VIRAL SEXUALLY TRANSMITTED DISEASES

Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – November 2023

To the CHI Original Viral Sexually Transmitted Diseases- Issued December 2019

Contents

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AIDS	Acquired Immunodeficiency Syndrome
Anti-HBc	Antibodies to Hepatitis B Core Antigen
Anti-HBs	Antibodies to Hepatitis B Surface Antigen
ART	Antiretroviral Therapy
BCA	Bichloroacetic Acid
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
CHI	Council of Health Insurance
CNS	Central Nervous System
CPG	Clinical Practice Guideline
DNA	Deoxyribonucleic Acid
EMA	European Medicines Agency
ETV	Entecavir
FDA	Food and Drug Administration
FTC	Emtricitabine
GR	Grade of Recommendation
GUD	Genital Ulcer Disease
HAS	Haute Autorité de Santé (French National Authority for Health)
HbeAg	Hepatitis B e Antigen
HBIG	Hepatitis B Immune Globulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HepB	Hepatitis B
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High-Grade Squamous Intraepithelial Lesion
HSV	Herpes Simplex Virus
HTA	Health Technology Assessment

IDF	CHI Drug Formulary
IM	Intramuscular
INR	International Normalized Ratio
IQWIG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen in German)
IS	Immunosuppressive
IUD	Intrauterine Device
IV	Intravenous
LAM	Lamivudine
LE	Levels of Evidence
LFT	Liver Function Test
Mo	Months
MSM	Men Who Have Sex with Men
N/A	Not Applicable
NICE	National Institute for Health and Care Excellence
OTC	Over-the-Counter
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase Chain Reaction
PE	Post-Exposure Prophylaxis
PEP	Post-Exposure Prophylaxis
PO	Per Os
PrEP	Pre-Exposure Prophylaxis
SFDA	Saudi Food and Drug Authority
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TAF	Tenofovir Alafenamide
TCA	Trichloroacetic Acid
TDF	Tenofovir Disoproxil Fumarate

Executive Summary

Sexually transmitted diseases or infections (STDs/STIs) fall into two categories: viral and bacterial. While the virus persists in the body indefinitely, its symptoms may not be constantly apparent[1].

Sexually transmitted viral infections include human papillomavirus (HPV), herpes (herpes simplex virus or HSV), human immunodeficiency virus (HIV), and hepatitis B[2]. Other viruses that can also be transmitted sexually, although with less efficiency and hence not classified as STIs, include hepatitis C virus, Molluscum contagiosum virus, and moneybox virus.

HPV can cause cauliflower-like warts on the skin or genitals, and precancerous cellular changes of the cervix or anus[3]. A first-time outbreak of herpes usually involves a painful eruption of multiple small blisters called vesicles, sometimes accompanied by a fever or swollen lymph nodes. Subsequent outbreaks tend to be less dramatic, with one or more painful lesions preceded by an itchy or tingling sensation at the blister eruption site[4].

Many hepatitis B infected patients are asymptomatic after acute infection. Some patients, however, may present with acute liver failure with jaundice, abdominal pain, dark urine, nausea, and vomiting[5]. Chronic hepatitis B, which is defined as persistence of hepatitis B surface antigen (HBsAg) for 6 months or more after acute infection, will lead eventually to liver cirrhosis.

HIV has different stages and varying presentations (for additional information, please refer to “Human Immunodeficiency (HIV)” indication report).

STDs/STIs can affect the oral, genital, and anal regions of the body. While a few of these infections can be transmitted through direct skin-to-skin contact, the primary mode of transmission for STDs/STIs is through engaging in oral, vaginal, or anal sexual activity with an infected partner. Additionally, some STDs/STIs can be passed from an infected mother to her child during the childbirth process[1].

Whether an infection is viral or bacterial, the infection can have long-term effects on the body, such as infertility or sterility, and can leave the body vulnerable to more serious diseases, such as HIV. Ultimately, untreated STDs/STIs can affect numerous organ systems in the body[1].

Vaccinations, routine testing, and screening for STDs/STIs, HIV, hepatitis B and hepatitis C through a health care provider is critical for treatment and prevention of complications[1]. STDs/STIs are preventable through abstinence from oral, vaginal, and anal sex or through the proper and consistent use of a latex or polyurethane condom during every sexual encounter. Birth control methods like the pill, patch, ring, and IUD are very effective at preventing pregnancy, but they do not protect against STDs and HIV[1].

More than 1 million sexually transmitted infections (STIs) are acquired every day worldwide, the majority of which are asymptomatic[2]. The average annual incidence of STIs per 100,000 population for Saudis and non-Saudis, respectively, was as follows: 0.6 and 8.0 for HIV, 1.4 and 0.7 for genital warts, 0.1 and 0.4 for genital herpes[6].

In 2018, STIs acquired that year cost the American healthcare system nearly $16 billion in direct medical costs alone (in 2018 dollars)[7].

The mainstay of treatment for STDs involves antiviral medications targeting the causable virus. These medications can help manage symptoms and reduce the transmission of some viral STDs, however, they do not always eliminate the virus from the body entirely.

CHI issued Viral Sexually Transmitted Diseases (STDs) clinical guidance after thorough review of renowned international and national clinical guidelines in December 2019. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Viral Sexually Transmitted Diseases clinical guidance and seeks to offer guidance for the effective management of Viral STDs. It provides an **update on the Viral STDs Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being the issuance of **updated versions of previously reviewed guidelines** namely the CDC Sexually Transmitted Diseases Treatment Guidelines **(2021)**, and the WHO guidelines for the management of symptomatic sexually transmitted infections **(2021). New guidelines** were also added to the report: the ACOG practice bulletin on the management of genital herpes in pregnancy **(2020)**, the Australian guidelines for anogenital warts **(2022),** the Australian guidelines for genital herpes **(2022)**, a review article on the treatment and prevention of acute hepatitis B virus **(2021),** and the Chinese Medical Association guidelines for prevention and treatment of chronic hepatitis B **(2021).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that there have been **no withdrawals** for the treatment of Viral STDs, however, there have been **newly approved drugs** for the treatment of Viral STDs such as Hepatitis B Immunoglobulin (Hepatect CP® or HepaGam B®). Additionally, there have been **updates** regarding certain previously mentioned drugs in terms of drug information and prescribing edits since December 2019.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in

all tables reflecting specific drug classes' role in the therapeutic management of Viral STDs.

Below is a table summarizing the major changes based on the different Viral STDs treatment guidelines used to issue this report:

Table 1. General Recommendations for the Management of Viral STDs

Management of Viral STDs		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The first-line options for genital herpes are the three FDA-approved antiviral medications: acyclovir, valacyclovir, and famciclovir. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged.	Not graded	CDC Guidelines 2021[8]
Intravenous (IV) acyclovir therapy (5–10 mg/kg body weight IV every 8 hours) should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningitis or encephalitis). IV therapy should be considered until clinical improvement followed by oral antiviral therapy to complete >10 days of total therapy. Longer duration is recommended for CNS complications. Oral antiviral therapy with valacyclovir 1 g 3 times/day, to complete a 10- to 14-day course of total therapy, is recommended.	Not graded	CDC Guidelines 2021[8]
For patients with previous episodes of documented HSV-2 meningitis, oral valacyclovir may be used for the entire course during episodes of recurrent HSV-2 meningitis. HSV meningitis should be distinguished from encephalitis, which requires a longer course (14–21 days) of IV therapy.	Not graded	CDC Guidelines 2021[8]
Symptomatic sex partners should be evaluated and treated in the same manner as patients who have symptomatic genital herpes.	Not graded	CDC Guidelines 2021[8]

Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described.	Not graded	CDC Guidelines 2021[8]
Antiviral-Resistant HSV Infection: • Foscarnet (40–80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. • Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective.	Not graded	CDC Guidelines 2021[8]
Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV	Not graded	CDC Guidelines 2021[8]
• Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. • For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. • Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women.	Level B	ACOG Guidelines 2020[9]
• For women with active genital herpes simplex virus lesions and preterm prelabor rupture of membranes, when expectant management is elected, treatment with an antiviral is recommended. • The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes	Not graded	ACOG Guidelines 2020[9]
• For breastfeeding women with active herpes simplex virus: Valacyclovir appears to be safe	Not graded	ACOG Guidelines

for breastfeeding women. • Although acyclovir was found in the breast milk in concentrations that were higher than the maternal serum, the amount of acyclovir in the breast milk was only 2% of that used for therapeutic doses in neonates		2020[9]
• The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.	Not graded	CDC Guidelines 2021[8]
Anogenital Warts - HPV • Because warts might spontaneously resolve in < 1 year, an acceptable alternative for certain persons is to forego treatment and wait for spontaneous resolution. • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • No definitive evidence indicates that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts. • Combination of treatments might be used.	Not graded	CDC Guidelines 2021[8]
Pregnancy – HPV • Imiquimod appears to pose low risk but should be avoided until more data is available. • Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete.	Not graded	CDC Guidelines 2021[8]
• Two products have been approved for HBV prevention: hepatitis B immune globulin (HBIG) for PEP and hepatitis B vaccine. • HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically	Not graded	CDC Guidelines 2021[8]

used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination.		
• Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV.	Not graded	CDC Guidelines 2021[8]
Management of Persons Who Are HBsAg Positive: • Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing. • Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule.	Not graded	CDC Guidelines 2021[8]
• Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination.	Not graded	CDC Guidelines 2021[8]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Viral STDs clinical and therapeutic management.** Additionally, **appendices** are provided for treatment algorithms and further information on the topic.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Viral STDs report, while the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the December 2019 CHI Viral STDs Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1.1. **CDC** Sexually Transmitted Diseases Treatment Guidelines, **2015**	**CDC** Sexually Transmitted Diseases Treatment Guidelines **2021**
1.1.2. **WHO** guidelines for the Treatment of Genital Herpes Simplex Virus **2016**	**WHO** Guidelines for the Management of Symptomatic Sexually Transmitted Infections **2021**
1.1.3. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents **2020**	N/A*

: *No updated versions available

1.1.1 CDC Sexually Transmitted Diseases Treatment Guidelines (2021)

*Please refer to **Section 1.1** of CHI Viral STDs original clinical guidance.*

The Centers for Diseases Control and Prevention (CDC) published in July 2021 treatment guidelines for the management of sexually transmitted infections (STIs)[8]. While the report covered a vast array of pathogens, this report will focus solely on viral causes. The main recommendations are summarized below:

Genital Herpes Management:

- Antiviral medication offers clinical benefits to symptomatic patients and is the mainstay of management.

- Systemic antiviral drugs can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued.
    - Randomized trials have indicated that three FDA-approved antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir.
- Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration, allowing for less frequent dosing than acyclovir. Famciclovir also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged.
- First Clinical Episode of Genital Herpes
    - All patients with first episodes of genital herpes should receive antiviral therapy.
    - Recommended Regimens for First Clinical Episode of Genital Herpes (Treatment can be extended if healing is incomplete after 10 days of therapy):
        - Acyclovir 400 mg orally 3 times/day for 7–10 days (Acyclovir 200 mg orally 5 times/day is also effective but is not recommended because of the frequency of dosing)

          or
        - Famciclovir 250 mg orally 3 times/day for 7–10 days

          or
        - Valacyclovir 1 g orally 2 times/day for 7–10 days
- Recurrent HSV-2 Genital Herpes
    - Almost all persons with symptomatic first-episode HSV-2 genital herpes subsequently experience recurrent episodes of genital lesions.
    - Intermittent asymptomatic shedding occurs among persons with HSV-2 genital herpes infection, even those with longstanding clinically silent infection.
    - Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy

suppressive therapy, which has the additional advantage of decreasing the risk for transmitting HSV-2 genital herpes to susceptible partners.

- Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir.
- Quality of life is improved for many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.
- Patients should follow up on annual basis whether they want to continue suppressive therapy, neither treatment discontinuation nor laboratory monitoring is necessary because adverse events and development of HSV antiviral resistance related to long-term antiviral use are uncommon.
- Treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission for discordant heterosexual couples in which a partner has a history of genital HSV-2 infection.
- Among HSV-2 seropositive persons without HIV infection, oral TDF/FTC and intravaginal tenofovir are ineffective at reducing the risk for HSV-2 shedding or recurrences.
- Recommended Regimens for Suppression of Recurrent HSV-2 Genital Herpes
    - Acyclovir 400 mg orally 2 times/day

      Or
    - Valacyclovir 500 mg orally once a day (this regimen might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year).

      Or
    - Valacyclovir 1 g orally once a day

      Or
    - Famciclovir 250 mg orally 2 times/day (Famciclovir appears somewhat less effective for suppression of viral shedding)

- Recurrent HSV-1 Genital Herpes
    - Recurrences are less frequent after the first episode of HSV-1 genital herpes, compared with genital HSV-2 genital herpes, and genital shedding rapidly decreases during the first year of infection.

- No data is available regarding the efficacy of suppressive therapy for preventing transmission among persons with HSV-1 genital herpes infection.
- Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision making between the patient and the provider.

- Episodic Therapy for Recurrent HSV-2 Genital Herpes
  - Episodic treatment of recurrent herpes is most effective if therapy is initiated within 1 day of lesion onset or during the prodrome that precedes some outbreaks.
  - The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.
  - Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes.
  - Recommended Regimens for Episodic Therapy for Recurrent HSV-2 Genital Herpes (Acyclovir 400 mg orally 3 times/day for 5 days is also effective but is not recommended because of frequency of dosing)
    - Acyclovir 800 mg orally 2 times/day for 5 days

      Or
    - Acyclovir 800 mg orally 3 times/day for 2 days

      Or
    - Famciclovir 1 g orally 2 times/day for 1 day

      Or
    - Famciclovir 500 mg orally once, followed by 250 mg 2 times/day for 2 days

      Or
    - Famciclovir 125 mg orally 2 times/day for 5 days

      Or
    - Valacyclovir 500 mg orally 2 times/day for 3 days

      Or
    - Valacyclovir 1 g orally once daily for 5 days

- Severe disease – Genital Herpes
    - Intravenous (IV) acyclovir therapy (5–10 mg/kg body weight IV every 8 hours) should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningitis or encephalitis).
    - IV therapy should be considered until clinical improvement followed by oral antiviral therapy to complete >10 days of total therapy. Longer duration is recommended for CNS complications.
    - Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5–10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended.
    - For patients with previous episodes of documented HSV-2 meningitis, oral valacyclovir may be used for the entire course during episodes of recurrent HSV-2 meningitis.
    - A randomized clinical trial indicated that suppressive therapy (valacyclovir 500 mg 2 times/day) did not prevent recurrent HSV-2 meningitis episodes; however, the dose might not have been sufficient for CNS penetration.
    - Valacyclovir 500 mg 2 times/day is not recommended for suppression of HSV-2 meningitis; higher doses have not been studied in clinical trials.
    - HSV meningitis should be distinguished from encephalitis, which requires a longer course (14–21 days) of IV therapy.
    - Impaired renal function warrants an adjustment in acyclovir dosage.
- Prevention for HSV-2 transmission:
    - Randomized clinical trials have demonstrated that PrEP with daily oral TDF/FTC decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships.
    - Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women.
    - Among medical male circumcision (MSM) and transgender women, daily oral TDF/FTC decreases the risk for severe ulcers with symptomatic genital HSV-2 infection but not for HSV-2 acquisition.

- Insufficient evidence exists that TDF/FTC use among those who are not at risk for HIV acquisition will prevent HSV-2 infection, and it should not be used for that sole purpose.
- Oral TDF does not prevent HSV-2 acquisition among persons with HIV infection who are taking TDF as part of their ART regimen.

Hepatitis with HSV infection:

- Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation.

Management of sex partners:

- Symptomatic sex partners should be evaluated and treated in the same manner as patients who have symptomatic genital herpes.
- Asymptomatic sex partners of patients who have symptomatic genital herpes should be asked about a history of genital symptoms and offered type-specific serologic testing for HSV-2.
- For partners without genital herpes, no data are available on which to base a recommendation for PEP or PrEP with antiviral medications or that they would prevent acquisition, and this should not be offered to patients as a prevention strategy.

Drug Allergy, Intolerance, or Adverse Reactions:

- Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described.

HIV Infection:

- Clinical manifestations of genital herpes might worsen during immune reconstitution early after initiation of ART.
- Recommended therapy for first-episode genital herpes is the same as for persons without HIV infection, although treatment courses might need to be extended for lesion resolution.
- Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV.
- The risk for genital ulcer disease (GUD) increases during the first 6 months after starting ART, especially among persons who have a CD4+ T-cell count <200 cell/mm3.

- Suppressive antiviral therapy reduces the risk for GUD among this population and can be continued for 6 months after ART initiation when the risk for GUD returns to baseline levels.
- Suppressive antiviral therapy among persons with HIV and HSV infection does not reduce the risk for either HIV transmission or HSV-2 transmission to susceptible sex partners.
- Suppressive antiviral therapy does not delay HIV disease progression and is not associated with decreased risk for HIV-related inflammation among persons taking ART.
- For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.
- Recommended Regimens for Daily Suppression of Genital Herpes Among Persons with HIV Infection
    - Acyclovir 400–800 mg orally 2–3 times/day

      Or
    - Famciclovir 500 mg orally 2 times/day

      Or
    - Valacyclovir 500 mg orally 2 times/day
    - Recommended Regimens for Episodic Genital Herpes Infection Among Persons with HIV Infection
    - Acyclovir 400 mg orally 3 times/day for 5–10 days

      Or
    - Famciclovir 500 mg orally 2 times/day for 5–10 days

      Or
    - Valacyclovir 1 g orally 2 times/day for 5–10 days

Antiviral-Resistant HSV Infection:

- If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing.
- Such persons should be managed in consultation with an infectious disease specialist, and alternative therapy should be administered.
- All acyclovir-resistant strains are also resistant to valacyclovir, and the majority are resistant to famciclovir.

- Foscarnet (foscavir) (40–80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes.
- Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective.
- Foscarnet and cidofovir are nephrotoxic medications that require intensive laboratory monitoring and infectious disease specialist consultation. Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective.
- Topical cidofovir gel 1% can be applied to lesions 2–4 times daily; however, cidofovir must be compounded at a pharmacy.
- Prevention of antiviral resistance remains challenging among persons with HIV infection.
- Experience with another group of immunocompromised persons (e.g., hematopoietic stemcell recipients) demonstrated that persons receiving daily suppressive antiviral therapy were less likely to experience acyclovir-resistant HSV infection compared with those who received episodic therapy for outbreaks.

Genital Herpes During Pregnancy:

- Women who acquire HSV in the second half of pregnancy should be managed in consultation with maternal fetal medicine and infectious disease specialists.
- Many fetuses are exposed to acyclovir each year, and the medication is believed to be safe for use during all trimesters of pregnancy.
- Acyclovir is also believed to be safe during breastfeeding.
- Although data regarding prenatal exposure to valacyclovir and famciclovir are limited, data from animal trials indicate that these drugs also pose a low risk among pregnant women.
- Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV.
- Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases.

- No data support use of antiviral therapy among asymptomatic HSV-seropositive women without a history of genital herpes.
- In addition, the effectiveness of antiviral therapy among sex partners with a history of genital herpes to decrease the risk for HSV transmission to a pregnant woman has not been studied.
- Recommended Regimen for Suppression of Recurrent Genital Herpes Among Pregnant Women (Treatment recommended starting at 36 weeks' gestation)
    - Acyclovir 400 mg orally 3 times/day

      Or
    - Valacyclovir 500 mg orally 2 times/day

Neonatal Herpes:

- Newborn infants exposed to HSV during birth, as documented by virologic testing of maternal lesions at delivery or presumed by observation of maternal lesions, should be followed clinically in consultation with a pediatric infectious disease specialist.
- Surveillance cultures or PCR of mucosal surfaces of the neonate to detect HSV infection might be considered before the development of clinical signs of neonatal herpes to guide treatment initiation.
- In addition, administration of acyclovir might be considered for neonates born to women who acquired HSV near term because the risk for neonatal herpes is high for these newborn infants.
- All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir.
- The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.

Human Papillomavirus Infections:

The Advisory Committee on Immunization Practices (ACIP) recommendations for HPV vaccination include the following:

- Routine HPV vaccination for all adolescents at age 11 or 12 years.
- Administering vaccine starting at age 9 years.
- Catch-up vaccination through age 26 years for those not vaccinated previously.

- Not using HPV vaccination for all adults aged >26 years. Instead, shared clinical decision-making between a patient and a provider regarding HPV vaccination is recommended for certain adults aged 27–45 years not vaccinated previously.
- A 2-dose vaccine schedule (at 0- and 6–12-month intervals) is recommended for persons who initiate vaccination before their 15th birthday.
- A 3-dose vaccine schedule (at 0-, 1–2-, and 6-month intervals) for immunocompromised persons regardless of age of initiation.
- HPV vaccines are not recommended for use in pregnant women. HPV vaccines can be administered regardless of history of anogenital warts, abnormal Pap test or HPV test, or anogenital precancer. Women who have received HPV vaccine should continue routine cervical cancer screening.
- HPV vaccine is available for eligible children and adolescents aged <19 years
- HPV vaccination has not been associated with initiation of sexual activity or sexual risk behaviors
    - Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV.

Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. Precancerous lesions are detected through cervical cancer screening**Anogenital Warts - HPV**

- For most patients, treatment results in resolution of the warts.
- If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number.
- Because warts might spontaneously resolve in < 1 year, an acceptable alternative for certain persons is to forego treatment and wait for spontaneous resolution.
- Available therapies for anogenital warts might reduce, but probably do not eradicate, HPV infectivity. Whether reduction in HPV viral DNA resulting from treatment reduces future transmission remains unknown.
- Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience.
- No definitive evidence indicates that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts.

- Shared clinical decision-making between a patient and a provider regarding treatment algorithms has been associated with improved clinical outcomes and should be encouraged.
- Because all available treatments have shortcomings, clinicians sometimes use combination therapy (e.g., provider administered cryotherapy with patient-applied topical therapy between visits to the provider). However, limited data exist regarding the efficacy or risk for complications associated with combination therapy.
- Treatment regimens are classified as either patient-applied or provider-administered modalities.
- Patient applied modalities are preferred by certain persons because they can be administered in the privacy of their home. To ensure that patient-applied modalities are effective, instructions should be provided to patients while in the clinic, and all anogenital warts should be accessible and identified during the clinic visit. Follow-up visits after weeks of therapy enable providers to answer any questions about use of the medication, address any side effects experienced, and facilitate assessment of the response to treatment.
- Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus) (Persons with external anal or perianal warts might also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy)
    - Patient-applied:
        - Imiquimod 3.75% or 5% cream (Might weaken condoms and vaginal diaphragms)

        Or

        - Podofilox 0.5% solution or gel

        Or

        - Sinecatechins 15% ointment (Might weaken condoms and vaginal diaphragms)
    - Provider-administered:
        - Cryotherapy with liquid nitrogen or cryoprobe

        Or

        - Surgical removal by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery

        Or

        - Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

- Imiquimod is a patient-applied, topically active immune enhancer that stimulates production of interferon and other cytokines.
    - Imiquimod 5% cream should be applied once at bedtime, 3 times/week for <16 weeks. Similarly, imiquimod 3.75% cream should be applied once at bedtime every night for <8 weeks. With either formulation, the treatment area should be washed with soap and water 6–10 hours after the application.
    - Local inflammatory reactions, including redness, irritation, induration, ulceration or erosion, and vesicles might occur with using imiquimod, and hypopigmentation has also been described.
    - Limited case reports demonstrate an association between treatment with imiquimod cream and worsened inflammatory or autoimmune skin diseases (e.g., psoriasis, vitiligo, or lichenoid dermatoses).
    - Data from studies of human participants are limited regarding use of imiquimod during pregnancy; however, animal data indicate that this therapy poses low risk.
- Podofilox (podophyllotoxin) is a patient-applied antimitotic drug that causes wart necrosis.
    - Podofilox solution (using a cotton swab) or podofilox gel (using a finger) should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy.
    - This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2, and the total volume of podofilox should be limited to 0.5 mL/day.
    - If possible, the health care provider should apply the initial treatment to demonstrate proper application technique and identify which warts should be treated.
    - Mild to moderate pain or local irritation might develop after treatment. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before and after each application.
    - Podofilox is contraindicated during pregnancy

- Sinecatechins is a patient-applied, green-tea extract with an active product (catechins).
    - Sinecatechins 15% ointment should be applied 3 times/day (0.5-cm strand of ointment to each wart) by using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for >16 weeks. The medication should not be washed off after use. Genital, anal, and oral sexual contact should be avoided while the ointment is on the skin.
    - The most common side effects of sinecatechins are erythema, pruritus or burning, pain, ulceration, edema, induration, and vesicular rash. This medication is not recommended for persons with HIV infection, other immunocompromised conditions, or genital herpes because the safety and efficacy of therapy has not been evaluated.
    - The safety of sinecatechins during pregnancy is unknown.
- Cryotherapy is a provider-administered therapy that destroys warts by thermal-induced cytolysis.
    - Health care providers should be trained on the correct use of cryotherapy because overtreatment or undertreatment can result in complications or low efficacy.
    - Pain during and after application of the liquid nitrogen, followed by necrosis and sometimes blistering, is common.
    - Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large.
- Surgical therapy has the advantage of eliminating the majority of warts at a single visit, although recurrence can occur.
    - Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit.
- Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by CO2 laser, or by curettage.
    - For patients with large or extensive warts, surgical therapy, including CO2 laser, might be most beneficial; such therapy might also be useful for intraurethral warts, particularly for those persons whose warts have not responded to other treatments.

- Treatment of anogenital and oral warts should be performed in a ventilated room by using standard precautions and local exhaust ventilation (e.g., a smoke evacuator)
- Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) are provider-administered caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly.
    - TCA solution has a low viscosity, comparable with that of water, and can spread rapidly and damage adjacent tissues if applied excessively. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid.
    - TCA or BCA treatment can be repeated weekly if necessary.
- Alternative Regimens for External Genital Warts:

- Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir.
- Shared clinical decision making between the patient and provider regarding benefits and risks of these regimens should be provided.
- In addition, alternative regimens might be associated with more side effects.
- Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours.
- Podophyllin resin 10%–25% in a compound tincture of benzoin might be considered for provider-administered treatment under conditions of strict adherence to recommendations.
- Podophyllin should be applied to each wart and then allowed to air dry before the treated area comes into contact with clothing. Overapplication or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas and possible systemic toxicity.
- The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, application

should be limited to <0.5 mL of podophyllin or an area of <10 cm2 of warts per session; the area to which treatment is administered should not contain any open lesions, wounds, or friable tissue; and the preparation should be thoroughly washed off 1–4 hours after application.

- Podophyllin resin preparations differ in the concentration of active components and contaminants. Shelf life and stability of podophyllin preparations are unknown. The safety of podophyllin during pregnancy has not been established.
- Recommended Regimens for Urethral Meatus Warts:
    - Cryotherapy with liquid nitrogen

      Or
    - Surgical removal
- Recommended Regimens for Vaginal Warts:
    - Cryotherapy with liquid nitrogen

      The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.

      Or
    - Surgical removal

      Or
    - Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution
- Recommended Regimens for Cervical Warts:
    - Cryotherapy with liquid nitrogen

      Or
    - Surgical removal

      Or
    - Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

      Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude HSIL should be performed before treatment is initiated.

- Recommended Regimens for Intra-Anal Warts:
    - Cryotherapy with liquid nitrogen

      Or
    - Surgical removal

      Or
    - Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution
- Management of intra-anal warts should include consultation with a colorectal specialist.

Management of Sex Partners – HPV

- Partners should be counseled that they might already have HPV despite no visible signs of warts; therefore, HPV testing of sex partners of persons with genital warts is not recommended.

Pregnancy – HPV

- Podofilox, podophyllin, and sinecatechins should not be used during pregnancy.
- Imiquimod appears to pose low risk but should be avoided until more data is available.
- Anogenital warts can proliferate and become friable during pregnancy.
- Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete.

HIV and Other Causes of Immunosuppression – HPV

- Persons with HIV infection or who are otherwise immunosuppressed are more likely to develop anogenital warts than those who do not have HIV.
- Moreover, such persons can have larger or more numerous lesions, might not respond to therapy as well as those who are immunocompetent, and might have more frequent recurrences after treatment.
- Despite these factors, data do not support altered approaches to treatment for persons with HIV infection.

High-Grade Squamous Intraepithelial Lesions

- Biopsy of an atypical wart might reveal HSIL or cancer of the anogenital tract. In this instance, referral to a specialist for treatment is recommended.

Cancers and Precancers Associated with Human Papillomavirus

- Persistent infection with high-risk (oncogenic) types of HPV has a causal role in approximately all cervical cancers and in certain vulvar, vaginal, penile, anal, and oropharyngeal cancers.
- However, cervical cancer is the only HPV-associated cancer for which routine screening is recommended.

Hepatitis B Virus Infection

- Persons with chronic HBV infection should be referred for evaluation to a provider experienced in managing such infections. Therapeutic agents approved by FDA for treatment of chronic HBV infection can achieve sustained suppression of HBV replication and remission of liver disease.
- Prevention – HepB Virus infection:
    - Two products have been approved for HBV prevention: hepatitis B immune globulin (HBIG) for PEP and hepatitis B vaccine.
    - HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination.
    - HBIG is prepared from plasma known to contain high concentrations of anti-HBs. The recommended dose of HBIG is 0.06 mL/kg body weight.
- Postexposure Prophylaxis - HepB Virus Infection:
    - Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV.
    - HBIG alone also has been demonstrated to be effective in preventing HBV transmission; however, with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.
- Exposure to a Source Who Is HBsAg Positive
    - Unvaccinated persons or persons known not to have responded to a complete hepatitis B vaccine series should receive both HBIG and hepatitis vaccine as soon as possible (preferably ≤24 hours) after a discrete, identifiable exposure to blood or body fluids that contain blood from a person with HBsAg.

    - Hepatitis B vaccine should be administered simultaneously with HBIG at a separate anatomic site, and the vaccine series should be completed by using the age-appropriate vaccine dose and schedule.
    - Exposed persons who are not fully vaccinated because they have not completed the vaccine series should receive HBIG (i.e., 0.06 mL/kg body weight) and complete the vaccine series.
    - Persons who have written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing should receive a single vaccine booster dose.
    - Exposed persons who are known to have responded to vaccination by postvaccination testing are considered protected; therefore, they need no additional doses of vaccine or HBIG.
    - All persons with an occupational exposure to blood or body fluids that contain HBV should be managed according to guidelines.
- Exposure to a Source with Unknown HBsAg Status:
    - Unvaccinated persons and persons with previous nonresponse to hepatitis B vaccination who have a discrete, identifiable exposure to blood or body fluids containing blood from a person with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated as soon as possible after exposure (preferably <24 hours) and the series completed according to the age-appropriate dose and schedule.
    - Exposed persons who are not fully vaccinated but started the series should complete the vaccine series. Exposed persons with written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing require no further treatment.
- Management of Persons Who Are HBsAg Positive:
    - Household, sexual, and needle-sharing contacts of persons with chronic infection should be evaluated.
    - Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing.
    - Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule.
    - Sex partners of persons with HBsAg should be counseled to use latex condoms to protect themselves from sexual exposure to infectious

body fluids (e.g., semen and vaginal secretions), unless they have been demonstrated to be immune after vaccination (anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive).

    - To prevent or reduce the risk for transmission to others in addition to vaccination, persons with HBsAg also should be advised to cover cuts and lesions, refrain from donating blood and sharing household articles.
    - To protect the liver from further harm, persons with HBsAg should be advised to avoid or limit alcohol, refrain from starting OTC, herbal or prescription medications, and get vaccinated against hepatitis A

- Pregnancy – HBV infection
    - Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination.
    - All pregnant women with HBsAg should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist.
- HIV with HBV infection
    - Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate and should be managed in consultation with an infectious disease specialist.

1.1.2 WHO Guidelines for the Management of Symptomatic Sexually Transmitted Infections (2021)

The objectives of these guidelines published by the World Health Organization (WHO) in 2021 are to provide updated, evidence-informed clinical and practical recommendations on the case management of people with symptoms of STIs; and to support countries in updating their national guidelines for the case management of people with symptoms of STIs. While the WHO recommendations also cover infections cause by bacterial of fungal pathogens, this report will only focus on those cause by viruses, mainly the herpes virus. The main recommendations are summarized below[10]:

- For people with confirmed anogenital ulcers, WHO recommends the following: Treat for herpes simplex virus according to the results available on the same day of the visit or treat syndromically and revise management according to the results when available. (Strong recommendation; moderate certainty evidence)

- For people with confirmed anogenital ulcers, WHO suggests the following (Conditional recommendation; moderate certainty evidence):
    - Treat syndromically for herpes simplex virus on the same day.
    - Treat for herpes simplex virus if the ulcer is recurrent or vesicular and treat for syphilis if the person has no history of recent treatment for syphilis (in the past three months).
- Recommendations for the management of anorectal discharge Treat, additionally, for herpes simplex virus if there is anorectal pain. (Strong recommendation; moderate certainty evidence)
- For persons with recurrent ulcers that are too frequent (such as 4–6 episodes or more a year) or with severe symptoms or causing distress, suppressive therapy may be proposed and preferred to episodic treatment. People receiving suppressive therapy may be assessed after one year and asked whether they want to continue or to change to episodic therapy. Note that recurrence rates may revert to the period before suppressive therapy started, and patients need to be aware of that.
- For people living with HIV and immunosuppressed individuals, dose adjustments are recommended for valaciclovir and famciclovir but not for acyclovir.
- For recurrent episodes, valaciclovir 500 mg is recommended for five days instead of three days, and famciclovir is recommended at a dose of 500 mg twice daily for five days instead of 250 mg.
- For suppressive therapy, valaciclovir is recommended at 500 mg twice daily instead of once daily and famciclovir at 500 mg twice daily instead of 250 mg twice daily.
- Table 3 and 4 list the recommended treatment options for genital ulcer disease and anorectal discharge cause by genital herpes.

Table 3. Recommended Treatment Options for Genital Ulcer Disease (Adapted from the WHO 2021 Guidelines)

Infections covered	First-line options	Effective substitutes	For pregnant and breastfeeding women and people younger than 16 years
Genital herpes	**Primary infection** Acyclovir 400 mg, orally, 3 times a day for 10 days or Acyclovir 200 mg, orally, 5 times a day for 10 days	**Primary infection** Valaciclovir 500 mg, twice a day for 10 days or Famciclovir 250 mg, orally, 3 times a day for 10 days	**Primary infection** Use acyclovir only when the benefit outweighs the risk. The dosage is the same as for primary infection in nonpregnancy.
	Recurrent infection – episodic therapy Acyclovir 400 mg, orally, 3 times a day for 5 days or Acyclovir 800 mg, orally, twice daily for 5 days or Acyclovir 800 mg, 3 times a day for 2 days	**Recurrent infection – episodic** Valaciclovir 500 mg, twice daily for 5 days or Famciclovir 250 mg, orally, twice daily for 5 days	**Recurrent infection – episodic therapy** Acyclovir 400 mg, orally, 3 times a day for 5 days or Acyclovir 800 mg, orally, twice daily for 5 days or Acyclovir 800 mg, 3 times a day, for 2 days
	Suppressive therapy for recurrent herpes Acyclovir 400 mg, orally, twice daily or Valaciclovir 500 mg, once daily	**Suppressive therapy for recurrences** Famciclovir 250 mg, orally, twice daily	**Suppressive therapy for recurrent herpes** Acyclovir 400 mg, orally, twice daily or Valaciclovir 500 mg, once daily

Table 4. Recommended Treatment Options for People with Anorectal Discharge (Adapted from the WHO 2021 Guidelines)

Infections covered	First-line options	Effective substitutes
Genital herpes	**Recurrent infection**: Acyclovir 400 mg, orally, 3 times a day for 5 days or Acyclovir 800 mg, orally, 3 times a day for 2 days or Acyclovir 800 mg, orally, 2 times a day for 5 days	**Recurrent infection:** Valaciclovir 500 mg, twice daily for 3 days
	Primary genital herpes: Acyclovir 400 mg, orally, 3 times a day for 10 days or Acyclovir 200 mg, 5 times a day for 10 days	**Primary genital herpes:** Valaciclovir 500 mg, orally, twice daily for 10 days
	Suppressive therapy for recurrent herpes Acyclovir 400 mg, orally, twice daily or Valaciclovir 500 mg, once daily For duration, see the genital ulcer disease section	**Suppressive therapy for recurrences** Famciclovir 250 mg, orally, twice daily (Famciclovir 500 mg, twice daily for people living with HIV or immunocompromised)

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Viral STDs report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines
ACOG Practice Bulletin: Management of Genital Herpes in Pregnancy (2020)
The Australian Guidelines for Genital Warts (2022)
The Australian Guidelines for Genital Herpes Simplex Virus (HSV) (2022)
Review Article: Treatment and Prevention of Acute Hepatitis B Virus (2021)
The Chinese Medical Association Guidelines for Prevention and Treatment of Chronic Hepatitis B (2021)

1.2.1 ACOG Practice Bulletin: Management of Genital Herpes in Pregnancy (2020)

The American College of Obstetricians and Gynecologists (ACOG) published in 2020 updated clinical guidelines for the management of genital herpes in pregnancy. Levels of evidence are outlined in table 4 below[9]:

Table 6. ACOG 2020 Guidelines' Level of Evidence

ACOG 2020 Guidelines' Level of Evidence	
LE	**Definition**
A	Recommendations are based on good and consistent scientific evidence
B	Recommendations are based on limited or inconsistent scientific evidence
C	Recommendations are based primarily on consensus and expert opinion

The guidelines recommend the following[9]:

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation.
- For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered.
- Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women.

- Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate viral shedding.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- In women with preterm prelabor rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV. When expectant management is elected, treatment with an antiviral is recommended.

Antiviral medications available to treat herpes simplex virus during pregnancy:

- The three oral antiviral agents that are commonly used to treat HSV infections are acyclovir, valacyclovir, and famciclovir.
- These drugs are approved for the treatment of primary genital herpes, the treatment of episodes of recurrent disease, and the daily treatment for suppression of outbreaks of recurrent genital herpes.
- Topical antiviral therapy has not been shown to be of benefit.
- Of the three medications, acyclovir is the most well studied in pregnancy, and animal and human data suggest that it is safe in pregnancy, including in the first trimester, and can effectively reduce viral shedding and persistence of lesions.
- Valacyclovir is a prodrug of acyclovir and is rapidly converted to acyclovir after metabolism in the liver. Therefore, valacyclovir is presumed to have a safety profile that is similar to acyclovir.
- Because valacyclovir has increased bioavailability and can be taken less often, patient adherence with valacyclovir may be increased compared with acyclovir. However, valacyclovir is generally more expensive than acyclovir.
- There are no published data on the use of famciclovir in pregnancy.
- There are no documented increases in adverse fetal or neonatal effects because of acyclovir exposure.
- Development of viral resistance to acyclovir has not been a problem in immunocompetent patients. In two large, laboratory-based studies, a low prevalence of acyclovir resistance in viruses isolated from immunocompetent patients has been estimated, whereas acyclovir resistant HSV infections occur more commonly among patients who are immunocompromised.

Antiviral therapy recommended for a primary or a nonprimary first-episode herpes simplex virus outbreak in pregnancy:

- At the time of the initial outbreak, antiviral treatment should be administered orally to pregnant women to reduce the duration and the severity of the symptoms as well as reduce the duration of viral shedding.
- In patients who have severe disease, oral treatment can be extended for more than 10 days if lesions are incompletely healed at that time.
- Acyclovir may be administered intravenously to pregnant women with severe genital HSV infection or with disseminated herpetic infections.
- Women with a primary or nonprimary first-episode outbreak in pregnancy, as well as women with a clinical history of genital herpes, should be offered suppressive therapy beginning at 36 weeks of gestation.
- Alternatively, for primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered.

Antiviral therapy recommended for a recurrent herpes simplex virus infection in pregnancy:

- In women with a recurrent HSV outbreak during pregnancy, antiviral treatment should be administered orally to reduce the duration and the severity of the symptoms and to reduce the duration of viral shedding.
- Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation.
- For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered.
- Suppressive therapy beginning at 36 weeks of gestation in women diagnosed with herpes before or during pregnancy has been shown to reduce the risk of clinical recurrence of HSV at the time of delivery, cesarean birth for recurrent herpes, and asymptomatic shedding.
- Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women.
- Although neutropenia is a recognized, transient complication of acyclovir treatment of neonatal HSV infection, it has not been reported after maternal suppressive therapy.
- The acyclovir concentrations at which neutropenia occurred were approximately 5–30 times greater than were observed in umbilical vein plasma in a pharmacokinetic study of valacyclovir in pregnancy.

Women with active genital herpes simplex virus lesions and preterm prelabor rupture of membranes:

- In a patient with prelabor rupture of membranes and active genital HSV lesions, the risks of prematurity should be weighed against the risk of neonatal HSV disease in considering expectant management.
- In pregnancies remote from term, especially in women with recurrent disease, there is increasing support for continuing the pregnancy to gain benefit from time and use of corticosteroids In women with preterm prelabor rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV.
- When expectant management is elected, treatment with an antiviral is recommended.
- The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes.

Breastfeeding women with active herpes simplex virus:

- Valacyclovir appears to be safe for breastfeeding women.
- Although acyclovir was found in the breast milk in concentrations that were higher than the maternal serum, the amount of acyclovir in the breast milk was only 2% of that used for therapeutic doses in neonates.

1.2.2 Australian Guidelines for Genital Warts (2022)

These guidelines published in 2022 were developed by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) and endorsed by the Blood Borne Viruses and Sexually Transmitted Infections Standing Committee (BBVSS)[11]. The main recommendations for the treatment of anogenital warts are summarized below (ungraded):

- The recommended regimens for the management of genital warts are the following:
    - Patient applied podophyllotoxin paint topically applied, twice a day for 3 days, then 4 days off, repeated weekly for 4-6 cycles until resolution.

      Or
    - Patient applied imiquimod 5% cream topically, 3 times per week at bedtime (wash after 6-10 hours) until resolution (up to 16 weeks)
- An alternative regimen for the management of genital warts would be:
    - Clinician initiated cryotherapy weekly.
    - Rarely may need excision under local anesthetic or ablative therapy under general anesthetic. Seek specialist advice.
- Treatment is cosmetic rather than curative.

- HIV infection: genital warts can have a poor response to treatment and may require longer cycles of treatment and are more likely to recur.
- If warts are in the pubic region avoid shaving or waxing as this may facilitate local spread by autoinoculation of HPV into areas of microtrauma.
- Provide patient with factsheet.
- Offer HPV vaccination if not already vaccinated. Note that HPV vaccination is not a therapeutic vaccine but may protect people from future acquisition of other HPV types.
- Genital warts is not a notifiable condition.
- Consider seeking specialist advice before treating any complicated presentation.
- Consider other potential causes (e.g., syphilis presenting as condylomata lata).
- In case of complicated or disseminated infection: Consider referral for laser or diathermy. Persistent intra-anal lesions in people living with HIV should be considered for surgical excision and HPV DNA typing to inform follow-up.
- In case of pregnancy: Cryotherapy can have a poor response. Lesions often resolve spontaneously postnatally when immune function returns to normal following delivery.
- Meatal warts: treat with cryotherapy.
- Intra-anal warts: treat with cryotherapy or refer for surgical management.
- Cervical warts: initial cervical cytology and refer to gynecologist for consideration of colposcopy, biopsy and treatment as indicated.
- Contact tracing is not recommended. The majority of partners have probably acquired the infection subclinically.

1.2.3 Australian Guidelines for Genital Herpes Simplex Virus (2022)

Similar to the guidelines in section 1.2.2, the Australian guidelines for the treatment of genital HSV infections were developed by the ASHM and endorsed by the BBVSS. The guidelines recommend the following[11]:

Principle treatment options for the management of HSV are outlined in table 5.

Table 7. 2022 Australian Guidelines for the Management of Genital HSV: Principal Treatment Options

Principal treatment options		
Situation	**Recommended**	**Alternative**
Initial episode	Valaciclovir 500mg PO, BD for 5 -10 days	Aciclovir 400mg PO, TDS for 5 -10 days
Recurrence: episodic therapy Should be self-initiated at the first hint of symptoms	Valaciclovir 500mg PO, BD for 3 days	Famciclovir 1g PO for 1 day or Aciclovir 800mg TDS for 2 days
Recurrence: suppressive therapy	Valaciclovir 500mg PO, daily for 6 months	Famciclovir 250mg PO, BD for 6 months or Aciclovir 400mg BD
Suppression in pregnancy (see below for details)	Valaciclovir 500mg PO, BD from 36 weeks until birth	Aciclovir 400mg TDS from 36 weeks until birth

- Contact tracing is not recommended, but patients may need support if they wish to disclose to current or future sexual partners.
- Seek specialist advice regarding patients living with human immunodeficiency virus (HIV) or immunosuppression.
- Treatment should not be delayed for those presenting with moderate-to-severe episodes, particularly initial episodes.
- Initial episodes may require a 10-day course of treatment if symptoms are slow to resolve.
- The ability for the patient to adhere to the recommended dosing frequency should be considered when selecting the appropriate treatment.
- Choice of suppressive therapy, episodic therapy or no therapy depends on clinical features including frequency and severity of recurrences and psychosexual complications of the diagnosis (e.g., fear of transmitting the infection to intimate partners).
- Review the need for suppressive therapy 6 monthly as recurrences usually become less frequent and less severe with time.

- Those with frequent recurrences (e.g., 2 or 3 times per month) or immunosuppression may require higher doses (PBS authority required for increased amount of medication).
- Ongoing symptoms, despite antiviral treatment, should prompt consideration of other causes of genital symptoms (see anogenital ulcer and genital dermatology).
- Seek specialist advice before treating any complicated presentation.
- Special treatment situations are outlined in the table below:

Table 8. 2022 Australian Guidelines Special Treatment Situations for HSV Management

Pregnancy	Neonatal transmission may occur in pregnancy, during delivery or via skin-to-skin transmission in post-natal period (via oro-labial HSV transmission). The greatest risk of sequelae for the baby is when HSV is acquired in the third trimester or close to the time of delivery. Routinely commence HSV suppression from 36 weeks gestation in people who know they have the infection (with or without lesions). Commence at an earlier gestation in people with multiple recurrent lesions during pregnancy. For further information about HSV and pregnancy refer to a sexual health specialist. Talk to people with HSV about suppressive therapy to reduce transmission to their partner before or during pregnancy.
Allergy to principal treatment choice	Seek specialist advice.

1.2.4 Review Article: Treatment and Prevention of Acute Hepatitis B Virus (2021)

This review article published by Dekker et al. in the journal Clinical Liver disease in 2021 provides a solid overview on the treatment and prevention of acute hepatitis B virus infections[12]. The main recommendations are summarized below:

- Generally treatment of acute hepatitis B infection is supportive as only less than 5% of immunocompetent adults will develop chronic infection. . There

are known subgroups of patients whose prognosis is relatively worse (eg, patients who are immunocompromised, have concomitant infection with hepatitis C or human immunodeficiency virus [HCV or HIV], have preexisting liver disease, or are older adults) when developing acute hepatitis B infection. Antiviral medications like Tenofovir, Entecavir, Lamivudine or Telbivudine as monotherapy. Treatment can be stopped after confirmation that the patient has cleared HBsAg (two consecutive tests four weeks apart).

    - ETV or TDF are the preferred agents for the treatment of acute or fulminant hepatitis B and continues until HBsAg clearance.

- Indications for considering antiviral therapy in acute hepatitis B currently include fulminant liver disease and those with protracted, acute severe hepatitis persisting for more than 4 weeks, or those at higher risk for acute liver failure

    - Treatment is indicated for fulminant liver disease and those with protracted (> 4 weeks), acute severe hepatitis (total bilirubin >3 mg/dL, (or direct bilirubin >1.5 mg/dL), INR >1.5, encephalopathy, or ascites)

- Table 9 lists the treatment strategies and end points for acute hepatitis B virus:

Table 9. Treatment Strategies and End Points for Acute Hepatitis B Virus (Adapted from Dekker et al., 2021)

Indication	Treatment	End points
Acute/symptomatic hepatitis B or fulminant hepatitis B	TDF or ETV	Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplant
Presence of compensated cirrhosis, plus HBV DNA levels >2000 IU/mL or persistent ALT level elevation	TDF, TAF, or ETV	Lifelong therapy
Presence of decompensated cirrhosis	TDF or ETV	Lifelong therapy
Pregnant mothers with high viral load	TDF preferred	Initiate therapy at 28–30 wk gestation and monitor for flares if therapy is ceased after delivery

HBV/HIV coinfection	TDF + emtricitabine or LAM or ETV + ARV regimen	Lifelong unless the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment
HBsAg-positive, anti-HBc-positive patients who will receive malignancy or IS therapy	TDF, TAF, or ETV	6–12 mo beyond malignancy or IS therapy, >12 mo in anti- CD20 antibody therapy

For an in-depth review of the prevention and treatment of acute hepatitis B, please refer to the "Viral Hepatitis" report.

1.2.5 Chinese Medical Association Guidelines for Prevention and Treatment of Chronic Hepatitis B (2021)

To achieve the goal of the World Health Organization to eliminate viral hepatitis as a major public health threat by 2030, the Chinese Society of Infectious Diseases and the Chinese Society of Hepatology convened an expert panel in 2019 to update the guidelines for the prevention and treatment of chronic hepatitis B (CHB). The current guidelines cover recent advances in basic, clinical, and preventive studies of CHB infection and consider the actual situation in China. These guidelines are intended to provide support for the prevention, diagnosis, and treatment of CHB[13].

- ➔ The guidelines include recommendations on hepatitis B vaccination for newborns, for immunocompromised or non-responsive adults, and for people who accidentally are exposed to HBV. Catch-up vaccination schedules are also covered.
- ➔ Treatment goals, treatment with antiviral, PEG-interferon alpha, anti-inflammatory, antioxidant, and hepatoprotective and antifibrosis treatments are mentioned in this guideline.

For an in-depth review of the prevention and treatment of acute hepatitis B, please refer to the "Viral Hepatitis" report.

Section 2.0 Drug Therapy in Viral STDs

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

2.1.1 Hepatitis B Immunoglobulin

Information on HBIG is detailed in the table below[14]:

Table 10. Hepatitis B Immunoglobulin Drug Information

SCIENTIFIC NAME **Hepatitis B Immunoglobulin**	
SFDA Classification	Prescription
SFDA Approval	N/A
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	**B180** (chronic viral hepatitis B with delta agent), **B181** (chronic viral hepatitis B without delta agent), and **B191** (unspecified viral hepatitis B)
Drug Class	Blood Product Derivative
Drug Sub-class	Immune Globulin
ATC Code	J06BB04
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection or infusion
Route of Administration	IV or IM
Dose (Adult) [DDD]	0.06 ml/kg body weight[8]
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	**Perinatal exposure, prophylaxis** (CDC 2005): Infants born to HBsAg-positive mothers: IM: 0.5 mL as a repeat of birth dose if the hepatitis B vaccination series

	is delayed for as long as 3 months (hepatitis B vaccine should also be administered at the same time/different site) **Postexposure prophylaxis:** *Infants <12 months*: IM: 0.5 mL as soon as possible after exposure (eg, mother or primary caregiver with acute HBV infection); initiate hepatitis B vaccine series *Children ≥12 months and Adolescents*: IM: 0.06 mL/kg as soon as possible after exposure (ie, within 24 hours of needlestick, ocular, or mucosal exposure or within 14 days of sexual exposure); repeat at 28 to 30 days after exposure
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Renal impairment**: Adult and pediatrics: There are no dosage adjustments provided in the manufacturer's labeling **Hepatic Impairment**: Adult and pediatrics There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits	CU, ST, QL, PE, MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	It can be used simultaneously with hepatitis B vaccine at separate anatomic sites for prevention of transmission after exposure to HBV
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication must be prescribed by or in consultation with a physician who specializes in infectious diseases
PA (Prior Authorization)	N/A
QL (Quantity Limit)	HBIG provides **temporary** (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who

	have not responded to vaccination.
ST (Step Therapy)	HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as **an adjunct** to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	This medication should be given **as soon as possible** after exposure (ie, **within 24 hours** of needlestick, ocular, or mucosal exposure or **within 14 days** of sexual exposure); **repeat at 28 to 30 days** after exposure in non-responders to hepatitis B vaccine or in patients who refuse vaccination
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common >10%:** **Central nervous system**: Headache **Dermatologic**: Erythema **1% to 10%:** **Cardiovascular**: Hypotension **Central nervous system**: Malaise **Dermatologic**: Ecchymoses **Gastrointestinal**: Nausea, vomiting **Hematologic & oncologic**: Change in WBC count **Hepatic**: Increased serum alkaline phosphatase, increased liver enzymes **Local**: Pain at injection site **Neuromuscular & skeletal**: Myalgia, joint stiffness **Renal**: Increased serum creatinine **<1%, postmarketing, and/or case reports**: Abdominal pain, anaphylactic reaction (rare), angioedema, back pain, chills, diaphoresis, dizziness, dyspnea,

	fever, flu-like symptoms, hypersensitivity, increased serum lipase, increased serum transaminases, sinus tachycardia, tenderness at injection site, urticaria
Drug Interactions	No interactions of Risk X identified
Special Population	N/A
Pregnancy	Use of HBIG is not contraindicated in pregnant females and may be used for postexposure prophylaxis when indicated (CDC 2001). In addition, use of HBIG has been evaluated to reduce maternal to fetal transmission of hepatis B virus during pregnancy (ACOG 2007)
Lactation	It is not known if immune globulin from these preparations is present in breast milk. The manufacturer recommends that caution be used if administered to breastfeeding females. Endogenous immune globulins are present in breast milk (Agarwal 2011). Infants born to HBsAg-positive mothers (and receive postexposure prophylaxis) or to mothers with unknown HBsAg status may be breastfed (CDC [Schillie 2018]). Use of HBIG is not contraindicated in breastfeeding females (CDC 2001).
Contraindications	HepaGam B: Anaphylactic or severe systemic reaction to human globulin preparations; IgA deficiency; postexposure prophylaxis in patients with severe thrombocytopenia or other coagulation disorders which would contraindicate IM injections (administer only if benefit outweighs the risk).
Monitoring Requirements	For liver transplant cases: Serum HBsAg; LFTs; infusion-related adverse events
Precautions	**Anaphylaxis/hypersensitivity reactions**: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1

	mg/mL) should be available. Use with caution in patients with isolated immunoglobulin A deficiency or a history of systemic hypersensitivity to human immunoglobulins. **Infusion reactions**: When administered IV, do not exceed recommended infusion rates; may increase risk of adverse events. Patients should be monitored for adverse events during and after the infusion. **Thrombotic events**: Thrombotic events have been reported with administration of intravenous immune globulin; use with caution in patients of advanced age, with a history of atherosclerosis or cardiovascular and/or thrombotic risk factors, patients with impaired cardiac output, coagulation disorders, prolonged immobilization, or patients with known/suspected hyperviscosity. Consider a baseline assessment of blood viscosity in patients at risk for hyperviscosity.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews of Viral STDs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **Below are the HTA recommendations related to HBIG in Viral STDs treatment.**

Table 11. Hepatitis B Immunoglobulin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Hepatitis B Immunoglobulin	NICE	N/A
	CADTH	N/A
	HAS[15]	Hepatitis B immunoprophylaxis indications: • in accidental exposure in non-immunized people (including when vaccination is incomplete or unknown) • in hemodialysis patients pending vaccination being effective • in newborn babies of mothers carrying the hepatitis B virus • in patients who have not developed an immune response after vaccination against the hepatitis B virus (undetectable antibodies against hepatitis B) and who require continued protection against this disease. The committee **recommends** its inclusion. The actual benefit of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in the Marketing Authorization indications is substantial.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Hepatitis B Immunoglobulin

Hepatitis B Immunoglobulin is indicated for HBV prevention and postexposure prophylaxis. It is given at 0.06 ml/kg body weight. Hepatitis B Immunoglobulin ca be given either intravenously or intramuscularly. Its use is backed up by HAS HTA body in the indications mentioned above. The use of Hepatitis B Immunoglobulin is limited by the anaphylaxis/hypersensitivity reactions, infusion reactions, and thrombotic events.

2.1.2 Podophyllotoxin

Information on Podophyllotoxin is detailed in the table below[14]:

Table 12. Podophyllotoxin Drug Information

SCIENTIFIC NAME **Podophyllotoxin**	
SFDA Classification	Prescription
SFDA Approval	N/A
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	N/A
Indication (ICD-10)	A63.0 (Anogenital (venereal) warts)
Drug Class	Keratolytic Agent; Topical Skin Product
Drug Sub-class	Keratolytic Agent; Podophyllotoxins
ATC Code	D06BB04
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Cream SFDA REGISTERED
Route of Administration	Topical
Dose (Adult) [DDD]	Podofilox solution (using a cotton swab) or podofilox gel (using a finger) should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm2, and the total volume of podofilox should be limited to 0.5 mL/day. If possible, the health care provider should apply the initial treatment to demonstrate proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before

	and after each application[8,14].
Maximum Daily Dose Adults	The total volume of podofilox should be limited to 0.5 mL/day.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Renal impairment**: Adult: There are no dosage adjustments provided in the manufacturer's labeling **Hepatic Impairment**: Adult: There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits	QL, PE, MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication must be prescribed in consultation with a physician who specializes in infectious diseases, for better compliance to specific instructions
PA (Prior Authorization)	N/A
QL (Quantity Limit)	The drug's cycle can be repeated, as necessary, **for up to four cycles**. The total volume of podofilox should be **limited to 0.5 mL/day.**
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	It should be applied to anogenital warts **2 times/day for 3 days, followed by 4 days of no therapy**. This cycle can be repeated, as necessary, for up to four cycles. **The total wart area treated should not exceed 10 cm²**, and the total volume of podofilox should be limited to 0.5 mL/day. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before and after each application[8,14].
SAFETY	

Main Adverse Drug Reactions (Most common and most serious)	**Most common >10%:** Central nervous system: Localized burning, local pain Dermatologic: Skin erosion Hematologic & oncologic: Local hemorrhage Local: Local inflammation, local pruritus **1% to 10%:** Central nervous system: Headache Dermatologic: Stinging of the skin, erythema **<1%, postmarketing, and/or case reports:** Crusted skin, dermal ulcer, desquamation, edema, skin blister, skin discoloration, skin fissure, skin rash, skin tenderness, tingling of skin, xeroderma.
Drug Interactions	No interactions of Risk X identified
Special Population	N/A
Pregnancy	This drug is contraindicated in pregnancy
Lactation	It is not known if podofilox is present in breast milk. Due to the potential for adverse reactions in the breastfed infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, considering the importance of the treatment to the mother.
Contraindications	Hypersensitivity or intolerance to any component of the formulation. Canadian labeling: Additional contraindications (not in the US labeling): Concurrent use with other podophyllin-containing products; patients with open wounds or inflamed or bleeding lesions; children <12 years of age; pregnancy; breastfeeding. Significant drug interactions exist, requiring dose/frequency adjustment or

	avoidance. Consult drug interactions database for more information.
Monitoring Requirements	Treated areas for adequate healing; tolerability of treatment
Precautions	**Concerns related to adverse effects:** *Skin reactions*: Most skin reactions are mild to moderate and did not increase during the treatment period, however severe skin reactions can occur. Severe reactions are most frequent within the first two weeks of treatment. **Dosage form specific issues:** *Topical gel and solution*: Flammable; keep away from fire or flame. **Other warnings/precautions**: *Appropriate use*: For cutaneous use only; avoid contact with eyes. If product comes in contact with the eyes, flush with water and seek medical attention. Not intended for treatment of mucous membrane warts.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews of Viral STDs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **Below are the HTA recommendations related to Podophyllotoxin in Viral STDs treatment.**

Table 13. Podophyllotoxin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Podophyllotoxin HTA Analysis	NICE	N/A
	CADTH	N/A
	HAS[16]	The committee **recommends** its inclusion. Indicated for External condyloma acuminata with a surface area less than 4 cm2, in alternative to other therapies (cryotherapy, methods surgical...)
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Podophyllotoxin HTA Analysis

Podophyllotoxin is indicated for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus). It should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2, and the total volume of podofilox should be limited to 0.5 mL/day. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before and after each application.
The use of this drug is backed up by HAS HTA body in External condyloma acuminata with a surface area less than 4 cm2, in alternative to other therapies (cryotherapy, methods surgical...). The use of Podophyllotoxin is limited by the skin reactions and appropriate application.

2.2 Modifications

Below are the modifications made to the list of Viral STDs drugs since the CHI report in December 2019, reflecting the changes and updates:

Table 14. Prescribing Edits (PE) Modifications of Certain Viral STDs Drugs

Drugs	PE modifications
Acyclovir	**ST, MD, and QL were added:** **ST**: one of the first line FDA approved therapies for genital herpes simplex **MD**: Drug must be prescribed by or in consultation with a physician who specializes in infectious diseases

	QL: • Herpes simplex virus, genital infection: non-HIV-exposed-infected Children < 12 years: maximum daily dose of 1,200 mg/day • Herpes simplex virus, genital infection: HIV-exposed-infected Children: maximum dose of 400 mg/dose • Herpes simplex virus, genital infection: recurrent infection for children < 12 years (independent of HIV status): maximum dose of 400 mg/dose • Herpes simplex virus, genital infection: suppression, chronic non-HIV-exposed/-infected children < 12 years: maximum dose of 400 mg/dose • Herpes simplex virus, genital infection: suppression, chronic HIV-exposed/-infected infants, and children: maximum dose of 800 mg/day • HSV orolabial disease (i.e., gingivostomatitis, herpes labialis): Non-HIV-exposed/-infected: usual maximum dose: 800 mg/dose • HSV orolabial disease (i.e., gingivostomatitis, herpes labialis): HIV-exposed/-infected, Mild, symptomatic: maximum dose: 400 mg/dose. • Herpes simplex virus, mucocutaneous infection treatment: Immunocompetent host: Infants, Children, and Adolescents: maximum dose: 800 mg/dose • Herpes simplex virus, mucocutaneous infection suppression chronic: Immunocompetent host Infants, Children, and Adolescents: Limited data available; no pediatric data; some experts recommend oral 20 mg/kg/dose 2 to 3 times daily for 6 to 12 months, then reevaluate need; maximum dose: 400 mg/dose. • Herpes simplex virus, mucocutaneous infection, Immunocompromised host: Suppression, chronic (cutaneous, ocular) episodes: HIV-exposed/-infected: Infants and Children: maximum dose: 800 mg/dose; reassess after 12 months. • HSV prophylaxis; immunocompromised hosts, seropositive: HSCT in seropositive recipient: ▪ Prevention of early reactivation: Infants, Children, and Adolescents: <40 kg: IV: 250 mg/m2/dose every 8 hours or 125 mg/m2/dose every 6 hours; maximum daily dose: 80 mg/kg/day or Oral: 60 to 90 mg/kg/day in 2 to 3 divided

	doses; maximum dose: 800 mg/dose twice daily ▪ Prevention of late reactivation: Infants, Children, and Adolescents <40 kg: Oral: 60 to 90 mg/kg/day in 2 to 3 divided doses; maximum daily dose: 800 mg twice daily
Valacyclovir	**ST, MD, and QL were added:** **ST**: one of the first line FDA approved therapies for genital herpes simplex **MD**: Drug must be prescribed by or in consultation with a physician who specializes in infectious diseases **QL:** • Herpes simplex virus (HSV), orolabial infection: Note: Initiate at earliest symptom onset. Patients without HIV: Treatment: Weight-directed dosing: Limited data available: Infants ≥3 months, Children, and Adolescents: oral 20 mg/kg/dose every 12 hours; **maximum dose: 1,000 mg/dose.** • Herpes simplex virus (HSV), genital infection: Limited data available: ▪ First episode; treatment: Children and Adolescents: Oral: 20 mg/kg/dose every 12 hours; **maximum dose: 1,000 mg/dose**. ▪ Recurrent episode; treatment: Note: Most effective if started during prodrome or within 1 day lesion appearance, Children and Adolescents: Oral: 20 mg/kg/dose every 12 hours; **maximum dose: 1,000 mg/dose**. ▪ Suppressive therapy: Patients without HIV: Adolescents: Oral: 20 mg/kg/dose once daily; **maximum dose: 500 mg/dose**. In adolescents with frequent recurrences (ie, ≥10 per year), doses of 1,000 mg/day may be more effective. • Herpes simplex virus (HSV), prophylaxis in immunocompromised patients (alternative agent): Limited data available: ▪ Solid organ transplant recipients, seropositive: Note: Administer for ≥1 month after transplant and during treatment of rejection episodes. Children and Adolescents: Oral: 20 mg/kg/dose twice daily; **maximum dose: 500 mg/dose.**

Famciclovir	**ST and MD were added:** **ST:** one of the first line FDA approved therapies for genital herpes simplex **MD:** Drug must be prescribed by or in consultation with a physician who specializes in infectious diseases

2.3 Delisting

No medications have been withdrawn or are no longer recommended for the treatment of Viral STDs since December 2019.

Nevertheless, upon thorough review of the prior CHI excel spreadsheet, it is advisable to remove Acyclovir cream and ointment from the list. This recommendation is based on the 2021 CDC Guidelines for Sexually Transmitted Infections, which highlight that topical antiviral therapy provides minimal clinical benefit and is discouraged for the management of Genital Herpes[8]. Furthermore, the ACOG Guidelines on the Management of Genital Herpes in Pregnancy also indicate that topical antiviral therapy has not demonstrated any therapeutic advantage[9].

2.4 Other Drugs

The drugs detailed in table 12 are **not SFDA registered**. However, they have been recommended for the treatment of Viral STDs.

Table 15. Non-SFDA Approved Drugs for the Management of Viral STDs

Drug	Approval	Indication	Dose
Foscavir	**FDA** approved in 2017 for Mucocutaneous Acyclovir-Resistant HSV Infections in 2006	For acyclovir-resistant genital herpes	IV 40–80 mg/kg body weight every 8 hours until clinical resolution is attained[8]. Foscarnet is a nephrotoxic medication that require intensive laboratory monitoring and infectious disease specialist consultation[8].
Cidofovir	N/A	For acyclovir-resistant genital herpes	IV 5 mg/kg body weight once weekly. Topical cidofovir gel 1% can be applied to lesions 2–4 times

			daily; however, cidofovir must be compounded at a pharmacy. Cidofovir is a nephrotoxic medication that require intensive laboratory monitoring and infectious disease specialist consultation[8].
Sinecatechins patient-applied, green-tea extract with an active product (catechins)	**FDA** approved in 2006 the treatment of external genital and perianal warts (Condylomata acuminata) in immunocompetent patients 18 years and older. Not **EMA** approved	Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus)	Sinecatechins 15% ointment should be applied 3 times/day (0.5-cm strand of ointment to each wart) by using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for >16 weeks. The medication should not be washed off after use. Genital, anal, and oral sexual contact should be avoided while the ointment is on the skin. The most common side effects of sinecatechins are erythema, pruritus or burning, pain, ulceration, edema, induration, and vesicular rash. This medication is not recommended for persons with HIV infection, other immunocompromised conditions, or genital herpes because the safety and efficacy of therapy has not been evaluated. The safety of sinecatechins during pregnancy is unknown. Thus, this drug should not be used in pregnancy. This drug might weaken condoms and vaginal

			diaphragms[8].
Trichloroacetic acid (TCA)	N/A	Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus) Recommended for vaginal, cervical, and intra-anal Warts	TCA or BCA 80%–90% solution. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA or BCA treatment can be repeated weekly if necessary[8].
Bichloroacetic acid (BCA)	N/A	Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus) Recommended for vaginal, cervical, and intra-anal Warts	TCA or BCA 80%–90% solution A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA or BCA treatment can be repeated weekly if necessary[8].

Section 3.0 Key Recommendations Synthesis

- Randomized trials have indicated that three FDA-approved antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged[8].
    - Those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy suppressive therapy, which has the additional advantage of decreasing the risk for transmitting HSV-2 genital herpes to susceptible partners[8].
    - Recurrences are less frequent after the first episode of HSV-1 genital herpes, compared with genital HSV-2 genital herpes, and genital shedding rapidly decreases during the first year of infection. Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision making between the patient and the provider[8].
    - Episodic treatment of recurrent herpes is most effective if therapy is initiated within 1 day of lesion onset or during the prodrome that precedes some outbreaks. Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes[8].
- Severe disease – Genital Herpes
    - Intravenous (IV) acyclovir therapy (5–10 mg/kg body weight IV every 8 hours) should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningitis or encephalitis)[8].
    - IV therapy should be considered until clinical improvement followed by oral antiviral therapy to complete >10 days of total therapy. Longer duration is recommended for CNS complications[8].
    - Oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended[8].
    - For patients with previous episodes of documented HSV-2 meningitis, oral valacyclovir may be used for the entire course during episodes of recurrent HSV-2 meningitis. HSV meningitis should be distinguished from encephalitis, which requires a longer course (14–21 days) of IV therapy[8].

- Management of sex partners:
    - Symptomatic sex partners should be evaluated and treated in the same manner as patients who have symptomatic genital herpes[8].
- Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described[8].
- Antiviral-Resistant HSV Infection:
    - Foscarnet (foscavir) (40–80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes[8].
    - Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective[8].
    - Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective[8].
- Genital Herpes During Pregnancy:
    - Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV[8].
- The following recommendations are based on limited or inconsistent scientific evidence (Level B)[9]:
    - Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation.
    - For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered.
    - Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women.
- Women with active genital herpes simplex virus lesions and preterm prelabor rupture of membranes:
    - When expectant management is elected, treatment with an antiviral is recommended. The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes[9].
- Breastfeeding women with active herpes simplex virus:

- Valacyclovir appears to be safe for breastfeeding women. Although acyclovir was found in the breast milk in concentrations that were higher than the maternal serum, the amount of acyclovir in the breast milk was only 2% of that used for therapeutic doses in neonates[9].

- Neonatal Herpes:
  - The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS[8].

- Anogenital Warts - HPV
  - Because warts might spontaneously resolve in <1 year, an acceptable alternative for certain persons is to forego treatment and wait for spontaneous resolution[8].
  - Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience[8].
  - No definitive evidence indicates that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts[8].
  - Combination of treatments might be used[8].
  - Imiquimod 5% cream should be applied once at bedtime, 3 times/week for <16 weeks. Similarly, imiquimod 3.75% cream should be applied once at bedtime every night for < 8 weeks[8].
  - Podofilox solution (using a cotton swab) or podofilox gel (using a finger) should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy[8].
  - Sinecatechins 15% ointment should be applied 3 times/day (0.5-cm strand of ointment to each wart) by using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved[8].
  - Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) 80%–90% solution are provider-administered caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly[8].

- Pregnancy – HPV
  - Imiquimod appears to pose low risk but should be avoided until more data is available[8].

    - Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete[8].
- Prevention – HepB Virus infection:
    - Two products have been approved for HBV prevention: hepatitis B immune globulin (HBIG) for PEP and hepatitis B vaccine[8].
    - HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination[8].
- Postexposure Prophylaxis - HepB Virus Infection:
    - Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV[8].
- Management of Persons Who Are HBsAg Positive:
    - Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing[8].
    - Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule[8].
- Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination[8].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Viral STDs report** and aims to provide recommendations to aid in the management of Viral STDs. These recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Viral STDs. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Viral STDs Scope

Section	Rationale/Updates
Section 1.1.1 **CDC Sexually Transmitted Diseases Treatment Guidelines 2015**	**CDC Sexually Transmitted Diseases Treatment Guidelines 2021**[17] Updated recommendations: • **Genital Herpes Management:** o Antiviral medication offers clinical benefits to symptomatic patients and is the mainstay of management o Systemic antiviral drugs can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued o Randomized trials have indicated that three FDA-approved antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir o Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration, allowing for less frequent dosing than acyclovir. Famciclovir also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged. o First Clinical Episode of Genital Herpes ▪ All patients with first episodes of genital herpes should receive antiviral therapy ▪ Recommended Regimens for First Clinical Episode of Genital Herpes (Treatment can be extended if healing is incomplete after 10 days of therapy): ▪ Acyclovir 400 mg orally 3 times/day for 7–10 days (Acyclovir 200 mg orally 5 times/day is also effective but is not recommended because of the frequency of dosing) or ▪ Famciclovir 250 mg orally 3 times/day for 7–10 days or

	▪ Valacyclovir 1 g orally 2 times/day for 7–10 days • Recurrent HSV-2 Genital Herpes ▪ Almost all persons with symptomatic first-episode HSV-2 genital herpes subsequently experience recurrent episodes of genital lesions. ▪ Intermittent asymptomatic shedding occurs among persons with HSV-2 genital herpes infection, even those with longstanding clinically silent infection. ▪ Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy suppressive therapy, which has the additional advantage of decreasing the risk for transmitting HSV-2 genital herpes to susceptible partners ▪ Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. ▪ Quality of life is improved for many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. ▪ Patients should follow up on annual basis whether they want to continue suppressive therapy, neither treatment discontinuation nor laboratory monitoring is necessary because adverse events and development of HSV antiviral resistance related to long-term antiviral use are uncommon ▪ Treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission for discordant heterosexual couples in which a partner has a history of genital HSV-2 infection ▪ Among HSV-2 seropositive persons without HIV infection, oral TDF/FTC and intravaginal tenofovir are ineffective at reducing the risk for HSV-2 shedding or recurrences ▪ Recommended Regimens for Suppression of Recurrent HSV-2 Genital Herpes ▪ Acyclovir 400 mg orally 2 times/day Or ▪ Valacyclovir 500 mg orally once a day (this regimen might be less effective than other valacyclovir

	or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). Or ▪ Valacyclovir 1 g orally once a day Or ▪ Famciclovir 250 mg orally 2 times/day (Famciclovir appears somewhat less effective for suppression of viral shedding) • Recurrent HSV-1 Genital Herpes ▪ Recurrences are less frequent after the first episode of HSV-1 genital herpes, compared with genital HSV-2 genital herpes, and genital shedding rapidly decreases during the first year of infection ▪ No data are available regarding the efficacy of suppressive therapy for preventing transmission among persons with HSV-1 genital herpes infection. ▪ Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision making between the patient and the provider • Episodic Therapy for Recurrent HSV-2 Genital Herpes ▪ Episodic treatment of recurrent herpes is most effective if therapy is initiated within 1 day of lesion onset or during the prodrome that precedes some outbreaks. ▪ The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. ▪ Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes. ▪ Recommended Regimens for Episodic Therapy for Recurrent HSV-2 Genital Herpes (Acyclovir 400 mg orally 3 times/day for 5 days is also effective but is not recommended because of frequency of dosing) ▪ Acyclovir 800 mg orally 2 times/day for 5 days Or ▪ Acyclovir 800 mg orally 3 times/day for 2 days

Or

- Famciclovir 1 g orally 2 times/day for 1 day

Or

- Famciclovir 500 mg orally once, followed by 250 mg 2 times/day for 2 days

Or

- Famciclovir 125 mg orally 2 times/day for 5 days

Or

- Valacyclovir 500 mg orally 2 times/day for 3 days

Or

- Valacyclovir 1 g orally once daily for 5 days

- Severe disease – Genital Herpes
  - Intravenous (IV) acyclovir therapy (5–10 mg/kg body weight IV every 8 hours) should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningitis or encephalitis).
  - IV therapy should be considered until clinical improvement followed by oral antiviral therapy to complete >10 days of total therapy. Longer duration is recommended for CNS complications.
  - Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5–10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended.
  - For patients with previous episodes of documented HSV-2 meningitis, oral valacyclovir may be used for the entire course during episodes of recurrent HSV-2 meningitis.
  - A randomized clinical trial indicated that suppressive therapy (valacyclovir 500 mg 2 times/day) did not prevent recurrent HSV-2 meningitis episodes; however, the dose might not have been sufficient for CNS penetration.
  - Valacyclovir 500 mg 2 times/day is not recommended for suppression of HSV-2

	meningitis; higher doses have not been studied in clinical trials. ▪ HSV meningitis should be distinguished from encephalitis, which requires a longer course (14–21 days) of IV therapy. ▪ Impaired renal function warrants an adjustment in acyclovir dosage. • Prevention for HSV-2 transmission: ▪ Randomized clinical trials have demonstrated that PrEP with daily oral TDF/FTC decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. ▪ Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. ▪ Among medical male circumcision (MSM) and transgender women, daily oral TDF/FTC decreases the risk for severe ulcers with symptomatic genital HSV-2 infection but not for HSV-2 acquisition. ▪ Insufficient evidence exists that TDF/FTC use among those who are not at risk for HIV acquisition will prevent HSV-2 infection, and it should not be used for that sole purpose. ▪ Oral TDF does not prevent HSV-2 acquisition among persons with HIV infection who are taking TDF as part of their ART regimen • **Hepatitis with HSV infection**: • Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • **Management of sex partners**: • Symptomatic sex partners should be evaluated and treated in the same manner as patients who have symptomatic genital herpes. • Asymptomatic sex partners of patients who have symptomatic genital herpes should be asked about a history of genital symptoms and offered type-specific serologic testing for HSV-2. • For partners without genital herpes, no data are available on which to base a recommendation for PEP or PrEP with antiviral medications or that they would prevent acquisition, and this should not be offered to patients as a prevention strategy.

	• **Drug Allergy, Intolerance, or Adverse Reactions:**
	  • Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described
	• **HIV Infection:**
	  • Clinical manifestations of genital herpes might worsen during immune reconstitution early after initiation of ART.
	  • Recommended therapy for first-episode genital herpes is the same as for persons without HIV infection, although treatment courses might need to be extended for lesion resolution.
	  • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV.
	  • The risk for genital ulcer disease (GUD) increases during the first 6 months after starting ART, especially among persons who have a CD4+ T-cell count <200 cell/mm3.
	  • Suppressive antiviral therapy reduces the risk for GUD among this population and can be continued for 6 months after ART initiation when the risk for GUD returns to baseline levels.
	  • Suppressive antiviral therapy among persons with HIV and HSV infection does not reduce the risk for either HIV transmission or HSV-2 transmission to susceptible sex partners.
	  • Suppressive antiviral therapy does not delay HIV disease progression and is not associated with decreased risk for HIV-related inflammation among persons taking ART.
	  • For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.
	  • Recommended Regimens for Daily Suppression of Genital Herpes Among Persons with HIV Infection
	  ▪ Acyclovir 400–800 mg orally 2–3 times/day
	  Or
	  ▪ Famciclovir 500 mg orally 2 times/day
	  Or
	  ▪ Valacyclovir 500 mg orally 2 times/day

	• Recommended Regimens for Episodic Genital Herpes Infection Among Persons with HIV Infection ▪ Acyclovir 400 mg orally 3 times/day for 5–10 days Or ▪ Famciclovir 500 mg orally 2 times/day for 5–10 days Or ▪ Valacyclovir 1 g orally 2 times/day for 5–10 days • **Antiviral-Resistant HSV Infection:** • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected and a viral culture obtained for phenotypic sensitivity testing • Such persons should be managed in consultation with an infectious disease specialist, and alternative therapy should be administered. • All acyclovir-resistant strains are also resistant to valacyclovir, and the majority are resistant to famciclovir. • Foscarnet (40–80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. • Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Foscarnet and cidofovir are nephrotoxic medications that require intensive laboratory monitoring and infectious disease specialist consultation. Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Topical cidofovir gel 1% can be applied to lesions 2–4 times daily; however, cidofovir must be compounded at a pharmacy • Prevention of antiviral resistance remains challenging among persons with HIV infection. • Experience with another group of immunocompromised persons (e.g., hematopoietic stemcell recipients) demonstrated that persons receiving daily suppressive antiviral therapy were less likely to experience acyclovir-resistant HSV infection compared with those who received

episodic therapy for outbreaks.

- **Genital Herpes During Pregnancy:**
  - Women who acquire HSV in the second half of pregnancy should be managed in consultation with maternal fetal medicine and infectious disease specialists
  - Many fetuses are exposed to acyclovir each year, and the medication is believed to be safe for use during all trimesters of pregnancy.
  - Acyclovir is also believed to be safe during breastfeeding.
  - Although data regarding prenatal exposure to valacyclovir and famciclovir are limited, data from animal trials indicate that these drugs also pose a low risk among pregnant women.
  - Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV
  - Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases
  - No data support use of antiviral therapy among asymptomatic HSV-seropositive women without a history of genital herpes.
  - In addition, the effectiveness of antiviral therapy among sex partners with a history of genital herpes to decrease the risk for HSV transmission to a pregnant woman has not been studied.
  - Recommended Regimen for Suppression of Recurrent Genital Herpes Among Pregnant Women (Treatment recommended starting at 36 weeks' gestation)
    - Acyclovir 400 mg orally 3 times/day

      Or
    - Valacyclovir 500 mg orally 2 times/day
- **Neonatal Herpes:**
  - Newborn infants exposed to HSV during birth, as documented by virologic testing of maternal lesions at delivery or presumed by observation of maternal lesions, should be followed clinically in consultation with a pediatric infectious disease specialist

	○ Surveillance cultures or PCR of mucosal surfaces of the neonate to detect HSV infection might be considered before the development of clinical signs of neonatal herpes to guide treatment initiation. ○ In addition, administration of acyclovir might be considered for neonates born to women who acquired HSV near term because the risk for neonatal herpes is high for these newborn infants. ○ All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. ○ The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. • **Human Papillomavirus Infections:** ○ ACIP recommendations for HPV vaccination include the following: ▪ Routine HPV vaccination for all adolescents at age 11 or 12 years. ▪ Administering vaccine starting at age 9 years. ▪ Catch-up vaccination through age 26 years for those not vaccinated previously. ▪ Not using HPV vaccination for all adults aged >26 years. Instead, shared clinical decision-making between a patient and a provider regarding HPV vaccination is recommended for certain adults aged 27–45 years not vaccinated previously. ▪ A 2-dose vaccine schedule (at 0- and 6–12-month intervals) is recommended for persons who initiate vaccination before their 15th birthday. ▪ A 3-dose vaccine schedule (at 0-, 1–2-, and 6-month intervals) for immunocompromised persons regardless of age of initiation. ▪ HPV vaccines are not recommended for use in pregnant women. HPV vaccines can be administered regardless of history of anogenital warts, abnormal Pap test or HPV test, or anogenital precancer. Women who have received HPV vaccine should continue routine cervical cancer screening. ▪ HPV vaccine is available for eligible children and adolescents aged <19 years ▪ HPV vaccination has not been associated with initiation of sexual activity or sexual risk behaviors

	○ Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. ○ Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. Precancerous lesions are detected through cervical cancer screening • **Anogenital Warts - HPV** • For most patients, treatment results in resolution of the warts. • If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. • Because warts might spontaneously resolve in <1 year, an acceptable alternative for certain persons is to forego treatment and wait for spontaneous resolution. • Available therapies for anogenital warts might reduce, but probably do not eradicate, HPV infectivity. Whether reduction in HPV viral DNA resulting from treatment reduces future transmission remains unknown. • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • No definitive evidence indicates that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts. • Shared clinical decision-making between a patient and a provider regarding treatment algorithms has been associated with improved clinical outcomes and should be encouraged. • Because all available treatments have shortcomings, clinicians sometimes use combination therapy (e.g., provider administered cryotherapy with patient-applied topical therapy between visits to the provider). However, limited data exist regarding the efficacy or risk for complications associated with combination therapy. • Treatment regimens are classified as either patient-applied or provider-administered modalities. • Patient applied modalities are preferred by certain persons because they can be administered in the privacy of their home. To ensure that patient-applied modalities are effective, instructions

should be provided to patients while in the clinic, and all anogenital warts should be accessible and identified during the clinic visit. Follow-up visits after weeks of therapy enable providers to answer any questions about use of the medication, address any side effects experienced, and facilitate assessment of the response to treatment.

- Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus) (Persons with external anal or perianal warts might also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy)

▪ Patient-applied: Imiquimod 3.75% or 5% cream (Might weaken condoms and vaginal diaphragms)

Or

▪ Podofilox 0.5% solution or gel

Or

▪ Sinecatechins 15% ointment (Might weaken condoms and vaginal diaphragms)

▪ Provider-administered: Cryotherapy with liquid nitrogen or cryoprobe

Or

▪ Surgical removal by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery

Or

▪ Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

- Imiquimod is a patient-applied, topically active immune enhancer that stimulates production of interferon and other cytokines. Imiquimod 5% cream should be applied once at bedtime, 3 times/week for <16 weeks.
- Similarly, imiquimod 3.75% cream should be applied once at bedtime every night for <8 weeks.
- With either formulation, the treatment area should be washed with soap and water 6–10 hours after the application.
- Local inflammatory reactions, including redness, irritation, induration, ulceration or erosion, and vesicles might occur with using imiquimod, and hypopigmentation has also been described.
- Limited case reports demonstrate an association between treatment with imiquimod cream

	and worsened inflammatory or autoimmune skin diseases (e.g., psoriasis, vitiligo, or lichenoid dermatoses). • Data from studies of human participants are limited regarding use of imiquimod during pregnancy; however, animal data indicate that this therapy poses low risk. • Podofilox (podophyllotoxin) is a patient-applied antimitotic drug that causes wart necrosis. Podofilox solution (using a cotton swab) or podofilox gel (using a finger) should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2, and the total volume of podofilox should be limited to 0.5 mL/day. If possible, the health care provider should apply the initial treatment to demonstrate proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before and after each application. • Podofilox is contraindicated during pregnancy • Sinecatechins is a patient-applied, green-tea extract with an active product (catechins). • Sinecatechins 15% ointment should be applied 3 times/day (0.5-cm strand of ointment to each wart) by using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for >16 weeks. The medication should not be washed off after use. Genital, anal, and oral sexual contact should be avoided while the ointment is on the skin. • The most common side effects of sinecatechins are erythema, pruritus or burning, pain, ulceration, edema, induration, and vesicular rash. This medication is not recommended for persons with HIV infection, other immunocompromised conditions, or genital herpes because the safety and efficacy of therapy has not been evaluated. • The safety of sinecatechins during pregnancy is unknown. • Cryotherapy is a provider-administered therapy that destroys warts by thermal-induced cytolysis. • Health care providers should be trained on the correct use of cryotherapy because

	overtreatment or undertreatment can result in complications or low efficacy. • Pain during and after application of the liquid nitrogen, followed by necrosis and sometimes blistering, is common. • Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large. • Surgical therapy has the advantage of eliminating the majority of warts at a single visit, although recurrence can occur. • Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit. • Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by CO2 laser, or by curettage. • For patients with large or extensive warts, surgical therapy, including CO2 laser, might be most beneficial; such therapy might also be useful for intraurethral warts, particularly for those persons whose warts have not responded to other treatments. • Treatment of anogenital and oral warts should be performed in a ventilated room by using standard precautions and local exhaust ventilation (e.g., a smoke evacuator) • Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) are provider-administered caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. • TCA solution has a low viscosity, comparable with that of water, and can spread rapidly and damage adjacent tissues if applied excessively. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. • TCA or BCA treatment can be repeated weekly if necessary. • Alternative Regimens for External Genital Warts: ▪ Fewer data are available regarding the efficacy of alternative regimens for treating anogenital

	warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. ▪ Shared clinical decision making between the patient and provider regarding benefits and risks of these regimens should be provided. ▪ In addition, alternative regimens might be associated with more side effects. ▪ Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. ▪ Podophyllin resin 10%–25% in a compound tincture of benzoin might be considered for provider-administered treatment under conditions of strict adherence to recommendations. ▪ Podophyllin should be applied to each wart and then allowed to air dry before the treated area comes into contact with clothing. Overapplication or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas and possible systemic toxicity. ▪ The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, application should be limited to <0.5 mL of podophyllin or an area of <10 cm2 of warts per session; the area to which treatment is administered should not contain any open lesions, wounds, or friable tissue; and the preparation should be thoroughly washed off 1–4 hours after application. ▪ Podophyllin resin preparations differ in the concentration of active components and contaminants. Shelf life and stability of podophyllin preparations are unknown. The safety of podophyllin during pregnancy has not been established. • Recommended Regimens for Urethral Meatus Warts: ▪ Cryotherapy with liquid nitrogen Or ▪ Surgical removal • Recommended Regimens for Vaginal Warts: ▪ Cryotherapy with liquid nitrogen The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal

	perforation and fistula formation. Or ▪ Surgical removal Or ▪ Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution • Recommended Regimens for Cervical Warts: ▪ Cryotherapy with liquid nitrogen Or ▪ Surgical removal Or ▪ Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude HSIL should be performed before treatment is initiated. • Recommended Regimens for Intra-Anal Warts: ▪ Cryotherapy with liquid nitrogen Or ▪ Surgical removal Or ▪ Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution Management of intra-anal warts should include consultation with a colorectal specialist. • **Management of Sex Partners – HPV** • Partners should be counseled that they might already have HPV despite no visible signs of warts; therefore, HPV testing of sex partners of persons with genital warts is not recommended. • **Pregnancy – HPV** • Podofilox, podophyllin, and sinecatechins should not be used during pregnancy.

	• Imiquimod appears to pose low risk but should be avoided until more data are available. • Anogenital warts can proliferate and become friable during pregnancy. • Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete. • **HIV and Other Causes of Immunosuppression – HPV** • Persons with HIV infection or who are otherwise immunosuppressed are more likely to develop anogenital warts than those who do not have HIV. • Moreover, such persons can have larger or more numerous lesions, might not respond to therapy as well as those who are immunocompetent, and might have more frequent recurrences after treatment • Despite these factors, data do not support altered approaches to treatment for persons with HIV infection. • **High-Grade Squamous Intraepithelial Lesions** • Biopsy of an atypical wart might reveal HSIL or cancer of the anogenital tract. In this instance, referral to a specialist for treatment is recommended. • **Cancers and Precancers Associated with Human Papillomavirus** • Persistent infection with high-risk (oncogenic) types of HPV has a causal role in approximately all cervical cancers and in certain vulvar, vaginal, penile, anal, and oropharyngeal cancers • However, cervical cancer is the only HPV-associated cancer for which routine screening is recommended. • **Hepatitis B Virus Infection** o No specific therapy is available for persons with acute HBV infection; treatment is supportive. Persons with chronic HBV infection should be referred for evaluation to a provider experienced in managing such infections. Therapeutic agents approved by FDA for treatment of chronic HBV infection can achieve sustained suppression of HBV replication and remission of liver disease. o Prevention – HepB Virus infection:

	▪ Two products have been approved for HBV prevention: hepatitis B immune globulin (HBIG) for PEP and hepatitis B vaccine. ▪ HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination. ▪ HBIG is prepared from plasma known to contain high concentrations of anti-HBs. The recommended dose of HBIG is 0.06 mL/kg body weight. • Postexposure Prophylaxis - HepB Virus Infection: ▪ Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV. ▪ HBIG alone also has been demonstrated to be effective in preventing HBV transmission; however, with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination. • Exposure to a Source Who Is HBsAg Positive ▪ Unvaccinated persons or persons known not to have responded to a complete hepatitis B vaccine series should receive both HBIG and hepatitis vaccine as soon as possible (preferably ≤24 hours) after a discrete, identifiable exposure to blood or body fluids that contain blood from a person with HBsAg. ▪ Hepatitis B vaccine should be administered simultaneously with HBIG at a separate anatomic site, and the vaccine series should be completed by using the age-appropriate vaccine dose and schedule. ▪ Exposed persons who are not fully vaccinated because they have not completed the vaccine series should receive HBIG (i.e., 0.06 mL/kg body weight) and complete the vaccine series. ▪ Persons who have written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing should receive a single vaccine booster dose. ▪ Exposed persons who are known to have responded to vaccination by postvaccination testing are considered protected; therefore, they need no additional doses of vaccine or HBIG.

	▪ All persons with an occupational exposure to blood or body fluids that contain HBV should be managed according to guidelines • Exposure to a Source with Unknown HBsAg Status: ▪ Unvaccinated persons and persons with previous nonresponse to hepatitis B vaccination who have a discrete, identifiable exposure to blood or body fluids containing blood from a person with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated as soon as possible after exposure (preferably <24 hours) and the series completed according to the age-appropriate dose and schedule. ▪ Exposed persons who are not fully vaccinated but started the series should complete the vaccine series. Exposed persons with written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing require no further treatment. • Management of Persons Who Are HBsAg Positive: ▪ Household, sexual, and needle-sharing contacts of persons with chronic infection should be evaluated. ▪ Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing ▪ Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule. ▪ Sex partners of persons with HBsAg should be counseled to use latex condoms to protect themselves from sexual exposure to infectious body fluids (e.g., semen and vaginal secretions), unless they have been demonstrated to be immune after vaccination (anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive). ▪ To prevent or reduce the risk for transmission to others in addition to vaccination, persons with HBsAg also should be advised to cover cuts and lesions, refrain from donating blood and sharing household articles. ▪ To protect the liver from further harm, persons with HBsAg should be advised to avoid or limit alcohol, refrain from starting OTC, herbal or prescription medications, and get vaccinated against

	hepatitis A • Pregnancy – HBV infection ▪ Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination. ▪ All pregnant women with HBsAg should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist. • HIV with HBV infection ▪ Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate and should be managed in consultation with an infectious disease specialist
Section 1.1.2 **ACOG PRACTICE BULLETIN Management of Genital Herpes in Pregnancy 2020**[18]	• The following recommendations are based on limited or inconsistent scientific evidence (Level B): • Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. • For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. • Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women. • Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate viral shedding. • The following recommendations are based primarily on consensus and expert opinion (Level C): • In women with preterm prelabor rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV. When expectant management is elected, treatment with an antiviral is recommended. • Antiviral medications available to treat herpes simplex virus during pregnancy: • The three oral antiviral agents that are commonly used to treat HSV infections are acyclovir, valacyclovir, and famciclovir.

	• These drugs are approved for the treatment of primary genital herpes, the treatment of episodes of recurrent disease, and the daily treatment for suppression of outbreaks of recurrent genital herpes. • Topical antiviral therapy has not been shown to be of benefit. • Of the three medications, acyclovir is the most well studied in pregnancy, and animal and human data suggest that it is safe in pregnancy, including in the first trimester, and can effectively reduce viral shedding and persistence of lesions. • Valacyclovir is a prodrug of acyclovir and is rapidly converted to acyclovir after metabolism in the liver. Therefore, valacyclovir is presumed to have a safety profile that is similar to acyclovir. • Because valacyclovir has increased bioavailability and can be taken less often, patient adherence with valacyclovir may be increased compared with acyclovir. However, valacyclovir is generally more expensive than acyclovir. • There are no published data on the use of famciclovir in pregnancy. • There are no documented increases in adverse fetal or neonatal effects because of acyclovir exposure • Development of viral resistance to acyclovir has not been a problem in immunocompetent patients. In two large, laboratory-based studies, a low prevalence of acyclovir resistance in viruses isolated from immunocompetent patients has been estimated, whereas acyclovir resistant HSV infections occur more commonly among patients who are immunocompromised • Antiviral therapy recommended for a primary or a nonprimary first-episode herpes simplex virus outbreak in pregnancy: o At the time of the initial outbreak, antiviral treatment should be administered orally to pregnant women to reduce the duration and the severity of the symptoms as well as reduce the duration of viral shedding. o In patients who have severe disease, oral treatment can be extended for more than 10 days if lesions are incompletely healed at that time. o Acyclovir may be administered intravenously to pregnant women with severe genital HSV infection or with disseminated herpetic infections.

	○ Women with a primary or nonprimary first-episode outbreak in pregnancy, as well as women with a clinical history of genital herpes, should be offered suppressive therapy beginning at 36 weeks of gestation. ○ Alternatively, for primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. • Antiviral therapy recommended for a recurrent herpes simplex virus infection in pregnancy: ○ In women with a recurrent HSV outbreak during pregnancy, antiviral treatment should be administered orally to reduce the duration and the severity of the symptoms and to reduce the duration of viral shedding. ○ Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. ○ For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. ○ Suppressive therapy beginning at 36 weeks of gestation in women diagnosed with herpes before or during pregnancy has been shown to reduce the risk of clinical recurrence of HSV at the time of delivery, cesarean birth for recurrent herpes, and asymptomatic shedding. ○ Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women ○ Although neutropenia is a recognized, transient complication of acyclovir treatment of neonatal HSV infection, it has not been reported after maternal suppressive therapy ○ The acyclovir concentrations at which neutropenia occurred were approximately 5–30 times greater than were observed in umbilical vein plasma in a pharmacokinetic study of valacyclovir in pregnancy. • Women with active genital herpes simplex virus lesions and preterm prelabor rupture of membranes: ○ In a patient with prelabor rupture of membranes and active genital HSV lesions, the risks of prematurity should be weighed against the risk of neonatal HSV disease in considering

	expectant management. ○ In pregnancies remote from term, especially in women with recurrent disease, there is increasing support for continuing the pregnancy to gain benefit from time and use of corticosteroids In women with preterm prelabor rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV. ○ When expectant management is elected, treatment with an antiviral is recommended. ○ The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes • Breastfeeding women with active herpes simplex virus: ○ Valacyclovir appears to be safe for breastfeeding women. ○ Although acyclovir was found in the breast milk in concentrations that were higher than the maternal serum, the amount of acyclovir in the breast milk was only 2% of that used for therapeutic doses in neonates
HTA Pharmacoeconomics Analysis	Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Viral STDs:

Query	Filters	Search Details	Results
((((((((((((((((((((((((((((((Simplexvirus[MeSH Terms]) OR (Simplexviruses[Title/Abstract])) OR (Herpesvirus Hominis[Title/Abstract])) OR (Herpesvirus Homini[Title/Abstract])) OR (Homini, Herpesvirus[Title/Abstract])) OR (Hominis, Herpesvirus[Title/Abstract])) OR (Herpes Simplex Virus[Title/Abstract])) OR (Herpes Simplex Viruses[Title/Abstract])) OR (Herpes Labialis Virus[Title/Abstract])) OR (Herpes Labialis Viruses[Title/Abstract])) OR (Labialis Virus, Herpes[Title/Abstract])) OR (Labialis Viruses, Herpes[Title/Abstract])) OR (Virus, Herpes Labialis[Title/Abstract])) OR (Viruses, Herpes Labialis[Title/Abstract])) OR (Herpesvirus 1, Saimiriine[Title/Abstract])) OR (Saimiriine Herpesvirus 1[Title/Abstract])) OR (Herpes-T Virus[Title/Abstract])) OR (Herpes T Virus[Title/Abstract])) OR (Herpes-T Viruses[Title/Abstract])) OR (Herpesvirus 1, Saimirine[Title/Abstract])) OR (Saimirine Herpesvirus 1[Title/Abstract])) OR (Marmoset Herpesvirus[Title/Abstract])) OR (Herpesvirus, Marmoset[Title/Abstract])) OR (Herpesviruses, Marmoset[Title/Abstract])) OR (Marmoset Herpesviruses[Title/Abstract])) OR (Herpesvirus 1 (alpha), Saimirine[Title/Abstract])) OR (Herpesvirus Platyrhinae[Title/Abstract])) OR (Platyrhinae, Herpesvirus[Title/Abstract])) OR (Marmoset Virus[Title/Abstract])) OR (Marmoset Viruses[Title/Abstract])) OR (Herpesvirus 16,	Guideline, in the last 5 years	("simplexvirus"[MeSH Terms] OR "Simplexviruses"[Title/Abstract] OR "herpesvirus hominis"[Title/Abstract] OR (("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "Herpesvirus"[All Fields]) AND "Homini"[Title/Abstract]) OR ("Homini"[All Fields] AND "Herpesvirus"[Title/Abstract]) OR ("Hominis"[All Fields] AND "Herpesvirus"[Title/Abstract]) OR "herpes simplex virus"[Title/Abstract] OR "herpes simplex viruses"[Title/Abstract] OR "herpes labialis virus"[Title/Abstract] OR (("herpes labialis"[MeSH Terms] OR ("Herpes"[All Fields] AND "Labialis"[All Fields]) OR "herpes labialis"[All Fields]) AND "Viruses"[Title/Abstract]) OR ("Labialis"[All Fields] AND "virus herpes"[Title/Abstract]) OR ("Labialis"[All Fields] AND "viruses herpes"[Title/Abstract]) OR (("virology"[MeSH Subheading] OR "virology"[All Fields] OR "Viruses"[All Fields] OR "Viruses"[MeSH Terms] OR "virus s"[All Fields] OR "viruse"[All Fields] OR "Virus"[All Fields]) AND "herpes labialis"[Title/Abstract]) OR (("virology"[MeSH Subheading] OR "virology"[All Fields] OR "Viruses"[All Fields] OR "Viruses"[MeSH Terms] OR "virus s"[All Fields] OR "viruse"[All Fields] OR "Virus"[All Fields]) AND "herpes labialis"[Title/Abstract]) OR	7

Cercopithecine[Title/Abstract])) OR (Herpesvirus Papio 2[Title/Abstract])) OR (Cercopithecine Herpesvirus 16[Title/Abstract])		((("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "Herpesvirus"[All Fields]) AND "1"[All Fields]) AND "Saimiriine"[Title/Abstract]) OR "saimiriine herpesvirus 1"[Title/Abstract] OR "herpes t virus"[Title/Abstract] OR "herpes t virus"[Title/Abstract] OR ("Herpes-T"[All Fields] AND "Viruses"[Title/Abstract]) OR ((("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "Herpesvirus"[All Fields]) AND "1"[All Fields]) AND "Saimirine"[Title/Abstract]) OR ("Saimirine"[All Fields] AND "herpesvirus 1"[Title/Abstract]) OR "marmoset herpesvirus"[Title/Abstract] OR (("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "Herpesvirus"[All Fields]) AND "Marmoset"[Title/Abstract]) OR "herpesviruses marmoset"[Title/Abstract] OR (("callitrichinae"[MeSH Terms] OR "callitrichinae"[All Fields] OR "Marmoset"[All Fields] OR "callithrix"[MeSH Terms] OR "callithrix"[All Fields] OR "marmosets"[All Fields]) AND "Herpesviruses"[Title/Abstract]) OR ((((("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "Herpesvirus"[All Fields]) AND "1"[All Fields]) AND ("alpha"[All Fields] OR "alpha s"[All Fields] OR "alphas"[All Fields])) AND "Saimirine"[Title/Abstract]) OR ("Herpesvirus"[Title/Abstract]) OR	

		"marmoset virus"[Title/Abstract] OR (("callitrichinae"[MeSH Terms] OR "callitrichinae"[All Fields] OR "Marmoset"[All Fields] OR "callithrix"[MeSH Terms] OR "callithrix"[All Fields] OR "marmosets"[All Fields]) AND "Viruses"[Title/Abstract]) OR ((("herpesviridae"[MeSH Terms] OR "herpesviridae"[All Fields] OR "Herpesvirus"[All Fields]) AND "16"[All Fields]) AND "Cercopithecine"[Title/Abstract]) OR "herpesvirus papio 2"[Title/Abstract] OR "cercopithecine herpesvirus 16"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	
((((((((((((Human Papillomavirus Viruses[MeSH Terms]) OR (Human Papillomavirus Virus[Title/Abstract])) OR (Papillomavirus Virus, Human[Title/Abstract])) OR (Virus, Human Papillomavirus[Title/Abstract])) OR (Human Papillomavirus[Title/Abstract])) OR (Human Papillomaviruses[Title/Abstract])) OR (HPV, Human Papillomavirus Viruses[Title/Abstract])) OR (Human Papilloma Virus[Title/Abstract])) OR (Human Papilloma Viruses[Title/Abstract])) OR (Papilloma Virus, Human[Title/Abstract])) OR (Virus, Human Papilloma[Title/Abstract])) OR (HPV Human Papillomavirus[Title/Abstract])) OR (HPV Human Papillomaviruses[Title/Abstract])) OR (Human Papillomavirus, HPV[Title/Abstract])) OR (Human Papillomaviruses, HPV[Title/Abstract])	Guideline, in the last 5 years	("human papillomavirus viruses"[MeSH Terms] OR "human papillomavirus virus"[Title/Abstract] OR (("papillomaviridae"[MeSH Terms] OR "papillomaviridae"[All Fields] OR "Papillomavirus"[All Fields]) AND "virus human"[Title/Abstract]) OR "virus human papillomavirus"[Title/Abstract] OR "human papillomavirus"[Title/Abstract] OR "human papillomaviruses"[Title/Abstract] OR "hpv human papillomavirus viruses"[Title/Abstract] OR "human papilloma virus"[Title/Abstract] OR "human papilloma viruses"[Title/Abstract] OR "papilloma virus human"[Title/Abstract] OR "virus human papilloma"[Title/Abstract] OR "hpv human papillomavirus"[Title/Abstract] OR	29

		"hpv human papillomaviruses"[Title/Abstract] OR "human papillomavirus hpv"[Title/Abstract] OR "human papillomaviruses hpv"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	
(((((((((Sexually Transmitted Diseases, Viral[MeSH Terms]) OR (Viral Sexually Transmitted Disease[Title/Abstract])) OR (Venereal Diseases, Viral[Title/Abstract])) OR (Viral Venereal Diseases[Title/Abstract])) OR (Disease, Viral Venereal[Title/Abstract])) OR (Diseases, Viral Venereal[Title/Abstract])) OR (Venereal Disease, Viral[Title/Abstract])) OR (Viral Venereal Disease[Title/Abstract])) OR (Sexually Transmitted Disease, Viral[Title/Abstract])) OR (Viral Sexually Transmitted Diseases[Title/Abstract])	Guideline, in the last 5 years	("sexually transmitted diseases, viral"[MeSH Terms] OR "viral sexually transmitted disease"[Title/Abstract] OR (("veneral"[All Fields] OR "venerally"[All Fields] OR "Venereal"[All Fields] OR "venereally"[All Fields]) AND "diseases viral"[Title/Abstract]) OR "viral venereal diseases"[Title/Abstract] OR (("Disease"[MeSH Terms] OR "Disease"[All Fields] OR "Diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields]) AND "viral venereal"[Title/Abstract]) OR (("Disease"[MeSH Terms] OR "Disease"[All Fields] OR "Diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields]) AND "viral venereal"[Title/Abstract]) OR (("veneral"[All Fields] OR "venerally"[All Fields] OR "Venereal"[All Fields] OR "venereally"[All Fields]) AND "disease viral"[Title/Abstract]) OR (("virally"[All Fields] OR "virals"[All Fields] OR "virology"[MeSH Terms] OR "virology"[All Fields] OR "Viral"[All Fields]) AND "venereal disease"[Title/Abstract]) OR ((("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All	53

		Fields] OR "Sexually"[All Fields] OR "sexualities"[All Fields] OR "sexuality"[MeSH Terms] OR "sexuality"[All Fields] OR "sexualization"[All Fields] OR "sexualize"[All Fields] OR "sexualized"[All Fields] OR "sexualizing"[All Fields] OR "sexuals"[All Fields]) AND ("transmit"[All Fields] OR "transmited"[All Fields] OR "transmits"[All Fields] OR "Transmitted"[All Fields] OR "transmitting"[All Fields])) AND "disease viral"[Title/Abstract]) OR "viral sexually transmitted diseases"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithms of Viral STDs

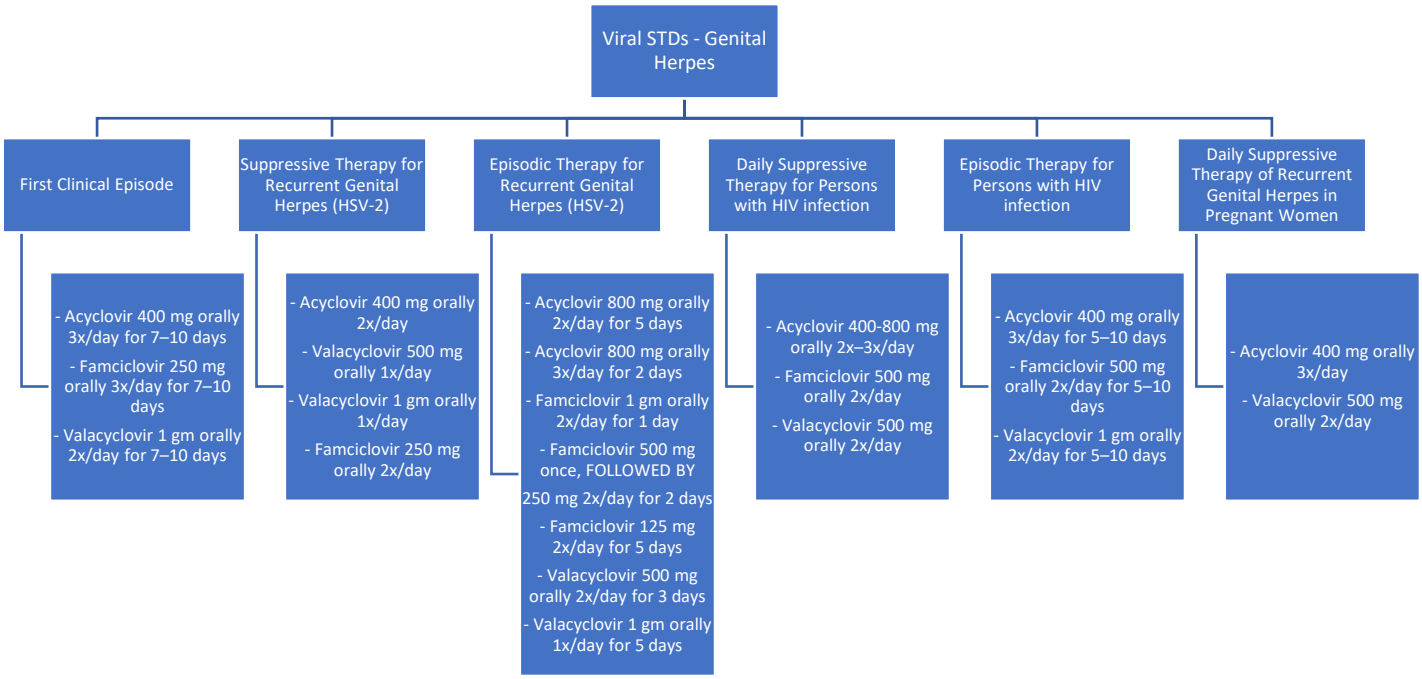

Figure 1. *Treatment Algorithm for the Management of Genital Herpes*

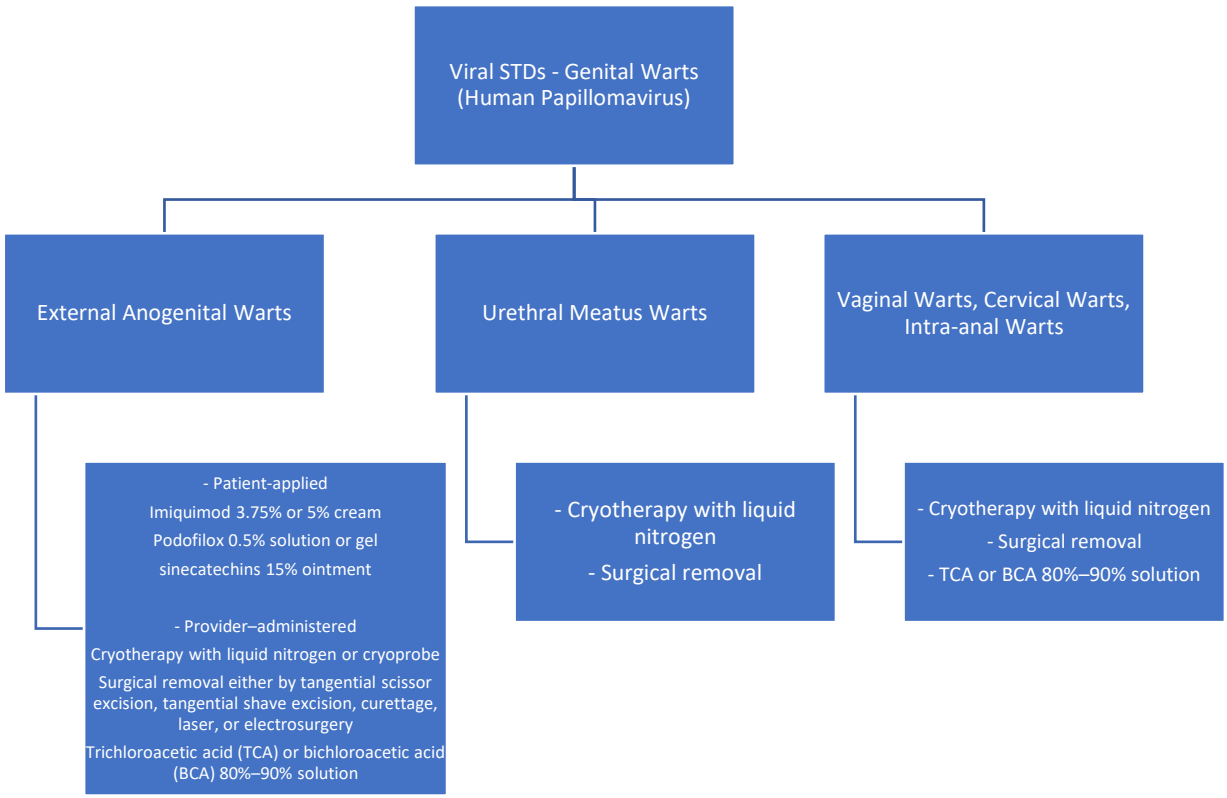

Figure 2. *Treatment Algorithm for the Management of Genital Warts (HPV)*

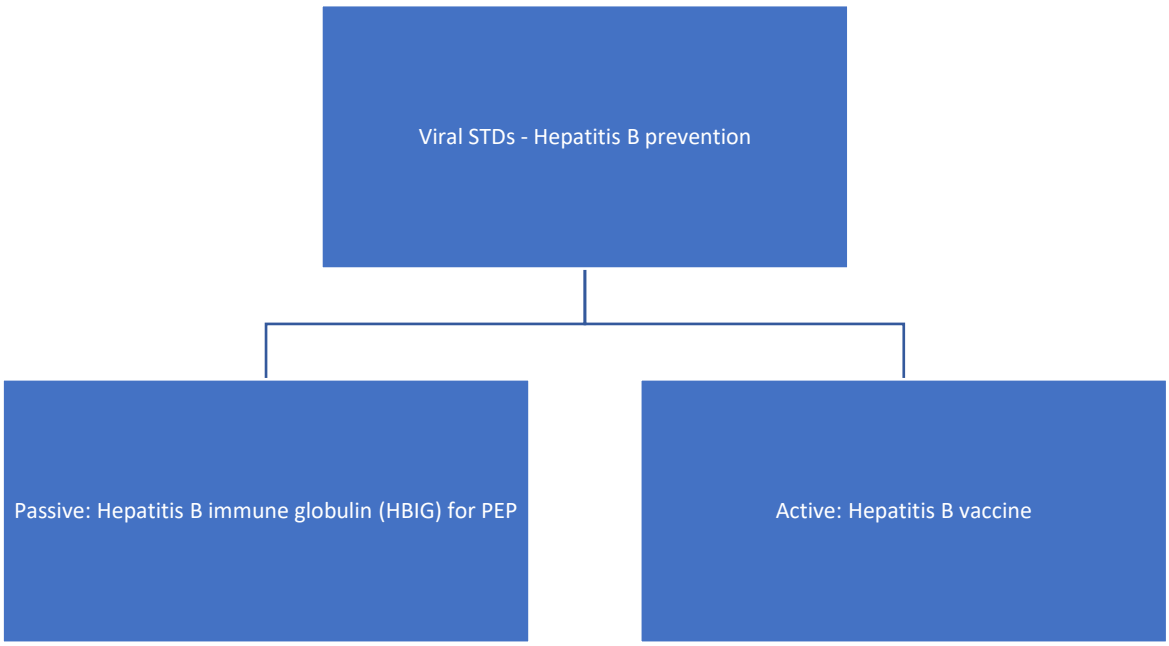

Figure 3. *Treatment Algorithm for the Prevention of Hepatitis B*

Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV.