CDC Treatment guidelines TABLES OF EVIDENCE

TREATMENT OF HSV

Citation	Study Design	Study Pop Type/ Setting	Exposure/ Intervention	Outcomes Measures	Reported Findings	Design Analysis Quality/ Biases
Bodsworth et al	RCT	Healthy adults with recurrent genital herpes n=873	2-day course of famciclovir 500 mg statim, then 250 mg twice daily versus 5-day course of 125 mg twice daily	Non-inferiority of famciclovir for recurrent genital lesions	The 2-day course was as safe and effective as the standard 5-day course. The proportion of evaluable recurrences with lesions present at 5.5 days was less in the 2-day arm (24%) than in the 5-day (28%) arm.	
Abudalu et al	RCT, double-blind	Healthy adults with recurrent genital herpes n=751	Famciclovir 1000mg bid for 1-day versus valacyclovir 500mg bid for 3-days	Time to healing of all nonaborted genital herpes lesions	Median time to healing: 4.25 days famciclovir vs. 4.08 days valacyclovir. HR=1.08 (95% CI, 0.88–1.32), P=.48	
Wald et al	RCT, double-blind	Healthy adults with recurrent genital herpes Study 1 n=320 Study 2 n=70	famciclovir 250 mg bid vs oral valacyclovir 500 mg q am	Study 1: proportion of patients who had a clinically confirmed recurrence. Study 2: proportion of days with HSV detected by PCR	Study 1: time to first recurrence was similar in famciclovir and valacyclovir recipients, hazard ratio (HR) 1.17 (95% CI, 0.78 –1.76). Time to first virologically confirmed recurrence was shorter among famciclovir recipients, HR 2.15 (95% CI, 1.00–4.60). Study 2, HSV was detected on 3.2% of days among famciclovir recipients and 1.3% of days among valacyclovir recipients, RR 2.33 (95% CI, 1.18–4.89).	Not able to analyze monthly frequency of recurrent episodes or the frequency of days with lesions during the observation period.

ACYCLOVIR-RESISTANT HSV

Citation	Study Design	Study Pop Type/ Setting	Outcomes Measures	Reported Findings	Design Analysis Quality/ Biases
Erard et al	Retrospective cohort	VZV- and HSV-seropositive autologous and allogeneic HCT recipients; 3 cohorts n=2049	Effect of 2 long-term regimens of ACV, sequentially introduced to prevent varicella-zoster virus (VZV)–reactivation after HCT on the incidence of ACV-resistant HSV.	ACV-resistant HSV disease developed in 10 patients in a cohort who received suppressive ACV for 30-days followed by episodic therapy (2-year probability, 1.3% [95% CI, 0.8%–2.7%]); in 2 patients in a cohort who received ACV for 1 year (2-year probability, 0.2% [95% CI, 0%–0.8%]; P=0.006), and in 0 patients in a cohort who used antivirals for over a year (cohort 2 vs. cohort 3, P=0.3).	Episodic rather than suppressive therapy will lead to emergence of acyclovir resistance in immunocompromised patients
Martinez et al	Case report	Treatment with topical imiquimod in 2 immunocompromised patients with mucocutaneous HSV Unresponsive to either ACV, FCV or CDV. n=2	Adverse events, lesion healing, and lesion recurrence	topical 5% imiquimod cream was successfully used in 2 immunocompromised patients who presented with chronical HSV infections resistant to oral and parenteral therapy with antiviral agents.	Clinical experience is limited, and further studies are needed.

PREVENTION OF HSV

Citation	Study Design	Study Pop Type/ Setting	Exposure/ Intervention	Outcomes Measures	Reported Findings	Design Analysis Quality/ Biases
Kim et al	Secondary analysis of an RCT	Heterosexual couples in monogamous relationships who were serodiscordant for HSV-2. n=1484	valacyclovir 500 mg qd versus placebo	Severity of HSV-2 in source partner as a predictor of transmission to sex partner	The rate of recurrences per year before study entry did not differ between source partners who transmitted and those who did not, 4.8 versus 5.1, respectively. The mean frequency of recurrences observed during the study also did not differ among those who transmitted versus those who did not for placebo recipients (4.4 vs. 4.8) or valacyclovir recipients (1.4 vs. 1.3).	
Wald et al	Retrospective cohort	Persons with laboratory-documented newly acquired genital herpes n=199	Effect of knowledge of having genital herpes	Time to acquisition of genital herpes	The median time to HSV-2 acquisition was greater among participants whose partners disclosed that they had genital herpes, compared with participants whose partners did not disclose their status (270 vs. 60 days;p=0.03). In multivariate models, having a partner who disclosed that he or she had genital herpes was protective against genital HSV-2 acquisition (HR, 0.48 [95% CI, 0.25–0.91]).	Condom use was not protective in this study – was also used infrequently
Tobin et al	RCT	HIV-negative, uncircumcised men between the ages of 15 and 49 n=5534	Circumcision	Time to the detection of HSV-2	At 24 months, the probability of HSV-2 seroconversion was 7.8% in the intervention group vs. 10.3% in the control group (adjusted HR in the intervention group, 0.72; 95% CI, 0.56 to 0.92; P=0.008).	Adult circumcision is rare in US
Mujugira et al	RCT	911 HSV-2 & HIV-1 discordant couples in sSA.	Acyclovir 400 mg bid	HSV-2 seroconversion	No difference in HSV-2 transmission from acyclovir vs. placebo treated index partners, HR=1.35 (95%CI 0.83-2.20, p=0.22).	Unprotected sex, vaginal drying, and fewer children were also risk factors for HSV-2 for women.

HSV AND HIV

Citation	Study Design	Study Pop Type/ Setting	Exposure/ Intervention	Outcomes Measures	Reported Findings	Design Analysis Quality/ Biases
Couppie et al	Retrospective cohort study	HIV-infected patients in a French Guiana hospital n=1551	Antiretroviral therapy	Incidence of genital herpes in patients receiving HAART compared to patients not on HAART	Patients receiving HAART for < 6 months had a higher risk of developing genital herpes compared to untreated patients. HAART <2 months HR 4.5, P=<0.0001 HAART 2-4 months, HR 4, P=<0.0001 HAART 4-6 months, HR 3, P=0.02	
Watson-Jones et al	RCT, double-blind	Women aged 18-35 involved in sex work who were HIV-seronegative and HSV-2–seropositive n=821	Acyclovir (400 mg twice daily) for 12-30 months	HIV-1 acquisition	The incidence of HIV infection was 4.27 per 100 person-years (27 participants in the acyclovir group and 28 in the placebo group), (rate ratio for the acyclovir group, 1.08; 95% CI, 0.64 to 1.83).	Median adherence according to counting of tablets was 90% although this was challenging to measure
Celum et al	RCT, double-blind	HIV-negative, HSV-2 seropositive women in Africa (n=679) and men who have sex with men (MSM) from sites in Peru and the USA (n=902)	Twice daily acyclovir 400 mg versus placebo for 12–18 months	HIV-1 acquisition	HIV-1 incidence was 3.9 per 100 person-years in the acyclovir group and 3.3 per 100 person-years in the placebo group (HR 1.16 [95% CI 0.83–1.62])	Large study among an international population.
Nagot et al	RCT, double-blind	Women who were infected with HIV-1 and HSV-2. n=136	500 mg of valacyclovir twice daily for 3 months vs placebo	Genital and plasma HIV-1 RNA levels by treatment arm	Valacyclovir therapy significantly decreased the frequency of genital HIV-1 RNA (OR, 0.41; 95% CI, 0.21 to 0.80) and the quantity of HIV (log_{10} copies/ml − 0.29; 95% CI, − 0.44 to − 0.15) and reduced the plasma HIV-1 RNA by 0.53 log_{10} copy/ml (95% CI, − 0.72 to − 0.35)	No evidence that the effect waned over time
Zuckerman et al	RCT, double-blind	ART–naive HIV-1/HSV-2–seropositive men who have sex with men in Lima, Peru n=20	valacyclovir 500 mg twice daily or placebo for 8 weeks, 2-week washout period, and then received the alternative regimen for 8 weeks	Rectal and plasma HIV-1 RNA levels by treatment arm	Valacyclovir resulted in a 0.16 (95% CI, 0.07–0.25; P=0.0008, 33% decrease) log_{10} copies/mL lower mean within subject rectal HIV-1 level and a 0.33 (95% CI, 0.23–0.42;P<0.0001; 53% decrease) log_{10} copies/mL lower plasma HIV-1 level.	Effect somewhat greater at higher CD4 count

HSV, HIV, AND PREGNANCY

Citation	Study Design	Study Pop Type/ Setting	Exposure/ Intervention	Outcomes Measures	Reported Findings	Design Analysis Quality/ Biases
Bollen et al	Secondary analysis of women who participated in a randomized perinatal HIV transmission trial in Thailand	Women participating in a clinical trial to assess the efficacy of short-course zidovudine for the prevention of perinatal HIV transmission. n=307	HSV-2 seropositivity and genital HSV-2 shedding	Overall and intrapartum perinatal HIV transmission.	228 (74.3%) were HSV-2 seropositive and 24 (7.8%) were shedding HSV-2. HSV-2 seropositivity was associated with ↑ overall perinatal HIV transmission [aOR, 2.6; 95% CI, 1.0–6.7)]. HSV-2 shedding was associated with ↑ intrapartum transmission (aOR, 2.9; 95% CI, 1.0–8.5). Median plasma HIV viral load was higher among HSV-2 shedders (4.2 vs. 4.1 log_{10}copies/ml; P=0.05).	The assessment of HSV-2 shedding was done at 38 weeks of gestation rather than at delivery.
Drake et al	Nested case control study within a perinatal cohort in Nairobi, Kenya	Case mother-infant pairs defined if infants acquired HIV-1 between birth and month 1; Control mother-infant pairs defined as infants not HIV-1 infected by 1 month postpartum n=175	HSV-2 seropositivity, HSV shedding and GUD	Increased risk of intrapartum HIV-1 transmission	152/175 (87%) mothers were HSV-2-seropositive. Among those, 9 (6%) had GUD at 32 weeks of gestation, and 13 (9%) were shedding HSV in cervical secretions. 31 intrapartum transmission occurred. Genital ulcers were associated with increased plasma HIV-1 RNA levels (P=.02) and an increased risk of intrapartum HIV-1 transmission (16% of transmitters versus 3% of nontransmitters had ulcers; P =.003)	The number of women who transmitted HIV-1 intrapartum was small.
Chen et al	Retrospective review of a Multicenter prospective study	HIV-infected pregnant women n=463	Clinical diagnosis of genital herpes during pregnancy	Risk of perinatal HIV transmission women clinically diagnosed with genital herpes during pregnancy.	46 (11.4%) study participants delivered HIV-infected infants. 21 (5.2%) had clinical diagnosis of genital HSV infection in pregnancy. Women with clinical diagnosis of genital herpes during pregnancy had a significantly increased risk of perinatal HIV transmission (aOR 4.8, 95% CI, 1.3–17.0; *P* = .02).	Misclassification as many women without clinically evident genital herpes also were HSV-2 seropositive, most likely
Chen et al	Nested case-control study	Women who transmitted HIV-1 to their infants (n=26) and control subjects who did not (n=52).	HSV-2 infection as measured by antibody status and HSV shedding	Perinatal HIV infection	65 women (83.3%) were found to be HSV-2 seropositive. 19/26 cases (73.1%) were HSV-2 seropositive. No association between HSV-2 coinfection in the antepartum period and risk of perinatal HIV-1 transmission (OR, 0.4;95% CI, 0.02-10.0; *P* = 1.0).	Women who did not transmit were more likely to be on ART and have lower plasma HIV and higher CD4 count

HSV IN PREGNANCY

Citation	Study Design	Study Pop Type/ Setting	Exposure/ Intervention	Outcomes Measures & Reported Findings
Gardella et al	Prospective cohort	Pregnant women and their partners N=315	HSV serologic testing for partner of HSV-2 seronegative pregnant women	To estimate the acceptance of HSV testing partners of HSV seronegative pregnant women. 77% of partners agreed to testing. Couples who were married or living as married were more likely to be tested than those who were not living together (aOR 7.72, 95% CI: 2.47,24.15).
Gardella et al	Prospective cohort	Pregnant women and their partners N=264	HSV serologic testing for partner of HSV-2 seronegative pregnant women	Primary outcome was the frequency of unprotected sex acts among women who knew that their partner had HSV-2 infection. 33 HSV-1 susceptible and 10 HSV-2 susceptible women. Percent of observed days on which vaginal sex occurred did not differ between those at risk (9%) and those not at risk for HSV-2 (10.6%, RR 0.79, 95% CI: 0.41-1.50, p=0.47). Women at risk for HSV-2 had lower rates of unprotected vaginal sex than those whose partners were HSV-2 seronegative: 2.9% vs. 9.6%, risk ratio 0.25 (95% CI 0.08-0.8, p=0.019).
Pinniiti et al	Case series	Multicenter referrals	Antiviral therapy at the end of pregnancy	8 infants with neonatal HSV whose mothers were treated with valacyclovir or acyclovir in 3rd trimester: 5 women were treated till delivery