Drug Use Research & Management Program
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Month/Year of Review: November 2013
PDL Classes: Oral Antivirals HSV

Date of Last Review: January 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: ACYCLOVIR TABLET, SUSPENSION, & CAPSULE
- Non-Preferred Agents: VALACYCLOIR, FAMCICLOVIR, ACYCLOVIR CREAM & OINTMENT (ZOVIRAX®), PENCICLOVIR TOPICAL (DENAVIR®), DOCOSANOL TOPICAL (ABREVA®)

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend including one or more agents from this category

PA Criteria: Prior authorization criteria are currently in place for non-preferred herpes simplex oral and topical antivirals to cover only for covered diagnoses and for medically appropriate conditions (Appendix 1). Patient must have an ICD9 diagnosis for uncomplicated herpes simplex AND documentation of a disease state or medication that causes immunosuppression.

Conclusions and Recommendations:

- No further review or research needed at this time

Methods:

A Medline OVID search was conducted with the following search terms: acute retinal necrosis, Bell's palsy, cytomegalovirus disease, herpes simplex, varicella, herpes genitalis, herpes labialis, herpes zoster, herpes ocular, HSV, antiviral, acyclovir, Zovirax, famciclovir, ganciclovir, valacyclovir, valganciclovir, penciclovir, docosanol. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to September week two 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

The Cochrane Collaboration performed a 2013 systematic review and meta-analysis to compare HSV antivirals efficacy in the treatment of cytomegalovirus (CMV). Trials (N=37) were included if they examined the efficacy of treatment of, or prophylaxis for, CMV with antivirals in subjects who had undergone a solid organ transplant. The primary endpoints were incidence of CMV and all-cause mortality. All studied antivirals significantly reduced the risk for CMV disease compared with placebo or no treatment: acyclovir (6 studies, n= 421) RR 0.45, 95% CI 0.29 to 0.69; ganciclovir (11 studies, n=917) RR 0.44, 95% CI 0.34 to 0.58; and valacyclovir (2 studies, n=643) RR 0.30, 95% CI 0.19 to 0.49. In head-to-head studies, ganciclovir was more effective than acyclovir in preventing CMV disease in all recipients (7 studies, n=1113): RR 0.37, 95% CI 0.23 to 0.60. There were no significant differences between the two in the risk of death due to CMV disease or all-cause mortality. Valacyclovir was compared with ganciclovir or valganciclovir in three studies (n=171) but no significant difference was seen in incidence of CMV or all-cause mortality. Individual trial quality was assessed for

selection bias (allocation concealment and randomization), performance bias and detection bias (blinding), attrition bias (incomplete outcomes) and reporting bias (selective reporting). Overall quality of the included trials was rated as low to moderate with poor ratings in performance, detection and selective bias.[1]

Guidelines:

In 2012, the American Academy of Family Physicians also updated their guidelines for the treatment of sexually transmitted genital herpes in adults.[2]

- Oral acyclovir (Zovirax), valacyclovir (Valtrex), and famciclovir (Famvir) are effective treatments for initial or recurrent episodes of genital HSV by decreasing symptom duration and viral shedding. Grade A recommendation
- In patients with symptomatic HSV outbreaks, daily acyclovir or valacyclovir should be considered to reduce transmission to seronegative partners. Famciclovir is less effective for reducing viral shedding and HSV transmission. Grade B recommendation

The American Academy of Neurology updated it's guidelines for the treatment of Bell's palsy in 2012. Recommendations were stratified by the level of evidence and strength of recommendation. Evidence was classified as the following: level I evidence generated from prospective, blinded, randomized, controlled clinical trials; level II evidence from prospective matched group cohort studies or a lesser quality RCT; level III evidence is derived from all other controlled trials; and lastly, level IV evidence is from uncontrolled studies, case series, case reports, or expert opinion. Strength of recommendation grading is built upon the level of evidence used and classified as either grade A, B, C, or U. Grade A recommendations are established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population, and requires at least two consistent Class I studies. Grade B recommendations are considered as probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population and requires at least one Class I study or two consistent Class II studies. Grade C recommendations are considered possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population and requires at least one Class II study or two consistent Class III studies. Lastly, grade U recommendations are derived from data established to be either inadequate or conflicting and that, given current knowledge, the treatment is unproven.[3]

- For patients with new-onset Bell's palsy, oral steroids should be offered to increase the probability of recovery of facial nerve function. Level A recommendation
- For patients with new-onset Bell palsy, antivirals (in addition to steroids) might be offered to increase the probability of recovery of facial function. Patients offered antivirals should be counseled that a benefit from antivirals has not been established, and, if there is a benefit, it is likely that it is modest at best. Level C recommendation

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 207 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

Perti et al compared effectiveness of valacyclovir and acyclovir in patients coinfected with genital herpes and HIV in an open label crossover trial. Patients with HIV (n=28) but not yet started on antiretroviral therapy were randomized to receive either valacyclovir 1000 mg twice daily or acyclovir 400 mg twice daily for twelve weeks. After twelve weeks patients had a two weeks wash-out period with no medication. They were then started on the alternative regimen for an additional twelve weeks. Primary outcomes were difference in HSV-2 shedding rate and decease in plasma HIV RNA. There was no statistical difference between valacyclovir and acyclovir in rate of HSV-2 viral shedding (7.8% vs. 8.2%; RR 0.95; 95% CI 0.66 to 1.37). Valacyclovir patients had a significantly lower amount of plasma HIV-1 RNA (0.27 $\log^{10}$ copies/mL difference) after treatment than acyclovir patients (95% CI: 20.41 to 20.14 $\log^{10}$ copies/mL). This was poor quality trial with many opportunities for bias due to the study design (open label, cross-over). In addition, the doses given to the patients were not equivalent: valacyclovir subjects were given a high dose regimen, while acyclovir members were given a normal suppressive dose regimen.[4]

Johnston et al conducted a series of three open label crossover trials to determine the effectiveness of different regimens in suppressing genital herpes outbreaks. Subjects with HSV-2 were randomized to receive either standard dose acyclovir (400 mg twice daily) or placebo in the first study (n=32) for four weeks on each medication. Subjects (n=31) were placed on standard dose valacyclovir (500 mg daily) or high dose acyclovir (800 mg three times daily) in the second study for seven weeks each. In the final study (n=50), subjects were randomized to five weeks on either standard dose valacyclovir or high dose valacyclovir (1000 mg twice daily). All three crossover studies had a two week washout period between regimens. The primary outcome was absence of genital HSV viral shedding. Both doses of acyclovir reduced the detection of HSV compared with the no medication cohort (both: $p \leq 0.003$). Subjects on high dose acyclovir had a lower incidence of HSV shedding than those on standard dose valacyclovir (4.2% vs 4.5%; incidence risk ratio [IRR] 0.79; 95% CI 0.63 to 1.00). High dose valacyclovir subjects also had less viral shedding than those on standard dose valacyclovir (3.3% vs. 5.8%; IRR 0.54; 95% CI 0.44 to 0.66). This was a poor quality study with many serious flaws. All three studies were open label; randomization procedures were not described. Subjects were responsible for collecting the swabs used for the primary outcome, and there was up to 3 days lag time before the swabs were delivered to the study administrators. Finally, although the participants were different individuals and the trial lengths each varied, the data from all three studies was pooled, compared and presented in one paper.[5]

References:
1. Hodson EM, Ladhani M, Webster AC, Strippoli GF, Craig JC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. In: The Cochrane Collaboration, Hodson EM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013. Available at: http://doi.wiley.com/10.1002/14651858.CD003774.pub4. Accessed September 30, 2013.

2. Roett MA, Mayor MT, Uduhiri KA. Diagnosis and management of genital ulcers. *Am Fam Physician*. 2012;85(3):254–262.

3. Gronseth GS, Paduga R. Evidence-based guideline update: Steroids and antivirals for Bell palsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2012;79(22):2209–2213. doi:10.1212/WNL.0b013e318275978c.

4. Perti T, Saracino M, Baeten JM, et al. High-Dose Valacyclovir Decreases Plasma HIV-1 RNA More Than Standard-Dose Acyclovir in Persons Coinfected with HIV-1 and HSV-2: A Randomized Crossover Trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2013;63(2):201–208. doi:10.1097/QAI.0b013e3182928eea.

5. Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. *The Lancet*. 2012;379(9816):641–647. doi:10.1016/S0140-6736(11)61750-9.

Appendix 1: Current PA Criteria

Antivirals, Oral and Topical – HSV

Goal(s): Cover oral and/or topical anti-virals only for covered diagnoses. HSV infections are covered only when complicated by an immunocompromised host.

Antivirals **Length of Authorization: Criteria Specific – up to 1 year**

Preferred Alternatives: **Oral** acyclovir DOES NOT require PA. See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.

Requires PA: HIC3 = Q5V

GENERIC	BRAND	ROUTE
Famciclovir	Famvir	Oral
Valacyclovir	Valtrex	Oral
Acyclovir	Zovirax	Topical
Penciclovir	Denavir	Topical
Docosanol	Abreva	Topical

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD9 code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml.	**No**: Go to #3
3. Is the diagnosis uncomplicated herpes simplex ICD9: 054.2, 054.6, 054.73, 054.9?	**Yes:** Go to #4	**No:** Pass to RPh; Go to #7
4. Is the patient immune compromised? Document ICD9 code. • Current (not history of) diagnosis of cancer AND is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment • Diagnosis of HIV/AIDS?	**Yes:** Approve for the shorter of expected therapy duration or90 days (applies to both topical and oral antivirals) (Immunocompromised Client)	**No:** Go to #5

<table>
<tr>
<td>5. Is client currently taking an immunosuppressive drug? Document drug:

(If drug not in list below, Pass to RPh for evaluation)

Immunosuppressive drugs include, but are not limited to:
<table>
<tr><th>Generic Names</th><th>Brand Names</th></tr>
<tr><td>Azathioprine
Basiliximab
Cyclosporine

Sirolimus
Tacrolimus
Methotrexate
Hydroxychloroquine
Etanercept
Leflunomide</td><td>Imuran
Simulect
Sandimmune,
Neoral
Rapamune
Prograf
Rheumatrex
Plaquenil
Enbrel
Arava</td></tr>
</table>
</td>
<td>Yes: Approve for the shorter of expected therapy duration or: 90 days (applies to topical or oral antivirals ; Immunocompromised Client).</td>
<td>No: If Diabetes or Sickle-Cell disease-go to #6. All others go to #7.</td>
</tr>
<tr>
<td>6. Does client have Diabetes or Sickle-Cell disease?

Note: Diabetes and Sickle-Cell is not considered as immunocompromisng for antivirals as it is for antifungal</td>
<td>Yes: Pass to RPH; Deny, (Not Covered by the OHP).</td>
<td>No: Pass to RPH to evaluate for immunosuppression.

➢ If not immunocompromised, Deny (Not Covered by the OHP).

➢ If immunocompromised, approve for 1 year.</td>
</tr>
<tr>
<td>7. RPH only
All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.

• <u>If above,</u> viral diagnoses can be approved for treatment course with “prn” renewals. If length of therapy is unknown, please approve for 3 months intervals only (This is an exception to above guidelines and should be discussed with Lead Pharmacist)

• <u>If below,</u> Deny, (Not Covered by the OHP).

• <u>Deny Non-viral diagnoses</u> (Medical Appropriateness).

• <u>Deny Viral ICD-9 codes</u> that do not appear on the OHP list pending a more specific diagnosis code. (Not Covered by the OHP)</td>
<td>If above the line and clinic provides supporting literature: approve for length of treatment.</td>
<td>If below the line: Deny, (Not Covered by the OHP).</td>
</tr>
</table>

Appendix 2: Abstracts of Randomized Control Trials

Perti T, Saracino M, Baeten JM, et al. High-Dose Valacyclovir Decreases Plasma HIV-1 RNA More Than Standard-Dose Acyclovir in Persons Coinfected with HIV-1 and HSV-2: A Randomized Crossover Trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2013;63(2):201–208. doi:10.1097/QAI.0b013e3182928eea.

Background: Standard doses of herpes simplex virus (HSV) suppressive therapy reduce plasma HIV-1 RNA levels (0.25–0.53 log10 copies per milliliter) among HIV-1/HSV-2 coinfected persons. Postulated mechanisms for this effect include direct inhibition of HIV-1 by acyclovir or indirect reduction by decreasing HSV-associated inflammation. We hypothesized that high-dose valacyclovir would further reduce plasma HIV-1 RNA and that the effect would be mediated by greater suppression of HSV shedding.

Methods: Thirty-four participants with HIV-1 and HSV-2 not on antiretroviral therapy were enrolled into a randomized, open-label crossover trial of valacyclovir 1000 mg twice daily or acyclovir 400 mg twice daily for 12 weeks, followed by a 2-week washout, and then the alternate treatment arm for 12 weeks. HSV DNA was measured from daily self-collected genital swabs for the initial 4 weeks of each arm, and HIV-1 RNA was quantified from weekly plasma samples.

Results: Twenty-eight participants provided plasma samples and genital swabs on both acyclovir and valacyclovir. The genital HSV-2 shedding rate was the same on valacyclovir and acyclovir [7.8% vs. 8.2% of days; relative risk: 0.95; 95% confidence interval (CI): 0.66 to 1.37; P = 0.78]. Plasma HIV-1 RNA was 0.27 log10 copies per milliliter lower on valacyclovir compared with acyclovir (95% CI: 20.41 to 20.14 log10 copies per milliliter; P , 0.001); this was unchanged after adjustment for genital HSV-2 shedding.

Conclusions: High-dose valacyclovir reduces plasma HIV-1 RNA levels more than standard-dose acyclovir in HIV-1/HSV-2–seropositive persons not receiving antiretroviral therapy. The incremental reduction in plasma HIV-1 RNA achieved is not mediated by greater genital HSV-2 suppression.

Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. *The Lancet*. 2012;379(9816):641–647. doi:10.1016/S0140-6736(11)61750-9.

Background—Recent studies indicate that short subclinical episodes of herpes simplex virus type 2 (HSV-2) are the predominant form of skin and mucosal viral shedding. We evaluated whether standard or high-dose antiviral therapy reduced the frequency of such shedding.

Methods—To determine whether short episodes of genital HSV shedding are suppressed on standard dose (SD) and high-dose (HD) antiviral therapy, HSV-2 seropositive, HIV seronegative persons in Seattle, WA were enrolled into three separate but complementary randomized, open label, cross-over studies comparing 1) no medication to aciclovir 400 mg twice daily (SD-ACV), 2) valaciclovir 500 mg daily (SD-VAL) to aciclovir 800 mg three times daily (TID) (HD-ACV), and 3) SD-VAL to HD-VAL (1 gm TID). Study arms lasted 4–7 weeks, separated by one week wash-out. Participants obtained genital swabs four times daily for quantitative HSV DNA PCR. The primary endpoint was within-person comparison of shedding rate on each study arm.

Results—Of 113 participants randomized, 90 were eligible for analysis of the primary endpoint. Participants collected 23,605 swabs; of these 1272 (5・4%) had HSV detected. HSV shedding was significantly higher during the no medication arm (18・1% of swabs) compared with SD-ACV (1.2% of swabs, IRR=0・05, 95% CI=0・03–0・08). Breakthrough reactivations occurred on all doses (SD-ACV 1・2%, SD-VAL 5・2%, HD-ACV 4・2%, and HD-VAL 3・3% of swabs). HD-VAL was associated with less shedding compared with SD-VAL (IRR=0・54, 95% CI=0・44–0・66), likely due to more rapid clearance of mucosal HSV (4・7 logs/6 hours on HD-VAL vs. 4・4 logs/6 hours on SD-VAL, (p=0・02)). However, the annualized breakthrough episodes was similar on SD-VAL (22・6) and HD-ACV (20・2, p=0・54) and SD-VAL (14.9) and HD-VAL (16・5, p=0・34). Regardless of dose, breakthrough episodes were short (median 7–10 hours) and 80% were subclinical. Studies were not designed to make inter-trial comparisons between antiviral doses. Except for increased incidence of headaches on HD-VAL, all regimens were well-tolerated.

Conclusions—Short bursts of subclinical genital HSV reactivation are frequent, even during high-dose antiherpes therapy, and likely account for continued transmission of HSV-2 during suppressive antiviral therapy. More potent antiviral therapy is needed to abolish HSV-2 transmission