes labialis outbreaks and call for a need to further investigation into this therapy.

 Dougal and Lee (2013) conducted a prospective randomized placebo-controlled clinical trial studying the effects of phototherapy on herpes labialis (HSL) as a potential treatment option for symptom reduction. Dougal and Lee evaluated the efficacy of low-level light therapy (1072 nm infrared light) in the treatment of HSL against that of a placebo utilizing n = 41 in the study group and n = 47 in the control (2013, p, 714). The treatment group received three-minute treatments three times a day for two days, versus the control receiving the same but from a “dummy” device (Dougal & Lee, 2013, p. 715). Patients were evaluated every two to three days to determine the healing time and allow for direct observation of their symptom management. Statistical analysis of the data was performed utilizing Epi Info, Excel, and the Wilcoxon rank sum test (Dougal & Lee, 2013, p. 715). Results showed a reduced median healing time of 48 hours that is statistically significant (P=0.01) (Dougal & Lee, 2013, p. 715).
 Hull et al. (2010) conducted a randomized double-blind active and placebo controlled study on 1,398 persons aimed at prevention of HSL lesions and reduction of associated symptoms (p.696.e2). All individuals within the study were 18 years of age or older and had three or more HSL outbreaks the previous year (Hull et al., 2010, p. 696e.2). The groups were randomized into three groups: 582 individuals in the treatment group, 591 utilizing acyclovir cream, and 225 receiving a placebo cream (Hull et al., 2010, p. 696.e5). Treatment consisted of ME-609 cream (5% acyclovir and 1% hydrocortisone) application five times a day for five days followed by data collection consisting of self-assessment and virology at pre-determined time frames (Hull et al., 2010, p. 696.e3). Data collected from the use of ME-609 showed statistical significance in both reduction of lesions, P = 0.14, and healing times , P <0.01 (Hull et al., 2010). These results provide strong and safe evidence for the use of ME-609 in treatment of herpes labialis and reduction of symptoms.

 Khemis et al. (2011) conducted a prospective randomized single-center assessor-blinded study on 106 outpatient adults to determine the efficacy and safety of CS20 (peroxidized corn oil 87.8%, micronized zinc oxide 1.0%, silicon dioxide 7.0%, orange-grapefruit flavouring 2.5%, mint flavouring1.5%) in treatment of herpes labialis. Of the 106 enrolled patients, (84 women, 22 men), 35 were in the CS20 group, 35 in acyclovir group, and 6 in the placebo group (Khemis et al., 2011, p. 1242). All patients experienced frequent recurring labial herpes and were being seen at a hospital dermatology clinic in Nice, France (Khemis, 2011). Labial recurrence during a six-month enrollment period, immunocompetence, and not currently using topical or systemic medications, which might affect viral activity/study results, were the inclusion criteria (Khemis, 2011, p. 1241). The patients were divided into three groups by treatment method. Treatment methods included: CS20 protective barrier lip gel, topical 5% acyclovir, and placebo (Khemis, 2011, p. 1241). When lesions were visible the groups were instructed to apply assigned cream/gel five times daily (Khemis, 2011, p. 1242). Following the start of treatment, all patients were evaluated on days 1, 2, 7 and 14 in addition to completing daily questionnaires regarding symptoms and pain (Khemis et al., 2011, p. 1242). Results were checked and compared utilizing the Shapiro-Wilks test, General Linear Model, Kruskal-Wallis test, Pearson chi-square test or the Fisher’s exact test (Khernis et al., 2011, p. 1242). Findings within this study exhibited increased symptom reduction with the use of CS20 (barrier gel) compared to acyclovir and the placebo, however total healing times were not statistically significant.

 Genital herpes (GH) can be a silent disease because its transmission can occur when carriers are asymptomatic thus making it difficult for providers and patients to find effective treatment options to limit its spread (Fife et al., 2006). Since outbreaks of GH can be particularly embarrassing and painful many patients favor therapy that suppresses the frequency of recurrences (Fife et al., 2006). Fife et al., (2006) performed a randomized, double-blind, placebo-controlled study that evaluated the effect of valacyclovir on viral shedding in patients that experience recurrent herpes-simplex virus 2 GH. One hundred fifty two patients originally began the study but as patients withdrew or were lost to follow-up only 134 patients remained to the study’s completion (Fife et al., 2006). The 134 remaining patients were randomly assigned to either receive one gram of valacyclovir orally per day or the equivalent dosage in placebo form for a total of sixty days (Fife et al., 2006). Additionally, all participants were instructed to complete daily anogenital and rectal swabs to quantify the amount, if any, of viral shedding. Viral shedding was measured by quantitative type-specific PCR (polymerase chain reaction) assay and then classified into clinical (presence of genital lesions) or subclinical (no lesions) categories, as well as evidence of shedding or no shedding (Fife et al., 2006). The study results demonstrated that daily use of oral valacyclovir reduced viral shedding in both clinical and subclinical days as well as highlighted the possibility of limited to no viral shedding (Fife et al., 2006). Limitations that could challenge validity within this study are the accuracy of self-directed swabbing and medication compliance since these patients completed the swabbing procedures and medication administration in their respective homes without supervision (Fife et al., 2006). Additionally, the ratio of patients in the valacyclovir group to placebo group was three to one, which could falsely elevate the end study results to favor the valacyclovir group rather than placebo group. An unforeseen benefit to having the study self-directed by the patients was that this mimics the current treatment process in the general population. Ultimately, this study supports the use of valacyclovir as suppressive therapy for recurrent GH to reduce the total HSV-2 shedding (Fife et al., 2006).

 A study conducted by Gupta et al. (2004) also looked to reduce the HSV viral shedding in the genital tract by comparing the use of valacyclovir and acyclovir to placebo therapy. Sixty-nine patients participated in a 21-week randomized, double blind, placebo-controlled, three-period crossover trial. The sixty-nine patients were randomly assigned to the valacyclovir group, acyclovir group, or placebo group for a 7-week period (Gupta et al., 2004). After the initial 7-week period was completed patients would crossover into a new second treatment (not same as first) option for another 7 weeks and again crossover to the third (different from 1st and 2nd) treatment option to complete the 21-week trial (Gupta et al., 2004). During each 7-week period patients would take the prescribed medication and perform genital mucosal swabbing. The swabbing was evaluated for presence of HSV viral shedding by quantitative PCR and culture. Gupta et al. (2004) study determined “genital HSV shedding detected by culture in 86% of patients on placebo therapy compared to 12% on valacyclovir and 24% receiving acyclovir.” Thus, suppressive therapy by means of either valacyclovir or acyclovir significantly limits the amount and frequency of HSV viral shedding in patients with and without visual symptoms (Gupta et al., 2004). Limitations were reliability and consistency of study participants with regards to medication compliance, swabbing techniques and return of swabs within the specified time frame. In order to generalize this study to an entire population more testing should be done on a larger amount of study participants and also more inclusive for race diversity (Gupta et. al., 2004).

 Since most drug therapy for GH focus exclusively on use of oral medications to limit viral shedding for treatment, a study was piloted by Khemis, Duteil, Tillet, & Ortonne (2014) to evaluate the effectiveness of topical antiviral medications for their activity and safety on GH recurrence symptoms. Sixty-one patients were enrolled in the prospective, randomized controlled three parallel group study comparing the effectiveness of CS 21 barrier gel to topical acyclovir and a topical placebo (vehicle) creams (Khemis et al., 2014). Patients were instructed to apply their designated treatment cream/gel five times per day initially following the onset of first symptoms for a maximum of fifteen days (Khemis et al., 2014). Khemis et. al. (2014) used statistical analysis to measure effectiveness by utilization of symptom intensity scores (VAS: Visual analogic scale) and clinical lesional scores (grading on 0(none)-3(severe) scale). When compared with topical acyclovir cream and placebo (vehicle) cream, CS 21 barrier gel was more efficient in moderate reduction of lesion duration and associated pain (Khemis et al., 2014). Thus, when CS 21 barrier cream is added to treatment regimen with an oral antiviral, viral shedding, length of lesion time and pain can be drastically reduced to provide enhanced symptom management for GH patients.

 A randomized, double blind placebo-controlled study was conducted by Mark et al. (2007) to explore the utilization of Resiquimod, a topical gel treatment modality, as a means to reduce HSV-2 genital shedding without the use of suppressive oral antiviral therapy. Seventy-five patients, men and women distributed evenly, were randomly assigned to either the Resiquimod group or placebo group with onset of first recurrence symptoms (Mark et al., 2007). Patients were instructed to apply their respective gel/cream to herpes lesions twice per week for a total of three weeks (Mark et al., 2007). Throughout the three-week application period participants were then instructed to collect daily anogenital swabs and to continue collection for a total of sixty days to assess for viral shedding during the treatment-free period (Mark et al., 2007). Viral shedding was assessed through serological PCR for the presence of HSV from the collected participant swabs. Resiquimod participants experienced two-thirds the shedding rate of placebo recipients (Mark et al., 2007). This study may be helpful to future providers because this is the first clinical trial to exhibit a positive effect on reduction of viral shedding through topical application.

 Helicase-primase inhibitors are one of the latest drug classes to emerge as potential treatment agents for genital herpes. More specifically, ASP2151 (non-nucleoside oxadiazol-phenyl drug) has surfaced as one of the more innovative helicase-primase inhibitors considered for GH treatment. In an effort to explore which antiviral therapy and at what oral dosing is most effective in the treatment of GH, Tyring et al. (2012) piloted a randomized, double blind, placebo and valacyclovir controlled study. In the study, 415 participants were randomly assigned to one of six treatment groups: ASP2151- 100mg, 200mg, or 400mg daily for three days, ASP2151 1200mg single dose, placebo for 3 days or valacyclovir 500mg twice daily for 3 days. Tyring et al. (2012) instructed study participants to initiate treatment with their assigned medications at first sign of symptom reccurence. There were strict swabbing schedules and routine labwork throughout the trial. In comparison to the placebo group, both ASP2151 and valacyclovir groups exhibited shorter lesion healing times, shorter duration of recurrence episodes, and reduced viral shedding duration (Tyring et al., 2012). This study could be of great use to providers whose patient’s GH have developed resistance to standard treatment measures. Since ASP2151 employs comparable, if not, slightly improved outcomes it may be plausible to consider this drug as adjunct therapy or principal therapy for patients who do not tolerate standard management (Tyring et al., 2012).

 A randomized, double blind placebo-controlled parallel study led by Wald et.al. (2014) was conducted in regards to the helicase-primase inhibitor Pritelivir and its influence on the reduction of lesion time and rates of HSV genital shedding. 156 patients with HSV2 GH were randomly assigned to one of five groups of varying doses weekly or a placebo. During the course of twenty-eight days, participants were instructed to perform daily genital skin and mucosa swabs and return them back to the study site weekly. Wald et al. (2014) discovered that the drug effects on viral shedding and length of lesion time were dose-related, noting higher strength Pritelivir had the greatest effect (Wald et al., 2014). Although this study did demonstrate an 85% reduction in viral shedding, break-through shedding was still present regardless of medication dosage (Wald et. al., 2014).

 A randomized controlled trial was performed by Mujugira et al. (2014) assessed the effect of suppressive therapy of acyclovir on HSV2 transmission rates among serodiscordant couples as well as frequency of genital ulcers. 911 participants were enrolled and randomized to either receive 400mg of acyclovir twice daily or equivalent placebo for two years. All participants and their respective partners were tested with herpeSelect-2 enzyme immunoassay and Western Blot prior to enrollment and then quarterly to track possible seroconversions, of HSV-2 and HIV-1 transmissions, from infected partners to non-infected partners (Mujugira et al., 2014, p. 1368). Overall, there were a total of 68 people (51men, 17 women) that experienced seroconversions, forty of which were noted to be from the acyclovir group (Mujugira et al., 2014, p. 1370). Mujugira et al. (2014) noted that suppressive therapy with acyclovir was helpful in the reduction in frequency of genital ulcers but not in transmission of HSV-2. Limitations in this study were the length of the study and sample size. Since the study was inclusive for couples with one infected and uninfected partner, each person would need to complete the same amount of regular testing, which may be difficult to track since they would have to drive to the study’s location (Mujugira et al., 2014). Also, it may be near impossible to track/account for outlying factors, such as unprotected sex outside of established relationship, which could hold considerable effect on transmission rates within the study.

 Although antiviral medications are currently utilized for their activity in the reduction of genital lesions and suppression of viral shedding among patients with HSV2 infections there is still question as to what dosage and frequency produces the most beneficial outcomes if any (Johnston et al., 2012). Johnston et al. (2012) explored “whether standard-dose or high-dose antiviral therapy reduces the frequency of skin and mucosal shedding” through three-randomized, open-label, crossover trials (p. 641). The first trial randomized thirty-two participants (symptomatic (active lesions) or non-symptomatic (no lesions)) into group that received no medication or standard dose acyclovir (400mg twice daily) for four weeks plus a one-week washout period followed by a crossover period of four additional weeks with the contrasting therapy (Johnston et al., 2012, p. 642). Johnston et al. (2012) noted standard-dose acyclovir was more effective in reduction of HSV shedding compared to no medication (p. 644). In trial two, thirty-one participants were randomized into groups that received either standard-dose valacyclovir (500mg daily) or high-dose acyclovir (800mg three times daily) for seven weeks followed by contrasting therapy for additional seven weeks (Johnston et al., 2012). In trial two, HSV-2 shedding was reduced for high-dose acyclovir group compared with standard-dose valacyclovir group (Johnston et al., 2012). Lastly, trial three explored standard-dose valacyclovir compared to high-dose valacyclovir (1g three times daily) among fifty randomized participants for a five-week period followed by crossover trial for additional five-weeks (Johnston et al., 2012). Johnston et al., (2012) determined, “ a dose effect on HSV shedding was noted on the high-dose valacyclovir compared to standard-dose valacyclovir” (p. 644). Of important note, “breakthrough reactivation of HSV 2 occurred at all drug doses,” however significantly less frequent in groups receiving antiviral therapy compared with no medication (Johnston et al., 2012, p. 644). Although antiviral therapy significantly reduces duration of lesions, pain and frequency of shedding, there is still evidence of HSV shedding irrespective of the treatment (Johnston et al., 2012).

**Conclusion**

 Based on the number of HSV infections and the symptoms associated, studies have been performed with end points of symptom reduction. Symptom severity reduction was a common theme illustrated among a majority of the studies reviewed. Treatment of recurrent herpetic lesions with phototherapy was found to be effective in reducing the size and edema of the outbreak, however was not statistically significant in reducing pain or reducing outbreak frequency (Carvalho et al., 2010). Adding to the efficacy of phototherapy treatment it was determined that with treatment of low-level light therapy reduced healing time by 48 hours (Dougal and Lee, 2013).

 When phototherapy is added to topical treatment of outbreaks, healing time and a reduction of symptoms has the potential to be further reduced. Hull et al. (2010) determined the significant reduction in the formation of ulcerative lesions when treatment of ME-609 cream was utilized on presentation of symptoms. Further influencing a positive effect of topical treatment on HSL symptoms (Khemis et al., 2011). Senti et al. (2012) also determined that the topical cream 2-HPBCD reduced the pain associated with relapses, although total outbreak time was not affected. These findings, although positive in terms of reducing the severity of symptoms, underscore a need to conduct further research that focuses on the reduction of time symptoms are present.

 Viral shedding in HSV-2 was shown to be significantly reduced, up to 97%, with the use of systemic oral antiviral medications (Fife et al., 2006) and Gupta et al.,2004). Furthermore, studies performed by Mark et al., (2007) and Khemis et al., (2014) strengthened the efficacy that topical treatment has on the reduction of viral shedding and symptoms severity with and without the use of oral antiviral medications. Studies performed by Tyring et al. (2012) and Wald et al. (2014) showed strong evidence of viral shedding reduction, symptom severity reduction, and shorter duration or reactivations. Viral shedding continues to take place in both active and latent GH patients despite the promising results of studies conducted on: topical, systemic, combination, and dosing therapies. These results emphasize the need to conduct further studies to determine whether viral shedding can be further reduced in addition to targeting more concrete avenues of prevention, vaccination or cure.

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**Appendix A**

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| **Author, Date, Title** | **Population, Demographics, Sample Size, Setting, Timing** | **Intervention** | **Comparative group/control** | **Outcome** | **Methodology/Type of study** | **Results** |
| Belshe, R., Leone, P., Bernstein, D., Wald, A., Levin, M., Stepleton, J., Gorfinkel, I., Morrow, R., Ewell, M., Stokes-Riner, A., Dubin, G., Heineman, T., Schulte, J., & Deal, C. (2012). | 8323 women ages 18-30 negative for HSV-1 or 2 from United States and Canada. | HSV vaccine vs. hepatitis A vaccine | HSV = 4,577 women vs. 3746 = Hep A vaccine. | Efficacy = 20% against genital herpes. Efficacy against HSV-1 genital disease = 58%. Efficacy against HSV 2 not observed. | Randomized, double-blind | Effective in prevention of HSV-1 genital (in multiple dose vaccination) but not in HSV-2 disease or infection. |
| Carvalho, R., Eduardo, F., Ramalho, K., Antunes, J., Bezinelli, L., Magalhães, M., Pegoretti, T., Freitas, P., & Eduardo, C. (2010). | 70 young adult patients (51 female 20 male) average age 28.8 from 03/’03 - 07/‘04. n=41 experimental, n=30 control.  | Phototherapy 10 sessions one per week vs topical acyclovir 5% cream 5 times a day with sings of infection | Phototherapy vs topical acyclovir | Experimental group - Size of herpes outbreak was less group P = 0.013, inflammatory edema was less P = 0.031, Pain levels were not significant P = 0.51 | Randomized clinical trial | Phototherapy does has a significant affect on decreasing the size of the recurrent herpetic lesion, along with decreased edema. More research into this treatment method needs to be conducted as a possible alternative treated. |
| Dougal, G., & Lee, S. (2013). | n = 87 total, n = 41 study group 7 men and 34 women with mean age of 40.2 (+ or - 12.9 years), n = 47 control grou 9 men and 37 women mean age 42.8 (+ or - 11.2 years), history of recurrent orofacial herpes with at least 3 episodes in previous year.  | 3 minute treatment three times daily for 2 days | Light treatment vs placebo | Healing time for treatment group was 129 hours compared to 177 for control. (P = 0.01) | Prospective, randomized, placebo-controlled, clinical trial | Low-level light therapy is effective in reducing healing time in herpes labials on the lips. |
| Fife, K., Warren, T., Ferrera, R., Young, D., Justus, S., Heitman, C., & Burroughs, S. (2006). | 134 patients, male & female, 18yrs or older, HSV-2 seropositive, immunocompetent, had 6+ episodes of GH/yr in absence of suppressive therapy  | Randomized to receive either 500mg Valacyclovir or matching film-coated placebo pill, genital & anal/rectal swabs collected x 60 days | Receiving film-coated placebo pill  | Reduction of viral shedding in patients with recurrent HSV-2 Genital Herpes with daily Valacyclovir | Randomized, Double-Blind, Placebo-controlled Clinical trial  | Valacyclovir significantly reduced total HSV-2 shedding when compared with placebo group |
| Gupta, R., Wald, A., Krantz, E., Selke, S., Warren, T., Vargas-Cortes, M., Miller, G., & Corey, L. (2004). | 69 immunocompetent patients with genital HSV-2 | Received oral Valacyclovir, Acyclovir and matching placebo each for 7 week periods & daily genital mucosal swabs | Valacyclovir Vs. Acyclovir Vs. Placebo results | Reduction in genital shedding treatment group vs valacyclovir P < 0.001 (97% reduction) and P < 0.001 (95% reduction) vs acyclovir.  | Randomized double-blind placebo-controlled, 3-period, crossover trial | Treatment with Valcyclovir or Acyclovir is effective in reducing subclinical and total HSV shedding. The frequency of both total and subclinical shedding decreased with antiviral therapy by 91%-97% (by culture) and 76%-82% (by PCR)  |
| Hull, C., Harmenberg, J., Arlander, E., Aoki, F., Bring, J., Darpo, B., Levin, M., & Spruance, S. (2010). | n = 1,443 treated with 1,398 completed. 07/’06 - 12/’07. U.S. & Canada at 51 sites. >18y.o. with history of HSL c/ >2 episodes in previous year. | Cream applied 5 times daily for 5 days at earliest sign of a cold sore. | ME-609 n = 582 completed 5% acyclovir n = 591 completed placebo n = 225 | Reduction in lesion development in treatment group P =0.14 versus acyclovir and P<.0001, Healing times were decreased with ME-609 and acyclovir P<.01 | Randomized, double-blind, active-and placebo-controlled study | ME-609 significantly prevents formation of ulcerative lesions with HSL when compared to acyclovir and placebo. |
| Johnston, C., Saracino, M., Kuntz, S., Magaret, A., Selke, S., Huang, M., Schiffer, J.T., Koelle, D.M., Corey, L., & Wald, A. (2012).  | n = 32 for trial 1, n = 31 for trial 2, n = 50 for trial 3. HSV-2 seropositive & HIV-seronegative health adults 18 years or older. Recurrence of HSV-2 at least 4 times in previous 6 months. | Standard dose of ascyclovir vs no meds, high dose acyclovir vs standard valacylovir, high dose valacyclovir vs standard dose valacyclovir. | Varying controls based on Trial #. | Trial 1: P< 0.001 Trial 2: P=0.052 Trial 3: P<0.001 | Complementary clinical studies | Standard- dose acyclovir more effective in reduction of HSV shedding compared to no medication, HSV detection was lower for high-dose acyclovir Vs. standard valacyclovir, Dose effect on HSV shedding was noted during high-dose valacyclovir compared to standard-dose valacyclovir |
| Khernis, A., Duteil, L., Coudert, A., Tillet, Y., Deueure, O., & Ortonne, J. (2011). | n = 106 (84 women and 22 men) with mean ago of 43 (+ or - 13 years) outpatients at hospital dermatology clinic with frequent recurring labial herpes in Nice, France. | Application of cream 5 times a day for 2 weeks | CS20 n = 35 (five men) Acyclovir n = 35 (nine men) Placebo n = 36 (eight men) | Reduction symptoms with treatment of CS20 versus placebo P = 0.012 after treatment day 1, P<0.0001 after day 7. | Prospective, randomized, single-centre, assessor-blinded study | CS20 decreases symptoms much quicker than topical acyclovir. |
| Khemis, A., Duteil, L.,Tillet, Y., Dereure, O., & Ortonne, J.P. (2014). | 61 patients, 18yrs or >, not on preventative treatment for GH, -HIV,-Hep B, & -Hep C |  application of gel/cream 5x/day from the onset of first symptoms to maximum of 15 days | CS 21 Barrier cream Vs.Topical acyclovir (Reference Treatment) Vs. Placebo Cream (Vehicle) | Efficacy of CS21 vs vehicle P = 0.013, vs. acyclovir P = 0.014. | Prospective randomized control three parallel groups clinical trial study  | CS 21 Gel significantly more efficient in reduction of functional symptoms/pain relief with GH, compared to reference treatment and placebo, Healing time was also reduced with CS 21 compared to placebo- however no difference in healing time when compared to reference treatment |
| Mark, K., Corey, L., Meng, T., Magaret, A., Huang, M., Selke, S., Slade, H., Tyring, S., Warren,T., Sacks,S., Leone, P., Bergland,V., & Wald, A. (2007). | 75 patients; 30 male patients 45 female patients with >4 but <12 GH recurrences, not currently on suppressive therapy and HIV - | Application of randomly assigned cream to herpes lesions 2x/week for 3 weeks, anogenital swabs collected daily for 60 days | Resiquimod cream Vs. Vehicle cream | Reduction of genital shedding rates after use of Resiquimod cream compared with Vehicle cream  | Randomized, Double-Blind, vehicle-controlled trial | Lesion and shedding rates were 2/3 lower with resiquimod compared to vehicle group however resiquimod did not influence recurrence length |
| Mujugira, A., Magaret, A. S., Celum, C., Baeten, J. M., Lingappa, J. R., Morrow, R. A., Fife, K.H., Delany-Moretlwe, S., Bruyn, G., Bukusi, E.A., Karita,E., Kapiga, S., Corey, L., & Wald, A. (2013). | 911 patients; Serodiscordant couples enrolled in the Partners in Prevention HSV/HIV transmission study  | Provided Daily acyclovir 400mg BID to the partner that is HIV+ HSV-2+ | Placebo group | HSV-2 seroconversoin P = .22 | Randomized Control Trial | Daily Suppressive therapy with acyclovir did not decrease the risk of HSV-2 transmission |
| Senti, G., Iannaccone, R., Graf, N., Felder, M., Tay, F., & Kundig, T. (2012). | n=40 (20 in each group) Placebo n=15, 2-HpBCD n=18 for efficacy. 73% women and 27% men to begin. 6/2009 - 11/2009, ages 18-50, experienced > 7 herpes labials relapses in previous year. | Apply cream to lips 2 times a day for 6 months. | 2-HPBCD vs. Placebo cream | Treatment group experienced higher herpes labials relapses than control p=0.003 | Randomized, Double-Blind, Placebo-Controlled study | 2-HPBCD is safe but not effective in reducing herpes labials relapses. Found to reduce pain associated with relapses. |
| Traen, S., Bochanen, N., Ieven, M., Schepens, T., Bruynseels, P., Verbrugghe, W., & Jorens, P. (2014). | n = 212 total Adult patients admitted for 10 or more days between 01/’04 - 03/’12 with + HSV-1 respiratory sample. | treatment group received acyclovir for 5 days or longer | n = 106 control n=106 treatment | Mortality reduction in hospital p=0.001 and p<0.001 for remainder of hospital | Retrospective review | Acyclovir use in HSV-1 in-hospital and ICU patients has a significant effect on reducing mortality |
| Tyring, S., Wald, A., Zadeikis, N., Dhadda, S., Takenouchi, K., & Rorig, R. (2012). | 695 adults; 18yrs or >, hx of HSV infection or + HSV ab test, > 4 episodes of GH w/in 1 yr, immunocompetent,  | Randomized into 6 groups: ASP2151(100,200,or 400md QD x3days), ASP2151(1200mg single dose), placebo for 3 days, or valacyclovir(500mg BID x3 days) | 6 group comparison with varying dosages of : ASP2151, Valacyclovir and Placebo | Reduction in healing times vary with dosage changes as follows: 100mg P=.065, 200mg P=.081, 400mg P=.25, 1200mg P=.007 | Phase II, double-blind, multicenter, randomized, active and placebo-controlled study | Three-day or single-day course of ASP2151 appear to be effective and safe options for treatment of episodes of recurrent genital herpes |
| Wald, A., Corey, L., Timmler, B., Margaret, A., Warren, T., Tyring, S., Johnston, C., Kriesel, J., Fife, K., Galitz, L., Stoelben, S., Huang, M., Selke, S., Stobernack, H., Ruebsamen-Schaeff, H., & Birkmann, A. (2014). | 156 patients; HSV-2 + with GH history | Randomly assigned to Pritelivir (5,25, or 75mg daily or 400mg weekly), or placebo for 28 days, daily genital swabs for HSV-2 shedding testing | 5 comparison group with varying dosages of Pritelivir or placebo | Treatment compared to placebo results: 5mg daily dose P=0.70, 25mg daily dose P=0.06, 75mg daily dose P<0.001, 400mg weekly dose P<0.001. | Randomized, parallel, double-blind, placebo-controlled study | Helicase-primase inhibitor(Pritelivir) significantly reduces the frequency of genital HSV shedding and lesions. The effect was dose-related, with a daily dose of 75mg having the greatest antiviral effect. Moreover, reduced the quantity of HSV in breakthrough shedding by more than 98% Coincidental finding: significant reductions in # of days of genital lesions at the 75mg & 400mg dosages |