

WHO GUIDELINES FOR THE

Treatment of *Genital Herpes Simplex Virus*



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World Health
Organization

WHO Library Cataloguing-in-Publication Data

WHO guidelines for the treatment of genital herpes simplex virus

I. World Health Organization.

ISBN 978 92 4 154987 5

Subject headings are available from WHO institutional repository

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Printed by the WHO Document Production Services, Geneva, Switzerland

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Web annexes available at:

[www.who.int/reproductivehealth/publications/rtis/genital- HSV-treatment-guidelines/en/](http://www.who.int/reproductivehealth/publications/rtis/genital-HSV-treatment-guidelines/en/)

Web annex D: Evidence profiles and evidence-to-decision frameworks

Web annex E: Systematic reviews for genital herpes simplex virus guidelines

Web annex F: Summary of conflicts of interest

ACKNOWLEDGEMENTS

The Department of Reproductive Health and Research at the World Health Organization (WHO) would like to thank the members of the STI Guideline Development Group for their consistent availability and commitment to making these guidelines possible. The Department is also grateful to the STI External Review Group for peer reviewing these guidelines, and appreciates the contribution of the WHO Steering Committee. The names of the members of each group are listed below, with full details provided in Annex A.

Special thanks to Dr Nancy Santesso, the guideline methodologist who also led the systematic review process, for her hard work and firm commitment to the guideline development process. We also thank the members of the Systematic Review Team from McMaster University.

We appreciate the overall support of the WHO Guidelines Review Committee Secretariat during the guideline development process, with grateful thanks to Dr Susan Norris.

We thank MsTheresa Ryle for the administrative support, and 400 Communications for assistance with the guideline design and layout. This guideline document was edited by Ms Jane Patten, of Green Ink, United Kingdom.

Dr Teodora Wi led the guideline development process and Dr Nathalie Broutet co-led the process under the supervision of Dr James Kiarie and leadership of Dr Ian Askew. Mr Lee Sharkey provided support during the guideline development process.

FUNDING

The preparation and printing of the guidelines were funded exclusively by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP). No external source of funding was solicited or utilized.

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
CI	confidence interval
DOI	declaration of interests
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUD	genital ulcer disease
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRP	UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
HSV	herpes simplex virus
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
MSH	Management Sciences for Health
MSM	men who have sex with men
NAAT	nucleic acid amplification test
PICO	population, intervention, comparator, outcome
POCT	point-of-care diagnostic test
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
WHO	World Health Organization

WHO GUIDELINES FOR THE TREATMENT OF GENITAL HERPES SIMPLEX VIRUS

EXECUTIVE SUMMARY

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. More than a million STIs are acquired every day.

Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcers in many countries. An estimated 19.2 million new HSV-2 infections occurred among adults and adolescents aged 15–49 years worldwide in 2012, with the highest rates among younger age groups. HSV-2 is a lifelong infection; the estimated global HSV-2 prevalence of 11.3% translates into an estimated 417 million people with the infection in 2012.

HSV type 1 (HSV-1) typically causes non-sexually-transmitted oral herpes infection. However, HSV-1 can also be transmitted to the genitals through oral sex and is increasingly noted as a cause of genital HSV, especially in high-income countries. Globally, an estimated 140 million people had genital HSV-1 infection in 2012.

HSV-2 infection is of particular concern due to its epidemiological synergy with HIV infection and transmission. People who are infected with HSV-2 are approximately three times more likely to become infected with HIV, and people with both HIV and genital HSV are more likely to transmit HIV to others.

Symptomatic genital HSV is a lifelong condition that can be characterized by frequent symptomatic recurrences. Most initial infections are asymptomatic or atypical, therefore the majority of people with HSV-2 infection have not been diagnosed. The classical clinical presentation of the first episode of symptoms of primary genital HSV infection is characterized by bilateral clusters of erythematous papules, vesicles or ulcerations on the external genitalia, in the perianal region or on the buttocks, occurring 4–7 days after sexual exposure. This classical syndrome occurs only in 10–25% of primary infections. Although HSV-1 and HSV-2 are usually transmitted by different routes and affect different areas of the body, the signs and symptoms overlap. The first episode of symptoms of genital HSV-1 infection cannot be clinically differentiated from genital HSV-2 infection; it is only through laboratory tests that these infections can be differentiated. When vesicles are not present, laboratory confirmation may be needed to rule out other causes of genital ulcers.

Most people will experience one or more symptomatic recurrences within one year after the first symptomatic episode of HSV-2 infection. With genital HSV-1 infection, symptomatic episodes are much less likely to recur. Symptomatic recurrences are generally less severe than the first episode. Established HSV-2 infection typically leads to intermittent viral shedding from the genital mucosa, even in the absence of symptoms. As a result, HSV-2 is often transmitted by people who are unaware of their infection or who are asymptomatic at the time of sexual contact.

RATIONALE FOR THE GUIDELINES

Since the publication of the World Health Organization (WHO) Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. These guidelines provide updated treatment recommendations for genital HSV infection based on the most recent evidence; they form one of several modules of guidelines for specific STIs. Other modules will focus on treatments for *Neisseria gonorrhoeae* (gonorrhoea), *C. trachomatis* (chlamydial infection) and *Treponema pallidum* (syphilis). In addition, future work will provide guidance for syphilis screening and treatment of pregnant women, STI syndromic approach, clinical management, STI prevention, and treatments of other STIs. It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols, adapting this guidance to the local epidemiological situation and antimicrobial susceptibility data.

OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of genital HSV infection; and
- to support countries to update their national guidelines for treatment of genital HSV infection.

METHODS

These guidelines were developed following the methods outlined in the 2014 WHO handbook for guideline development. The Guideline Development Group (GDG) included international STI experts, clinicians, researchers and programme managers. The GDG prioritized questions and outcomes related to treatment of genital HSV infections to include in this update, and a methodologist and a team of systematic reviewers from McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy, independently conducted systematic reviews of the effectiveness of different treatments for genital HSV infections. The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented to the GDG. Conflicts of interest were managed according to WHO guidelines and declared before the recommendations were discussed and finalized. Research implications were also developed by the GDG.

RECOMMENDATIONS

The current guidelines provide six treatment recommendations for genital HSV infections. Recommendations were not updated for rare conditions including HSV meningo-encephalitis and other conditions for which no new information became available since the 2003 WHO STI guidelines. Treatment recommendation for neonatal HSV and treatment of pregnant women to prevent neonatal HSV infection will be made in a separate module.

The recommendations summarized in Table 1 apply to all adults, adolescents (10–19 years of age), pregnant women, people living with HIV, people who are immunocompromised and key populations, including sex workers, men who have sex with men (MSM) and transgender persons.

Table 1. Summary of recommendations for treatment of chlamydial infections

Recommendations	Strength of recommendation and quality of evidence
First clinical episode of genital HSV infection	
<p>For adults and adolescents with a first clinical episode of genital HSV infection, the WHO STI guideline recommends treatment over no treatment.</p> <p><i>Remarks:</i> This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.</p>	<p><i>Strong recommendation, moderate quality evidence</i></p>
<p>For adults and adolescents with a first clinical episode of genital HSV infection, the WHO STI guideline suggests a standard dose of aciclovir over valaciclovir or famciclovir.</p> <p>Dosages:</p> <ul style="list-style-type: none"> • aciclovir 400 mg orally thrice daily for 10 days (standard dose) • aciclovir 200 mg orally five times daily for 10 days • valaciclovir 500 mg orally twice daily for 10 days • famciclovir 250 mg orally thrice daily for 10 days <p><i>Remarks:</i> Given that follow-up visits may not be possible during the course of treatment and symptoms of the first clinical episode may be prolonged, therapy is provided for 10 days. Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of medicine may also depend on compliance considerations. This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.</p>	<p><i>Conditional recommendation, moderate quality evidence</i></p>
Recurrent clinical episode of genital HSV infection (episodic therapy)	
<p>For adults and adolescents with a recurrent clinical episode of genital HSV infection, the WHO STI guideline suggests treatment over no treatment.</p> <p><i>Remarks:</i> Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase. That recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women.</p>	<p><i>Conditional recommendation, moderate quality evidence</i></p>

<p>For adults and adolescents with a recurrent clinical episode of genital HSV infection, the WHO STI guideline suggests the use of aciclovir over valaciclovir or famciclovir.</p> <p>Dosages for adults, adolescents and pregnant women:</p> <ul style="list-style-type: none"> • aciclovir 400 mg orally thrice daily for 5 days, 800 mg twice daily for 5 days, or 800 mg thrice daily for 2 days • valaciclovir 500 mg orally twice daily for 3 days • famciclovir 250 mg orally twice daily for 5 days <p>Dosages for people living with HIV and people who are immunocompromised:</p> <ul style="list-style-type: none"> • aciclovir 400 mg orally thrice daily for 5 days • valaciclovir 500 mg orally twice daily for 5 days • famciclovir 500 mg orally twice daily for 5 days <p><i>Remarks:</i> Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of dosage may depend on compliance considerations. Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase.</p>	<p><i>Conditional recommendation, moderate quality evidence</i></p>
<p>Recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress (suppressive therapy)</p>	
<p>For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, the WHO STI guideline suggests suppressive therapy over episodic therapy, and reassessment after one year.</p> <p><i>Remarks:</i> Individuals who have frequent recurrences (e.g. 4–6 times a year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy. To determine frequency or severity, episodes can be monitored for the first few months. This recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women.</p>	<p><i>Conditional recommendation, moderate quality evidence</i></p>
<p>For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, the WHO STI guideline suggests aciclovir over valaciclovir or famciclovir for suppressive therapy.</p> <p>Dosages for adults, adolescents and pregnant women:</p> <ul style="list-style-type: none"> • aciclovir 400 mg orally twice daily • valaciclovir 500 mg orally once daily • famciclovir 250 mg orally twice daily <p>Dosages for people living with HIV and people who are immunocompromised:</p> <ul style="list-style-type: none"> • aciclovir 400 mg orally twice daily • valaciclovir 500 mg orally twice daily • famciclovir 500 mg orally twice daily <p><i>Remarks:</i> Individuals who have frequent recurrences (e.g. 4–6 times a year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy. To determine frequency or severity, episodes can be monitored for the first few months. Although the benefits of the medicines may be similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of medicine may also depend on compliance considerations.</p>	<p><i>Conditional recommendation, low quality evidence</i></p>

OVERVIEW OF THE GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs

STI EPIDEMIOLOGY AND BURDEN

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. The prevention and control of STIs is an integral component of comprehensive sexual and reproductive health services that are needed to attain the related targets under Sustainable Development Goal (SDG) No. 3 (Ensure healthy lives and promote well-being for all at all ages), including: target 3.2 – to end preventable deaths of newborns and children under 5 years of age; target 3.3 – to end the epidemics of AIDS and other communicable diseases; target 3.4 – to reduce premature mortality from noncommunicable diseases and promote mental health and well-being; target 3.7 – to ensure universal access to sexual and reproductive health-care services; and target 3.8 – to achieve universal health coverage.

Worldwide, more than a million curable STIs are acquired every day. In 2012, there were an estimated 357 million new cases of curable STIs among adults aged 15–49 years worldwide: 131 million cases of chlamydia, 78 million cases of gonorrhoea, 6 million cases of syphilis and 142 million cases of trichomoniasis (1). The prevalence of some viral STIs is similarly high, with an estimated 417 million people infected with herpes simplex virus type 2 (HSV-2) (2), and approximately 291 million women harbouring human papillomavirus (HPV) at any point in time (3). The burden of STIs varies by region and gender, and is greatest in resource-poor countries.

When left undiagnosed and untreated, curable STIs can result in serious complications and sequelae, such as pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, fetal loss and congenital infections. In 2012, an estimated 930 000 maternal syphilis infections resulted in 350 000 adverse pregnancy outcomes, including stillbirths, neonatal deaths, preterm births and infected infants (4). Curable STIs accounted for the loss of nearly 11 million disability-adjusted life years (DALYs) in 2010 (5). The psychological consequences of STIs include stigma, shame and diminished sense of self-worth. STIs have also been associated with relationship disruption and gender-based violence (6).

Both ulcerative and non-ulcerative STIs are associated with a several-fold increased risk of transmitting or acquiring HIV (7, 8). Infections causing genital ulcers are associated with the highest HIV transmission risk; in addition to curable ulcer-causing STIs (e.g. syphilis and chancroid), highly prevalent HSV-2 infections substantially increase that risk (9). Non-ulcerative STIs, such as gonorrhoea, chlamydia and trichomoniasis, have been shown to increase HIV transmission through genital shedding of HIV (10). Treating STIs with the right medicines at the right time is necessary to reduce HIV transmission and improve sexual and reproductive health (11). Efforts should therefore be taken to strengthen STI diagnosis and treatment.

WHY NEW GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs?

Since the publication of the World Health Organization (WHO) Guidelines for the management of sexually transmitted infections in 2003 (12), changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. Indeed, 88% of countries have updated their national STI guidelines or recommendations since 2006 (13). Updated global guidance reflecting the most recent evidence and expert opinion is therefore needed to assist countries to incorporate new developments into an effective national approach to the prevention and treatment of STIs.

There is an urgent need to update global treatment recommendations to effectively respond to the changing antimicrobial resistance (AMR) patterns of STIs, especially for *Neisseria gonorrhoeae*. Effective treatment protocols that take into account global and local resistance patterns are essential to reduce the risk of further development of AMR. High-level gonococcal resistance to quinolones, a previously recommended first-line treatment, is widespread and decreased susceptibility to the extended-spectrum (third-generation) cephalosporins, another first-line treatment for gonorrhoea, is on the rise (14). Low-level resistance to *Trichomonas vaginalis* has also been reported for nitroimidazoles, the only available treatment. Resistance to azithromycin has been reported in some strains of *Treponema pallidum* and treatment failures have been reported for tetracyclines and macrolides in the treatment of *Chlamydia trachomatis* (15, 16). During the WHO STI expert consultation in 2008, it was recommended that the 2003 WHO STI guidelines should be updated with

regard to the first- and second-line treatments for *C. trachomatis*, increasing the dosage of ceftriaxone to 250 mg for treatment of *N. gonorrhoeae* with continued monitoring of antimicrobial susceptibility, and consideration of whether azithromycin (2 g, single dose) should be recommended in early syphilis (17).

The epidemiology of STIs is changing, with viral pathogens becoming more prevalent than bacterial etiologies for some conditions; this means that updated information is required to inform locally appropriate prevention and treatment strategies. An increasing proportion of genital ulcers are now due to viral infections as previously common bacterial infections, such as chancroid, approach elimination in many countries (17, 18). As recommended during the STI expert consultation, treatment guidelines for genital ulcer disease (GUD) should be updated to include HSV-2 treatment and a longer treatment duration for HSV-2 should be explored. In addition, suppressive therapy for HSV-2 should be considered in areas with high HIV prevalence (17). The chronic, lifelong nature of viral infections also requires that renewed attention be paid to developing effective prevention strategies, including expanding accessibility to available vaccines for HPV and development of new vaccines for HSV-2.

In the 2003 WHO STI guidelines, WHO recommended a syndromic approach for the management of STIs. The approach guides the diagnosis of STIs based on identification of consistent groups of symptoms and easily recognized signs and indicates treatment for the majority of organisms that may be responsible for producing the syndrome. The syndromic management algorithms need to be updated in response to the changing situation. In addition to changes to the GUD algorithm, other syndromes need to be re-evaluated, particularly vaginal discharge. The approach to syndromes for key populations also needs to be updated. For example, addition of a syndromic management algorithm for anorectal infections in men who have sex with men (MSM) and sex workers is urgently needed since a substantial number of these infections go unrecognized and untreated in the absence of guidelines (17).

New rapid, point-of-care diagnostic tests (POCTs) are changing STI management. Rapid syphilis diagnostic tests are now widely available, making syphilis screening more widely accessible and allowing for earlier initiation of treatment for those who test positive. Efforts are under way to develop POCTs for other STIs that will augment syndromic management of symptomatic cases and increase the ability to identify asymptomatic infections (13). Updated guidelines are needed that incorporate rapid tests into syndromic management of STIs and provide algorithms for testing and screening (17).

Although recent technological advances in diagnostics, therapeutics, vaccines and barrier methods offer better opportunities for the prevention and care of STIs, access to these technologies is still limited, particularly in areas where the burden of infection is highest. For optimal effectiveness, global guidelines for the management of STIs need to include approaches for settings with limited access to modern technologies, as well as for settings in which these technologies are available.

It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols, adapting this guidance to the local epidemiological situation and antimicrobial susceptibility data. Standardization ensures that all patients receive adequate treatment at every level of health-care services, optimizes the training and supervision of health-care providers and facilitates procurement of medicines. It is recommended that national guidelines for the effective management of STIs be developed in close consultation with local STI, public health and laboratory experts.

APPROACH TO THE REVISION OF STI GUIDELINES

To ensure effective treatment for all STIs, WHO plans a phased approach to updating the STI guidelines to address a range of infections and issues. Four phases have been proposed by the WHO STI Secretariat and agreed upon by the STI Guideline Development Group (GDG) members (see Annex A for members of these groups). Table 2 summarizes the proposed phases and timeline.

Table 2: Phases for development of the STI guidelines

Phases	Topics	Timeframe
Phase 1	Treatment of specific STIs: <i>Chlamydia trachomatis</i> (chlamydia), <i>Neisseria gonorrhoeae</i> (gonorrhoea), HSV-2 (genital HSV) and <i>Treponema pallidum</i> (syphilis)	November 2013 – April 2016
	Syphilis screening and treatment of pregnant women STI syndromic approach Clinical management package	May 2016 – December 2017
Phase 2	STI prevention: condoms, behaviour change communication, biomedical interventions and vaccines	2017–2018
Phase 3	Treatment of specific STIs and reproductive tract infections (RTIs) not addressed in Phase 1: <i>Trichomonas vaginalis</i> (trichomoniasis), bacterial vaginosis, <i>Candida albicans</i> (candidiasis), <i>Hemophilus ducreyi</i> (chancroid), <i>Klebsiella granulomatis</i> (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), <i>Sarcoptes scabiei</i> (scabies) and <i>Phthirus pubis</i> (pubic lice)	2017–2018
Phase 4	STI laboratory diagnosis and screening	2017–2018

Phase 1 will focus on treatment recommendations for specific STIs as well as other important and urgent STI issues. Recommendations for the treatment of specific infections will be developed and published as independent modules:

- *Chlamydia trachomatis* (chlamydia)
- *Neisseria gonorrhoeae* (gonorrhoea)
- HSV-2 (genital HSV)
- *Treponema pallidum* (syphilis)
- Syphilis screening and treatment of pregnant women.

In addition, guidelines for the STI syndromic approach and a clinical management package will be developed later in Phase 1. Phase 2 will focus on guidelines for STI prevention. The independent Phase 1 and 2 modules will later be consolidated into one document and published as comprehensive WHO guidelines on STI case management. Phase 3 will address treatment of additional infections, including *Trichomonas vaginalis* (trichomoniasis), bacterial vaginosis, *Candida albicans* (candidiasis), *Hemophilus ducreyi* (chancroid), *Klebsiella granulomatis* (donovanosis), HPV (genital warts/cervical cancer), *Sarcoptes scabiei* (scabies) and *Phthirus pubis* (pubic lice). Phase 4 will provide guidance on laboratory diagnosis and screening of STIs.

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01

INTRODUCTION

1.1 EPIDEMIOLOGY, BURDEN AND CLINICAL CONSIDERATIONS

Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcers in many countries. An estimated 19.2 million new HSV-2 infections occurred among adults and adolescents aged 15–49 years worldwide in 2012, with the highest rates among younger age groups. HSV-2 is a lifelong infection; the estimated global HSV-2 prevalence of 11.3% translates into an estimated 417 million people with the infection in 2012. The prevalence of HSV-2 is highest in the WHO African Region (31.5%), followed by the Region of the Americas (14.4%). Despite lower prevalence, the WHO South-East Asia and Western Pacific Regions also harbour a large number of people with the infection due to the large populations of some countries in the region. The HSV-2 infection rate is consistently higher in females compared to males; there were an estimated 11.8 million new infections and 267 million prevalent infections among women in 2012 versus 7.4 million new and 150 million prevalent infections among men. The higher infection rate among women is most likely due to their greater biological susceptibility to HSV-2 infection (1).

HSV type 1 (HSV-1) typically causes non-sexually-transmitted oral herpes infection. However, HSV-1 can also be transmitted to the genitals through oral sex and is increasingly noted as a cause of genital HSV infection, especially in high-income countries. Globally, an estimated 140 million people had genital HSV-1 infection in 2012.

HSV-2 is of particular concern due to its epidemiological synergy with HIV infection and transmission. People who are infected with HSV-2 are approximately three times more likely to become infected with HIV (2), and people with both HIV and HSV-2 are more likely to transmit HIV to others (3). In addition, infection with HSV-2 in people living with HIV is often more severe and can lead to serious, although rare, complications, such as brain, eye or lung infections (4).

CLINICAL PRESENTATION

HSV-2 infection is the most common cause of recurrent genital ulcer disease (GUD) worldwide. Symptomatic genital HSV is a lifelong condition that can be characterized by frequent symptomatic recurrences. Most initial infections are asymptomatic or atypical, therefore the majority of people with HSV-2 infection have not been diagnosed.

The classical clinical presentation of the first episode of symptoms of primary genital HSV infection is characterized by bilateral clusters of erythematous papules, vesicles or ulcerations on the external genitalia, in the perianal region or on the buttocks, occurring 4–7 days after sexual exposure. This classical syndrome occurs only in 10–25% of primary infections. Patients present with genital pain and itching and 80% of women also report dysuria. Constitutional symptoms, such as fever, headache, myalgias and malaise are common. Cervicitis and tender inguinal and femoral lymphadenopathy frequently accompany initial infections. Over a period of 2–3 weeks, new lesions appear and existing lesions progress to vesicles and pustules and then coalesce into ulcers before crusting over and healing. Lesions on mucosal surfaces may be ulcerative without initially presenting as vesicles (5). Atypical presentations of infections due to HSV-2 may include small erosions and fissures, as well as dysuria or urethritis without lesions.

Although HSV-1 and HSV-2 are usually transmitted by different routes and affect different areas of the body, the signs and symptoms overlap (6). The first episode of symptoms of genital HSV-1 infection cannot be clinically differentiated from genital HSV-2 infection; it is only through laboratory tests that these infections can be differentiated.

Most people will experience one or more symptomatic recurrences within one year after the first symptomatic episode of HSV-2 infection. With genital HSV-1 infection, symptomatic episodes are much less likely to recur. Symptomatic recurrences are generally less severe than the first episode. After initial infection, chronic HSV-2 infection typically leads to intermittent viral shedding from the genital mucosa, even in the absence of symptoms. As a result, HSV-2 is often transmitted by people who are unaware of their infection or who are asymptomatic at the time of sexual contact. Recurrences are often preceded by prodromal symptoms (including tingling, paresthesias and pain), are characterized by fewer lesions than the first episode, and are usually present unilaterally and without systemic symptoms. Pain is less severe during recurrences, and the lesions heal in 5–10 days without antiviral treatment. Immunocompromised patients, including those with HIV, generally have more frequent recurrences with more severe symptoms. Recurrent ulcers can cause significant physical and psychological morbidity (5).

LABORATORY DIAGNOSIS

Genital HSV infection is often diagnosed clinically. However, laboratory testing is required to differentiate between HSV-1 and HSV-2. When vesicles are not present, laboratory confirmation may be needed to rule out other causes of genital ulcers. Laboratory methods for the diagnosis of HSV-2 include direct detection from lesions and indirect serological methods. Available tests for HSV-2 include antigen detection, isolation of virus by culture and nucleic acid amplification tests (NAATs) for viral DNA. Serological assays are also available to screen for HSV-2 infection by detection of type-specific antibodies, which develop in the first several weeks after initial infection and persist indefinitely. Although viral culture has previously been considered the gold standard for HSV-2 diagnosis, NAATs are increasingly preferred due to higher sensitivity, ease of specimen collection and transportation, and faster results (7).

1.2 RATIONALE FOR NEW RECOMMENDATIONS

The 2003 WHO STI guidelines for treatment of genital HSV infection (8) need to be updated to respond to the changing epidemiology of HSV-2, taking into account the synergy between HSV-2 and HIV transmission. HSV-2 has become, in many countries, the most common causative agent of GUD. Global guidance on the optimal dose and duration of aciclovir treatment for symptomatic initial and recurrent episodes is essential. As recommended during a WHO STI expert consultation in Montreux, Switzerland, in April 2008, a longer duration of treatment with aciclovir should be explored. Since the presentation of genital HSV infection is more severe in people who are immunocompromised, recommendations for treatment of HSV-2 infections in people living with HIV should also be updated. Suppressive therapy has been shown to reduce HIV viral shedding and HSV-2 viral shedding and recurrences, and recommendations that take into account the most recent body of evidence for when to provide suppressive therapy are needed, especially in areas of high HIV prevalence (9).

1.3 OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of genital HSV infection;
- to support countries to update their national guidelines for treatment of genital HSV infection.

1.4 TARGET AUDIENCE

These guidelines are primarily intended for health-care providers at all levels (primary, secondary and tertiary) of the health-care system involved in the treatment and management of people with STIs in low-, middle- and high-income countries. They are also intended for individuals working in sexual and reproductive health programmes, such as HIV/AIDS, family planning, maternal and child health and adolescent health, to ensure appropriate STI diagnosis and management.

The guidelines are also useful for policy-makers, managers, programme officers and other professionals in the health sector who are responsible for implementing STI management interventions at regional, national and subnational levels.

1.5 STRUCTURE OF THE GUIDELINES

These guidelines provide evidence-based recommendations for the treatment of specific clinical conditions caused by genital HSV infection. These guidelines provide direction for countries as they develop national treatment recommendations; however, national guidelines should also take into account the local pattern of antimicrobial resistance (AMR), as well as health service capacity and resources.

Updated treatment recommendations based on the most recent evidence are included for the most important common conditions caused by HSV. Recommendations were not updated for rare conditions including HSV meningo-encephalitis and other conditions for which no new information became available since the 2003 WHO STI recommendations were issued (8). Treatment recommendations for neonatal HSV infection, and for treatment of pregnant women to prevent neonatal HSV infection, will be made in a separate module.

Treatment recommendations for the following conditions caused by HSV are included in these guidelines:

- first clinical episode of genital HSV infection;
- recurrent clinical episode of genital HSV infection (episodic therapy);
- recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress (suppressive therapy).

02

METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the WHO handbook for guideline development (10) (see Annex B for a detailed description).

2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

To update the WHO guidelines for the prevention, treatment and management of STIs, a GDG was established, comprising 33 international STI experts, including clinicians, researchers and programme managers (Annex A). A core subgroup to focus on the guidelines related to genital herpes simplex virus (HSV) was created within the GDG, to provide more intensive feedback throughout the process (Annex A). The GDG participated in meetings and teleconferences to prioritize the questions to be addressed, discuss the evidence reviews and finalize the recommendations. The GDG reviewed and approved the final version of the guidelines.

2.2 QUESTIONS AND OUTCOMES

In December 2013 the first GDG meeting was held to identify and agree on the key PICO (population, intervention, comparator, outcome) questions that formed the basis for the systematic reviews and the

recommendations. Following this meeting, a survey of GDG members was conducted to prioritize the questions and outcomes according to clinical relevance and importance. Seven PICO questions were identified for the update on the treatment of genital HSV infection (see Annex B). These questions pertained to adults and other special populations, namely: adolescents; pregnant women; people living with HIV; and populations at high risk of acquiring and transmitting STIs, such as men who have sex with men (MSM), transgender persons and sex workers. Only outcomes that were ranked as critical or important to patients and decision-making were included: clinical and microbiological cure, and adverse effects (including maternal and fetal effects in pregnant women) (see Annex B).

2.3 REVIEWS OF THE EVIDENCE

The systematic reviews for each priority question were conducted by McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy. Evidence for desirable and undesirable outcomes, patient values and preferences, resources, acceptability, equity and feasibility were reviewed from published and unpublished literature. Comprehensive searches for previously conducted systematic reviews, randomized controlled trials and non-randomized studies were performed from March to October 2015. Additional searches were conducted to identify studies on patient values and preferences (e.g. qualitative research designs) and resource implications (e.g. cost of interventions, cost–benefit and cost–effectiveness studies). Two members of the Systematic Review Team screened studies, extracted and analysed the data, and assessed the quality/certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.¹

The quality/certainty of the evidence was assessed at four levels:

- **High** – We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** – We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** – Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low** – We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

1 For more information, see: <http://www.gradeworkinggroup.org/>

In addition, the direct costs of medicines were estimated using the 2014 Management Sciences for Health (MSH) International drug price indicator guide (11). References for all the reviewed evidence are listed in Annex C. All evidence was summarized in GRADE evidence profiles and in evidence-to-decision frameworks (see Web annex D).

2.4 MAKING RECOMMENDATIONS

Recommendations were developed during a second meeting of the GDG in October 2015, which was facilitated by two co-chairs, one with expertise in GRADE and the other with clinical STI expertise. The methodologist presented the GRADE evidence profiles and evidence-to-decision frameworks at the meeting. When formulating the recommendations, the GDG considered and discussed the desirable and undesirable effects of the interventions, the value placed on the outcomes, the associated costs and use of resources, the acceptability of the interventions to all stakeholders (including people affected by STIs), the impact on health equity and the feasibility of implementation. Treatments were judged according to the above criteria, and final decisions and guideline recommendations were agreed. The discussion was

facilitated by the co-chairs with the goal of reaching consensus across the GDG. Disagreements among the GDG members were noted in the evidence-to-decision framework for each judgement. In the case of failure to reach consensus for a recommendation, the planned procedure was for the GDG to take a vote and record the results. However, no votes were taken because the GDG reached consensus during discussion for all of the recommendations. Following the meeting, the recommendations were finalized via teleconference and final approval was obtained from all GDG members electronically. These guidelines were subsequently written up in full and then peer reviewed. The External Review Group approved the methods and agreed with the recommendations made by the GDG (members are listed in Annex A).

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations are presented using the wording "The WHO STI guideline recommends...", while conditional recommendations are worded as "The WHO STI guideline suggests..." throughout the guidelines. The implications of the differing strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 3.

Table 3. Implications of strong and conditional recommendations using the GRADE approach

Implications	Strong recommendation "The WHO STI guideline recommends..."	Conditional recommendation "The WHO STI guideline suggests..."
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

2.5 MANAGEMENT OF CONFLICTS OF INTEREST

Management of conflicts of interest was a key priority throughout the process of guideline development. WHO guidelines for declaration of interests (DOI) for WHO experts were implemented (12). DOI statements were obtained from all GDG members prior to assuming their roles in the group. At the GDG meetings (December 2013 and October 2015), the members disclosed their interests, if any, at the beginning of each meeting. Their DOI statements are summarized in Web annex F.

After analysing each DOI, the STI team concluded that no member had financial or commercial interests related to STI treatment. Other notified interests were minor; they were either not related to STI or were non-commercial grants or interests. The STI team concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the guideline development process. Therefore, options for conditional participation, partial or total exclusion of any GDG member were not discussed.

03

DISSEMINATION,
UPDATING AND
IMPLEMENTATION OF
THE GUIDELINES**3.1 DISSEMINATION**

These guidelines will be made available as a printed publication, as a download on the website of the WHO Department of Reproductive Health and Research (where there will also be links to all supporting documentation)², and in the WHO Reproductive Health Library (RHL)³. The recommendations will also be available in a guideline application (“app”) created with the GRADEpro GDT software. The guidelines will be announced in the next edition of the RHL newsletter and in the Reproductive Health and Research departmental newsletter, and other relevant organizations will be requested to copy the announcement in their respective newsletters.

WHO headquarters will work with WHO’s regional offices and country offices to ensure that countries receive support in the adaptation, implementation and monitoring of these guidelines using the WHO Department of Reproductive Health and Research guidance on Introducing WHO’s reproductive health guidelines and tools into national programmes (13). All levels of WHO (headquarters, regional offices and country offices) will work with regional and national partners – including the United Nations Population Fund (UNFPA), the United Nations Children’s Fund (UNICEF), the Joint United Nations Programme on

HIV/AIDS (UNAIDS), nongovernmental organizations (NGOs) and other agencies implementing sexual and reproductive health and STI services – to ensure that the new recommendations are integrated and implemented in sexual and reproductive health, family planning, and maternal, neonatal, child and adolescent health services. Reference to this document will be made within other relevant WHO guidelines. These guidelines will also be disseminated at major conferences related to STIs and HIV and the aforementioned programme areas.

3.2 UPDATING THE STI GUIDELINES AND USER FEEDBACK

A system of monitoring relevant new evidence and updating the recommendations as new findings become available will be established within a year of implementing the guidelines. An electronic follow-up survey of key end-users of the STI guidelines will be conducted after the release of the guidelines. The results of the survey will be used to identify challenges and barriers to the uptake of the guidelines, to evaluate their usefulness for improving service delivery, and to identify topics or gaps in treatment that need to be addressed in future editions.

3.3 IMPLEMENTATION OF THE WHO GUIDELINES FOR THE TREATMENT OF GENITAL HERPES SIMPLEX VIRUS**ADAPTATION, IMPLEMENTATION AND MONITORING**

These guidelines provide recommendations for treatment of genital herpes simplex virus (HSV) infection based on the best global evidence available at the time of compilation. However, the epidemiology and antimicrobial resistance (AMR) of STIs vary by geographical location and are constantly changing, sometimes rapidly. It is recommended that countries conduct good quality studies to gather the information needed to adapt these guidelines to the local STI situation as they update their national guidelines. In areas lacking local data as a basis for adaptation, the recommendations in these guidelines can be adopted as presented.

For further guidance on adaptation, implementation and monitoring of national guidelines please refer to Introducing WHO’s reproductive health guidelines and tools into national programmes: principles and processes of adaptation and implementation (13).

² These guidelines and all supporting documents will be available at: www.who.int/reproductivehealth/publications/rtis/genital-HSV-treatment-guidelines/en/

³ RHL is available at: <http://apps.who.int/rhl/en/>

In adapting the guidelines for national use, recommended treatments should have an efficacy of at least 95%. The criteria to be considered for the selection of medicines are listed in Box 1. Recommended medicines should meet as many of the criteria as possible, taking into account local availability, efficacy, route and frequency of administration.

BOX 1. CRITERIA FOR THE SELECTION OF MEDICINES FOR THE TREATMENT OF STIs

- High efficacy (at least 95% cure rate)
- High quality (potent active ingredient)
- Low cost
- Low toxicity levels
- Organism resistance unlikely to develop or likely to be delayed
- Single dose
- Oral administration
- Not contraindicated for pregnant or lactating women

Appropriate medicines should be included in the national essential medicines lists. When selecting medicines, consideration should be given to the competencies and experience of health-care providers.

Budgeting for medicines is critical. If the national ministry of health does not provide medicines for free and the patient cannot afford to buy the medicines, then there will essentially be no possibility of curtailing the spread of infection and the occurrence of complications. At the national level it is important that decision-makers, politicians and fiscal controllers understand the need to subsidize STI medicines. Low-cost STI medicines can be obtained through international vendors of generic products, non-profit organizations with procurement schemes such as UNICEF, UNFPA and UNHCR, and through joint medicine procurement schemes. By way of such schemes, national programmes can join other national programmes to jointly procure medicines, thus reducing the overall costs by sharing the overhead costs and taking advantage of discounts for purchasing in bulk. Placing STI medicines on national lists of essential medicines increases the likelihood of achieving a supply of these medicines at low cost.

IDENTIFYING AND PROCURING STI MEDICINES

It is important not only to identify medicines that will be recommended as first-line treatment for STIs but also the estimated quantities of the medicines that will be required. Quantifying medication needs is important in order to estimate costs, to reconcile financial requirements with available budget, and to make orders in advance so that the unit and freight costs can be minimized.

In order to estimate the quantity of medicines needed, it will be necessary to review the medicines that are recommended for treatment, their unit prices, the quantity required per treatment and the epidemiological information on the prevalence of infection. One can estimate medicine needs by multiplying the estimated number of cases by the total quantity of medicine specified for treatment of one case. These figures can be derived from health centres providing care, but they must be verified to avoid wasteful over-ordering.

04

RECOMMENDATIONS
FOR TREATMENT OF
GENITAL HERPES
SIMPLEX VIRUS

The recommendations presented here (and summarized in Table 1 in the executive summary) apply to adults and adolescents (10–19 years of age), including pregnant women, people living with HIV, people who are immunocompromised, and key populations (including sex workers, men who have sex with men and transgender persons).

4.1 FIRST CLINICAL EPISODE OF GENITAL HSV INFECTION

RECOMMENDATION 1

For adults and adolescents with a first clinical episode of genital HSV infection, the WHO STI guideline recommends treatment over no treatment.

Strong recommendation, moderate quality evidence

Remarks: This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.

RECOMMENDATION 2

For adults and adolescents with a first clinical episode of genital HSV infection, the WHO STI guideline suggests a standard dose of aciclovir over valaciclovir or famciclovir.

Conditional recommendation, moderate quality evidence

Dosages:

- aciclovir 400 mg orally thrice daily for 10 days (standard dose)
- aciclovir 200 mg orally five times daily for 10 days
- valaciclovir 500 mg orally twice daily for 10 days
- famciclovir 250 mg orally thrice daily for 10 days

Remarks: Given that follow-up visits may not be possible during the course of treatment and symptoms of the first clinical episode may be prolonged, therapy is provided for 10 days. Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of medicine may also depend on compliance considerations. This recommendation also applies to people living with HIV, people who are immunocompromised, people with a severe episode and pregnant women.

SUMMARY OF THE EVIDENCE

The evidence for treatment of a first clinical episode of genital HSV infection compared to no treatment was of moderate quality. Data from eight randomized controlled trials were reported in six articles comparing aciclovir to no treatment or placebo. In these trials, various oral dosages of aciclovir were used over periods of 5–10 days. One study assessed intravenous administration. The findings indicate that the duration of symptoms and lesions is probably reduced (2–4 days fewer) with aciclovir compared to placebo. Pain may be reduced by two more days (mean difference [MD]: 2.1 days fewer; 95% confidence interval (CI): 2.95–1.25). The duration of viral shedding may be reduced by nine more days (MD: 9.2 days fewer; 95% CI: 11.1–7.29). Adverse events may also be reduced with treatment compared to placebo. No studies were found comparing valaciclovir or famciclovir to no treatment. The Guideline Development Group (GDG) agreed that the magnitude of the benefits of treatment was moderate and the adverse events trivial.

The overall quality of the evidence for the comparisons between aciclovir, valaciclovir and famciclovir was moderate to low. Two studies compared aciclovir (200 mg five times daily for 7 or 10 days) to valaciclovir (300 mg or 1000 mg twice daily for 7 or 10 days). The findings indicate that the duration of symptoms, viral shedding and pain, and levels of compliance and risk of adverse events are probably similar with either medicine. Different dosages of famciclovir (125, 250, 500 or 750 mg thrice daily for 5 or 10 days) were compared to aciclovir (200 mg five times daily for 5 or 10 days) in three studies. Findings indicate that the duration of lesions, symptoms and viral shedding and risk of adverse events are probably similar with either medicine, and probably similar between 5- or 10-day treatment duration with 250 mg and 500 mg famciclovir. One other small study compared a standard dose of aciclovir at 1000 mg daily to 4000 mg daily for 10 days. Although the evidence is uncertain (i.e. very low quality for this comparison), the findings indicate that the higher daily dose (4000 mg) may reduce the duration of pain by two days, but may increase the duration of lesions by one day and may increase the risk of adverse events; the duration of viral shedding was shown to be similar with either dose.

Overall, the GDG agreed that there were trivial differences between medicines in terms of the benefits or adverse events, and trivial increases in the benefits gained from higher doses of aciclovir. The GDG also agreed that pharmacokinetic data for the different medicine regimens supported those using fewer tablets and shorter treatment durations (e.g. for 5 days). However, follow-up visits may not be possible during the course of treatment in some settings and symptoms of the first clinical episode may be prolonged, in addition to the fact that neurologic complications, such as meningitis and urinary retention, tend to occur towards the end of the episode. Therefore, although these complications are rare, the GDG agreed that therapy should be provided for a longer duration than 5 days, given the safety of the medicine, the potential benefits of the medicine and lack of concern about resistance. As there is a high probability of patients not returning for follow-up, and to facilitate procurement, packaging and dispensing, the GDG recommended a 10-day regimen rather than a range (for 7–10 days). For all medicines in the studies reviewed, quality of life and transmission of HSV or HIV were not measured. Viral shedding was measured in some studies, but the GDG agreed that this measure was not a useful surrogate for HSV transmission.

The GDG agreed that there would be little variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely to be placed on reducing the number and frequency of tablets taken. Research relating to other

conditions indicates that adherence to treatment regimens may be improved with simpler regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between medicines and regimens. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended.

In summary, there are probably moderate benefits of treatment over no treatment, and trivial differences between medicines in terms of the benefits and adverse events. There is probably no important uncertainty or variability in patients values and preferences relating to the different medicines and treatment regimens, but acceptability may vary depending on the medicine dosages. All medicines are feasible to provide, but aciclovir costs less than famciclovir or valaciclovir.

4.2 RECURRENT CLINICAL EPISODE OF GENITAL HSV INFECTION (EPISODIC THERAPY)

RECOMMENDATION 3

For adults and adolescents with a recurrent clinical episode of genital HSV infection, the WHO STI guideline suggests treatment over no treatment.

Conditional recommendation, moderate quality evidence

Remarks: Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase. This recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women.

RECOMMENDATION 4

For adults and adolescents with a recurrent clinical episode of genital HSV infection, the WHO STI guideline suggests the use of aciclovir over valaciclovir or famciclovir.

Conditional recommendation, moderate quality evidence

Dosages for adults, adolescents and pregnant women:

- aciclovir 400 mg orally thrice daily for 5 days, 800 mg twice daily for 5 days, or 800 mg thrice daily for 2 days
- valaciclovir 500 mg orally twice daily for 3 days
- famciclovir 250 mg twice daily for 5 days

Dosages for people living with HIV and people who are immunocompromised:

- aciclovir 400 mg orally thrice daily for 5 days
- valaciclovir 500 mg orally twice daily for 5 days
- famciclovir 500 mg orally twice daily for 5 days

Remarks: Although the benefits of the medicines are probably similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of dosage may depend on compliance considerations. Treatment should be given within the first 24 hours of the onset of symptoms or during the prodromal phase.

SUMMARY OF THE EVIDENCE

The evidence for treatment of recurrent clinical episodes of genital HSV infection that are not frequent compared to no treatment is of moderate quality, due to unclear randomization methods and/or unclear loss to follow-up in the trials. Data from 16 randomized controlled trials were reported in 13 articles, relating to the use of aciclovir (9 trials), valaciclovir (3 trials) and famciclovir (5 trials). The findings indicate that aciclovir in various dosages for 2–5 days probably reduces the duration of viral shedding (MD: 1.32 fewer days; 95% CI: 1.36–1.27), symptoms (MD: 2.02 fewer days; 95% CI: 3.27–0.77) and lesions (MD: 1.07 fewer days; 95% CI: 1.3–1.0) when compared to placebo. Valaciclovir in various dosages probably reduces the duration of viral shedding by a median of 2 days, and lesions and symptoms by 1–2 days when compared to placebo. Famciclovir in various dosages probably reduces the duration of viral shedding, lesions and symptoms by a median of 1–2 days when compared to placebo. The GDG agreed that the differences in benefits were small and the differences in harms were trivial between the medicines and no treatment. In most trials, quality of life, compliance, pain, genital HSV transmission, and HIV transmission and acquisition were not measured.

Aciclovir, valaciclovir and famciclovir were compared. Two trials compared aciclovir and valaciclovir and found that there is probably little to no difference between the two medicines in terms of duration of viral shedding, lesions and symptoms, and risk of adverse events (moderate quality evidence). One trial compared aciclovir to famciclovir and found that there may be little to no difference in the same outcomes (low quality evidence). Another trial compared famciclovir to valaciclovir and found that there is probably little to no difference in outcomes (moderate quality evidence). The GDG agreed that there were only trivial differences in benefits and harms between the medicines.

Different dosages of aciclovir were compared in two trials (200 mg five times daily for 5 days versus alternatives). The findings indicate that there may be little to no difference between the various doses in terms of duration of symptoms, lesions and viral shedding, and adverse events. Different dosages of valaciclovir were compared in four trials (500 mg twice daily for 5 days versus the same for 3 days, and versus 1000 mg twice daily for 5 days). Again findings indicate there is probably little to no difference in outcomes between the doses. Famciclovir at doses of 125, 250 or 500 mg twice daily for 5 days were compared and there may be little to no difference in outcomes across these different dosages.

There were data providing moderate to low quality evidence from three studies that compared aciclovir to placebo in people living with HIV, and two studies that compared different doses of aciclovir, valaciclovir and famciclovir. The effects were inconsistent across different doses, but most doses were provided for 5 days and generally resulted in benefits and few harms.

The GDG agreed that there would be little variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely to be placed on reducing the number and frequency of tablets taken. Research relating to other conditions indicates that adherence to treatment regimens may be improved with simpler regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between different medicines and treatment regimens. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Since the comparisons of different dosages of medicines compared to placebo and to each other showed few differences, the GDG agreed to recommend the dosages and regimens requiring fewer days of treatment and fewer tablets per day. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended.

In summary, there are probably small benefits and trivial side-effects of episodic therapy over no treatment, and moderate additional costs of providing episodic treatment versus no treatment. There may be trivial differences in benefits and side-effects between the different medicines and dosages. Although there is probably no important uncertainty or variability in the values patients place on reducing the duration of lesions and other symptoms, acceptability of episodic therapy may depend on the individual. All medicines are feasible to provide, but aciclovir costs less than famciclovir or valaciclovir.

4.3 RECURRENT CLINICAL EPISODES OF GENITAL HSV INFECTION THAT ARE FREQUENT, SEVERE OR CAUSE DISTRESS (SUPPRESSIVE THERAPY)

RECOMMENDATION 5

For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, the WHO STI guideline suggests suppressive therapy over episodic therapy, and reassessment after one year.

Conditional recommendation, moderate quality evidence

Remarks: Individuals who have frequent recurrences (e.g. 4–6 times a year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy.

To determine frequency or severity, episodes can be monitored for the first few months.

This recommendation also applies to people living with HIV, people who are immunocompromised and pregnant women.

RECOMMENDATION 6

For adults and adolescents with recurrent clinical episodes of genital HSV infection that are frequent, severe or cause distress, the WHO STI guideline suggests aciclovir over valaciclovir or famciclovir for suppressive therapy.

Conditional recommendation, low quality evidence

Dosages for adults, adolescents and pregnant women:

- aciclovir 400 mg orally twice daily
- valaciclovir 500 mg orally once daily
- famciclovir 250 mg orally twice daily

Dosages for people living with HIV and people who are immunocompromised:

- aciclovir 400 mg orally twice daily
- valaciclovir 500 mg orally twice daily
- famciclovir 500 mg orally twice daily

Remarks: Individuals who have frequent recurrences (e.g. 4–6 times a year or more), severe symptoms or episodes which cause distress will likely choose suppressive therapy over episodic therapy.

To determine frequency or severity, episodes can be monitored for the first few months. Although the benefits of the medicines may be similar, the costs of valaciclovir and famciclovir are higher than aciclovir, and therefore aciclovir is preferred. The choice of medicine may also depend on compliance considerations.

SUMMARY OF THE EVIDENCE

The evidence for suppressive therapy compared to episodic therapy of recurrent and frequent clinical episodes of genital HSV infection is of moderate quality for aciclovir therapies and valaciclovir therapies, but low quality for famciclovir therapies. Most studies included people with four or more recurrences per year and provided therapy for 6–12 months. The GDG agreed that there were large benefits with suppressive over episodic therapy and trivial differences in harms for people with frequently recurrent episodes of genital HSV infection. The GDG also agreed that treatment regimens including lower doses and fewer tablets should be recommended.

Six studies compared suppressive therapy with aciclovir (200 mg or 400 mg twice daily and 800 mg once daily) to episodic therapy with aciclovir (usually 200 mg five times daily for 5 days) and found that clinical recurrence is probably delayed and experienced by fewer people with suppressive therapy, with probably little difference in side-effects or compliance. The number of lesions with viral shedding is also probably reduced. Seven studies compared suppressive therapy with valaciclovir (250–1000 mg per day) to episodic therapy with valaciclovir (500 mg twice daily for 5 days). Clinical recurrence is probably delayed and experienced by fewer people with suppressive therapy, with probably little difference in side-effects or compliance. There may also be fewer days of pain and fewer genital HSV transmissions to partners. The number of lesions with viral shedding is also probably reduced. One study compared suppressive therapy with famciclovir (250 mg twice daily for 6 months) to episodic therapy with famciclovir (125 mg twice daily for 5 days) and found that clinical recurrence may be delayed and experienced by fewer people with suppressive therapy, and there may be little difference in quality of life, satisfaction with therapy, or side-effects.

Few studies directly compared different dosages of a specific suppressive therapy. One study compared aciclovir at 200 mg twice daily to 200 mg five times daily. The quality of evidence was low; the findings indicated little to no difference in recurrence, compliance or side-effects. Two studies compared valaciclovir 500 mg daily with 1000–3000 mg daily. There was very low quality evidence for little to no difference in the duration of episodes, genital HSV shedding and side-effects; and moderate quality evidence for little to no difference in the number of people who experienced a recurrence (risk ratio: 1.04; 95% CI: 0.94–1.16). Three studies compared famciclovir at doses greater than 250 mg twice daily to doses of 250 mg or less twice daily. The time to first recurrence is probably similar across doses with little to no difference in side-effects. There may be

fewer episodes per month with the higher dose regimen, as well as fewer days of genital HSV shedding. One study compared suppressive therapy with valaciclovir to aciclovir and found that there may be little to no difference in outcomes. Another study compared famciclovir to valaciclovir and found that there is probably little to no difference in recurrences and there may also be little to no difference in side-effects and compliance, but there may be more days of genital HSV shedding with famciclovir (risk ratio: 2.23; 95% CI: 1.18–4.89).

For people living with HIV, there is moderate to low quality evidence from 13 studies reporting various outcome measures. There may be more benefits with treatment versus no treatment and the results were similar across different medicines and dosages. Medicines and dosages evaluated were aciclovir 400 mg orally twice daily, valaciclovir 500 mg orally twice daily (or 1000 mg once daily), and famciclovir 500 mg orally twice daily. The GDG agreed to recommend these doses as there is experience with them.

The GDG agreed that there is probably no variability in patient values and preferences relating to the different medicines and treatment regimens. However, higher value is likely placed on avoiding genital HSV transmission (but there were few data) and reducing the number and frequency of tablets taken. Research relating to other conditions indicates that adherence may be improved with simpler medicine regimens, although when compliance was measured in the studies included for HSV treatments, compliance was similar between medicines. Overall, it was agreed that the different regimens and medicines are probably acceptable to most people. Since the comparisons of different dosages of medicines to placebo and to each other showed only small differences, the GDG agreed to recommend the dosages and regimens requiring fewer days of treatment and fewer tablets per day. There were no included studies for cost-effectiveness, but the GDG agreed that the costs would likely be high for any of the medicines and that costs depend on the setting. Although the cost may be high for an individual, there is a small population with frequent clinical episodes of genital HSV infection requiring suppressive therapy. There may also be a potential for cost savings in terms of work productivity and health care use. The impact on equity was unclear as genital HSV infection occurs most in disadvantaged populations who may not have access to suppressive therapy. However, equity could be increased with improved access. Both valaciclovir and famciclovir are more expensive than aciclovir, and famciclovir is more expensive than valaciclovir. Where the medicines are a direct cost to people with HSV, the more expensive medicines would probably reduce equity if recommended.

In summary, the benefits of suppressive therapy over episodic therapy are probably large and the side-effects trivial. The medicines and treatment regimens are probably feasible and acceptable to individuals, but there are large costs with suppressive therapy, which may reduce equity between some populations. Less expensive medicines, such as aciclovir, may reduce the potential for this inequity.

05

**RESEARCH
IMPLICATIONS**

Little evidence was found for some outcomes critical to making decisions in trials comparing medicines to placebo or comparing different medicines to treat first or recurrent episodes of genital HSV infection. Important patient outcomes should be measured in clinical trials, such as genital HSV transmission and acquisition, HIV transmission and acquisition, quality of life and pain. There were few available data for direct comparisons of different medicines, in particular for comparisons with famciclovir. There were also few studies comparing the different dosages of the medicines. Future research could use the dosages recommended in these guidelines as comparators. Equity issues, acceptance of and compliance with different medicines and regimens should also be explored in people with genital HSV infections. There were also few data for key populations, such as people living with HIV, people who are immunocompromised and pregnant women. In reports of clinical trials, more information can also be provided that would allow for the critical appraisal of the clinical trials; this can be done by following the standards for reporting of randomized controlled trials, in particular for reporting the methods of randomization and allocation concealment and blinding.

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ANNEX A: STI GUIDELINE DEVELOPMENT TEAMS

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AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region;
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EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region

ANNEX B: DETAILED METHODS FOR GUIDELINE DEVELOPMENT

QUESTIONS AND OUTCOMES

To determine which recommendations to update, in December 2013 the World Health Organization (WHO) Department of Reproductive Health and Research reviewed current recommendations of key international guidelines:

- Sexually transmitted diseases treatment guidelines, 2010, Department of Health and Human Services, United States Centers for Disease Control and Prevention (CDC)⁴;
- United Kingdom national guidelines for the management of sexually transmitted infections, British Association for Sexual Health and HIV (BASHH), 2006–2011⁵;
- Canadian guidelines on sexually transmitted infections, Public Health Agency of Canada, 2013–2014⁶;
- European sexually transmitted infections guidelines, International Union of Sexually Transmitted Infections (IUSTI)⁷;
- National management guidelines for sexually transmissible infections, Sexual Health Society of Victoria, Australia, 2008⁸;
- National guideline for the management and control of sexually transmitted infections (STIs), National Department of Health, South Africa, 2009⁹; and
- National guidelines on prevention, management and control of reproductive tract infections including sexually transmitted infections, Ministry of Health and Family Welfare, Government of India, August 2007.¹⁰

Based on the review, four proposed categories of sexually transmitted infection (STI) conditions were prioritized:

- a. STI conditions included in the 2003 WHO STI guidelines¹¹ that were selected by the GDG to be reviewed and updated in the new WHO STI guidelines. These are important and common conditions.
- b. STI conditions not included in the 2003 WHO STI guidelines that were selected by the GDG to be reviewed and added in the new WHO STI guidelines. These are important and common conditions.
- c. STI conditions included in the 2003 WHO STI guidelines that were not updated but were selected by the GDG to be included in the new WHO STI guidelines. These STI conditions are rare and diagnosis is not often made in the majority of settings, or it is unlikely that there is new information available as a basis for making any changes to the 2003 WHO STI recommendations.
- d. STI conditions not included in the 2003 WHO STI guidelines that are part of other national guidelines, but were not selected by the GDG to be included in the new WHO STI guidelines. These conditions are rare and difficult to diagnose in the majority of settings, or it is unlikely that new research or information has become available; there are existing recommendations for these conditions that can be applied in other settings (e.g. reference hospitals that manage complicated conditions).

A meeting was held in December 2013, at which the Guideline Development Group (GDG) discussed and decided on the initial list of population, intervention, comparator and outcome (PICO) questions identified by WHO. After the meeting, surveys pertaining to each of the four STI topic areas (i.e. gonorrhoea, chlamydia, syphilis and genital herpes simplex virus [HSV]) were administered among subgroups of the GDG members with expertise relating to the relevant STIs. The goal of the surveys was to rank the population, interventions and outcomes for each specific STI condition by importance. The surveys required the members of the STI subgroups to rank the population, interventions and outcomes on a scale of 1 to 9, from lowest to highest priority.

4 Available at: <http://www.cdc.gov/std/treatment/2010/std-treatment-2010-rr5912.pdf>

5 Available at: <http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx?hkey=072c83ed-0e9b-44b2-a989-7c84e4fbd9de>

6 Available at: <http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php>

7 Available at: <http://www.iusti.org/regions/europe/euroguidelines.htm>

8 Melbourne Sexual Health Centre Treatment Guidelines, available at: <http://mrshc.org.au/HealthProfessional/MSHCTreatmentGuidelines/tabid/116/Default.aspx#.V06yFJMrKV4>

9 Lewis DA, Maruma E. Revision of the national guideline for first-line comprehensive management and control of sexually transmitted infections: what's new and why? *South Afr J Epidemiol Infect.* 2009;24(2):6–9 (<http://apps.who.int/medicinedocs/documents/s18369en/s18369en.pdf>, accessed 6 September 2016).

10 Available at: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_117313.pdf

11 Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization; 2003 (<http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf>, accessed 6 September 2016).

Four different priority STI surveys were conducted, and each survey attained a 90–100% response rate from the STI subgroup members. The survey results for priority populations, interventions and outcomes were analysed. Populations, interventions and outcomes with an average rating of 7 to 9 were considered “critical”; those with an average rating of 4 to 6 were considered “important”; and those with an average rating of 1 to 3 were considered “not important” and were thus not covered in the guidelines. Some questions that scored less than 7 were kept for consistency.

The number of comparisons in each question was also reduced; only “critical” interventions were compared with each other and with important interventions. Thus, “important” interventions were not compared to each other.

A revised list of questions was then compiled and all members of the full STI GDG were requested to review the priority questions. The priority questions were then revised based on this feedback.

Seven questions were identified for the update of the genital herpes simplex virus (HSV) guideline. Each question is framed using the PICO format (population, intervention, comparator and outcome).

FIRST CLINICAL EPISODE OF GENITAL HSV INFECTION (RECOMMENDATIONS 1 AND 2)

Question 1: Should we treat or not treat first clinical episodes of genital HSV infection?

Question 2: How should we treat first clinical episodes of genital HSV infection?

Population	Intervention and comparator	Outcome
Adults and adolescents with first clinical episode of genital HSV infection, including people living with HIV, people who are immunocompromised and pregnant women	Aciclovir 200 mg orally 5 times daily x 5–10 days Aciclovir 400 mg orally thrice daily x 5–10 days Valaciclovir 500 mg – 1 g orally twice daily x 5–10 days Famciclovir 250 mg orally thrice daily x 5–10 days No treatment	Critical: Duration of clinical episode, HSV severity/pain, quality of life Important: Ulcer healing, side-effects, HSV transmission, duration of shedding, HIV transmission and acquisition, HIV viral load, compliance Additional critical outcomes for pregnant women: Maternal outcomes (caesarean section), fetal outcomes (neonatal herpes [including meningo-encephalitis, fever, hepatitis], teratogenicity, fetal loss, toxicity, neonatal death)

RECURRENT CLINICAL EPISODE OF GENITAL HSV INFECTION (EPISODIC THERAPY) (RECOMMENDATIONS 3 AND 4)

Question 3: Should we treat or not treat recurrent (not frequent) genital HSV infection with episodic therapy?

Question 4: How should we treat recurrent (not frequent) genital HSV infection with episodic therapy?

Episodic therapy for recurrent infection (all populations, including pregnant women)

Population	Intervention and comparator	Outcome
Adults and adolescents taking episodic therapy for recurrent HSV infection, including people living with HIV, people who are immunocompromised and pregnant women	Aciclovir 200 mg orally 5 times daily x 5 days Aciclovir 400 mg orally thrice daily x 3–5 days Aciclovir 800 mg orally twice daily x 5 days Aciclovir 800 mg orally thrice daily x 2 days Valaciclovir 500 mg orally twice daily x 3–5 days Valaciclovir 1 g orally twice daily x 3–5 days Famciclovir 125 mg orally twice daily x 5 days Famciclovir 1 g orally twice daily x 1 day No treatment	Critical: HSV transmission, HSV shedding, HIV transmission and acquisition Important: HSV severity/pain, quality of life, side-effects, HIV viral load, compliance, ulcer healing, duration of clinical episode Additional critical outcomes for pregnant women: Maternal outcomes (caesarean section), fetal outcomes (neonatal herpes, teratogenicity, fetal loss, toxicity, neonatal death)

RECURRENT CLINICAL EPISODES OF GENITAL HSV INFECTIONS THAT ARE FREQUENT, SEVERE OR CAUSE DISTRESS (SUPPRESSIVE THERAPY) (RECOMMENDATIONS 5 AND 6)

Question 5: Should we treat recurrent, frequent genital HSV infection with suppressive or episodic therapy?

Question 6: How should we treat recurrent, frequent genital HSV infection with suppressive therapy?

Suppressive therapy for recurrent infection (all populations, including pregnant women)

Population	Intervention and comparator	Outcome
Adults and adolescents taking suppressive therapy for recurrent HSV infection, including people living with HIV, people who are immunocompromised and pregnant women	Aciclovir 200 mg orally 4 times daily Aciclovir 400 mg orally twice daily Valaciclovir 500 mg orally once daily Valaciclovir 1 g orally once daily Famciclovir 250 mg orally twice daily No treatment	Critical: Recurrent clinical episodes, HSV severity/pain, quality of life, HSV transmission, HSV shedding Important: Side-effects, HIV transmission and acquisition, HIV viral load, compliance Additional critical outcomes for pregnant women: Maternal outcomes (caesarean section), fetal outcomes (neonatal herpes, teratogenicity, fetal loss, toxicity, neonatal death)

SEVERE CLINICAL EPISODE OF GENITAL OR ANORECTAL HSV INFECTION (ALL POPULATIONS, INCLUDING PREGNANT WOMEN) (RECOMMENDATION 1)

Question 7: How should we treat severe clinical episodes of genital or anorectal HSV infection?

Population	Intervention and comparator	Outcome
Adults and adolescents with severe clinical episodes of genital or anorectal HSV infection, including people living with HIV, people who are immunocompromised and pregnant women	Aciclovir 400 mg orally 3–5 times daily Aciclovir 5–10 mg/kg IV every 8 hours Foscarnet 40 mg/kg IV every 8 hours Cidofovir 5 mg/kg once weekly	Critical: Duration of clinical episode, ulcer healing, HSV severity/pain, quality of life Important: Side-effects, HIV viral load, compliance, HSV transmission, HSV shedding duration, HIV transmission and acquisition

IV: intravenous

REVIEW OF THE EVIDENCE

SEARCH FOR EVIDENCE FOR EFFECTS OF INTERVENTIONS

To avoid duplication of reviews that have been previously published, evidence was searched using a hierarchical approach. The team first searched for synthesized evidence then searched the primary studies for all factors needed to complete the evidence to decision framework for each question (i.e. benefits and harms, patient values, acceptability, feasibility, equity and costs).

The hierarchical approach consisted of identifying pre-existing synthesized evidence, including from previously published guidelines that included systematic reviews of the literature. When synthesized evidence about benefits and harms for an intervention was not available or the synthesized evidence was not up to date, a new systematic review of randomized controlled trials (RCT) and non-randomized studies was conducted.

The search strategies were developed by an information specialist trained in systematic reviews. The strategies included the use of keywords from the controlled vocabulary of the database and text words based on the PICO questions. The keywords used included herpes, shingles, zoster, varicella and HSV. There were no restrictions based on language, publication status or study design. RCTs were included for critical and important outcomes, and non-randomized studies for critical outcomes when no evidence was available from RCTs. Additional strategies included contacting Cochrane review groups and authors of study protocols.

The Cochrane Library suite of databases (Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment [HTA] database and the American College of Physicians [ACP] Journal Club) was searched for published systematic reviews and protocols from January 2004 to February 2015. The Cochrane Central Register of Controlled Trials (CENTRAL) and the MEDLINE and Embase databases were searched for primary studies from their origin up to May 2015. The strategies included searching for subject headings and text words related to HSV and specific interventions (e.g. medication names and classes). Additional strategies included checking reference lists and consulting with the GDG for any missed articles.

SCREENING STUDIES, DATA EXTRACTION AND ANALYSIS

Two researchers independently screened titles and abstracts of systematic reviews identified through database searching to determine studies eligible for inclusion in the analysis. Disagreements were resolved by discussing study inclusion with a third member of the research team. Data were extracted using a pilot-tested form for patient characteristics (including the subgroups identified by the GDG), diagnosis, treatment (dose, schedule, etc.), setting, follow-up and outcomes. Two investigators independently abstracted data. Risk of bias of each study was also assessed and abstracted

using risk of bias tools appropriate for RCTs (http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm) and using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I; previously called ACROBAT) tool to assess non-randomized studies (www.riskofbias.info).

To measure the treatment effect, the data were analysed using RevMan 5.2.¹²

For dichotomous outcomes, we calculated relative risks with 95% confidence intervals (e.g. risk ratios and odds ratios) by pooling results from RCTs and pooling results from non-randomized studies using the random effects model. Moderate to high heterogeneity ($I^2 > 50\%$) was explored. Effects were converted to absolute effects using the calculated relative effect and a representative baseline risk (agreed upon by the GDG). When non-randomized studies with one group were included, a pooled proportion of an event (and confidence intervals) were calculated across the studies using the generic inverse variance. For continuous outcomes, a mean difference or a standardized mean difference (when studies used different scales to measure an outcome) was calculated. When possible, the forest plots created by the meta-analyses were made available to the GDG.

When data were not able to be pooled across studies, narrative synthesis methods were used (see <http://methods.cochrane.org/sites/methods.cochrane.org/files/Mckenzie.pdf>). Results were presented in tables (e.g. median effects with interquartile ranges), or were narratively described by direction of the effect or by statistical significance as reported in the primary study.

PATIENT VALUES AND PREFERENCES, ACCEPTABILITY, EQUITY AND FEASIBILITY

Studies on patient values and preferences, acceptability, equity and feasibility were searched for and screened using two methods. First, while screening studies for the effects of treatments and costs, two investigators identified studies of potential relevance in these areas. Secondly, a separate search was conducted for any study design in MEDLINE, Embase and PsychINFO from January 2000 to July 2015. Text words and keywords for the different STIs were used in combination with words such as "preference", "adherence", "satisfaction", "attitudes", "health utilities" and "value", "equity" and "feasibility". The results included 2563 unique references. Two investigators screened the studies, and 162 studies were identified for full text retrieval. Any study design was included that addressed equity or feasibility. In addition, when adherence was measured in RCTs or non-randomized studies, the data were collected, synthesized and presented in the evidence profiles for each PICO question.

The following study designs were included:

- a. Patient utilities and health status values studies: These studies examine how patients value alternative health states and their experiences with treatment. The measurement techniques used can include: standard gamble, time trade-off, visual analogue scale, or mapping results based on generic surveys (EuroQol five dimensions health questionnaire [EQ-5D] or the 36-Item Short Form Health Survey [SF-36]) or specific measurement (e.g. St George Respiratory Questionnaire) of health-related quality of life.
- b. Studies of patients' direct choices when presented with decision aids: These studies examine the choices patients make when presented with decision aids for management options (i.e. probabilistic trade-off techniques).
- c. Studies on non-utility measurement of health states: These studies quantitatively examine patients' views, attitudes, satisfaction or preferences through questionnaires or scales; these are neither utility studies nor studies of patients' responses to decision aids. Patients are asked about how desirable or aversive a particular outcome is for them. This category includes some studies that use questionnaires or scales.
- d. Qualitative studies: These studies explore patients' views, attitudes, satisfactions or preferences related to different treatment options based on qualitative research methods including focus group discussions, interviews, etc.

From the search, we included 17 studies reporting information relating to different STIs. In many instances, data for all infections informed the evidence for HSV specifically.

RESOURCES

The published and unpublished literature was searched for evidence on use of resources, and data were obtained on direct costs of medicines.

Based on the list of possible treatments identified by the GDG, an estimate of the cost associated with each alternative was calculated. This costing estimate refers only to the actual market price of the medication and does not include the cost of other resources that could be involved such as syringes, injection time or needle disposal.

Data were presented in a table and included: treatment, dose per day, treatment duration, days, medicine cost per dose, medicine cost per full course of treatment, and 25% of procurement costs (as defined in the 2014

¹² RevMan (Computer Program). Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration; 2012.

Management Sciences for Health [MSH] International drug price indicator guide)¹³. A final price for a full course of treatment for each medicine by dosage was calculated as the number of doses per day, multiplied by the number of days of the treatment, plus 25% of the procurement costs for the medicines used. The unit price of the medicine was obtained from the median prices provided in the 2014 MSH International drug price indicator guide and information available on the Internet. In order to determine a precise and reliable estimate, the price per unit (all expressed in US dollars) was provided only when the information available matched the dosage of interest (grams per pill or 1000 units per vial). No calculations were made based on assumptions about the cost per unit of hypothetical packaging not listed in the directory.

The major medical databases were also searched (MEDLINE, Embase and the Cochrane Library for Economic Evaluation and Technology Assessment reports) from January 2005 to July 2015. In addition, while screening studies for the effects of treatments, two investigators also identified studies of potential relevance for costs. No studies were identified for resource use relating to treatment of genital HSV infections.

APPLYING THE GRADE APPROACH TO MAKING THE RECOMMENDATIONS

EVIDENCE PROFILES

An evidence profile was made for each PICO using the GRADEpro software (www.grade.org). Each profile included the critical and important outcomes, the relative and absolute effects, and the quality of evidence according to the GRADE domains (see the GRADE handbook)¹⁴. Briefly, the GRADE approach assesses the quality of evidence for treatment interventions using well-established criteria for the design, risk of bias, inconsistency, indirectness, imprecision, effect size, dose–response curve and other considerations that may affect the quality of evidence. Two investigators used the GRADE approach to assess the quality and level of certainty of the evidence. The evidence profiles for each recommendation are available in Web annex D.

EVIDENCE-TO-DECISION FRAMEWORKS

Evidence-to-decision frameworks were also developed using GRADEpro software (www.grade.org). Evidence-to-decision frameworks present the desirable and undesirable effects of the interventions, the value of the outcomes, the costs and resource use, the acceptability of the interventions to all stakeholders, the impact on health equity, and the feasibility of implementation (i.e. the GRADE criteria for making decisions). The evidence-to-decision frameworks are based on a population perspective for these recommendations. All GRADE criteria were considered from this perspective.

MAKING THE RECOMMENDATIONS

In October 2015, the GDG met to make the recommendations. This meeting was facilitated by two co-chairs – one with expertise in GRADE and the other with clinical expertise in genital HSV. During the meeting, the evidence profiles and evidence-to-decision frameworks were presented by the methodologist. The GDG discussed each GRADE criterion and judged which intervention was favoured. Then a final decision and guideline recommendation was developed. The goal was to arrive at agreement across all members of the GDG and this was facilitated by the chairpersons through discussion. When there was disagreement for a criterion, it was noted in the evidence-to-decision framework for the relevant judgement. If there was disagreement for any of the final recommendations, the plan was for the GDG to vote and the numbers to be recorded. Because there was no disagreement for any of the final recommendations, however, votes were not taken or reported in these guidelines.

The GDG made a strong or conditional recommendation for or against each intervention and described special circumstances in the remarks. Research implications were also developed and presented, based on the gaps identified in the evidence. Following the meeting, the recommendations were finalized via teleconference, and final approval was obtained from the GDG electronically. All decisions and discussions from the GDG for each recommendation are available in the evidence-to-decision frameworks in Web annex D.

13 International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 (http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2014.pdf, accessed 6 September 2016).

14 Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook. Hamilton, Ontario: McMaster University and Evidence Prime Inc.; 2013 (http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html, accessed 6 September 2016).

ANNEX C: LISTS OF REFERENCES FOR REVIEWED EVIDENCE

First clinical episode of genital HSV infection in adults and adolescents (including people living with HIV, people who are immunocompromised and pregnant women)

RECOMMENDATION 1

Question 1: Should we treat or not treat first clinical episodes of genital HSV infection?

Systematic review

1. Heslop R, Roberts H, Flower D, Jordan V. Interventions for men and women with their first episode of genital herpes. *Cochrane Database Syst Rev.* 2016;(8):CD010684.

Included studies

1. Bryson YJ, Dillon M, Lovett M. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. A randomized double-blind controlled trial in normal subjects. *N Engl J Med.* 1983;308(16):916–21.
2. Kinghorn GR, Abeywickreme I, Jevons M. Efficacy of combined treatment with oral and topical acyclovir in first episode genital herpes. *Genitourin Med.* 1986;62(3):186–8.
3. Nilsen AE, Aasen T, Halsos AM. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet.* 1982;2(8298):571–3.
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5. Corey L, Fife KH, Benedetti JK. Intravenous acyclovir for the treatment of primary genital herpes. *Ann Int Med.* 1983;98(6):914–20.
6. Weiss HA, Paz Bailey G, Phiri S, Gresenguet G, LeGoff J, Pepin J et al. Episodic therapy for genital herpes in sub-Saharan Africa: a pooled analysis from three randomized controlled trials. *PLoS One.* 2011;6(7):e22601. doi:10.1371/journal.pone.0022601.
 - a. Mayaud P, Legoff J, Weiss HA, Gresenguet G, Nzambi K, Bouhhal H et al.; ANRS 1212 Study Group. Impact of acyclovir on genital and plasma HIV-1 RNA, genital herpes simplex virus type 2 DNA, and ulcer healing among HIV-1-infected African women with herpes ulcers: a randomized placebo-controlled trial. *J Infect Dis.* 2009;200(2):216–26. doi:10.1086/599991.
 - b. Phiri S, Hoffman IF, Weiss HA, Martinson F, Nyirenda N, Kamwendo D et al. Impact of aciclovir on ulcer healing, lesional, genital and plasma HIV-1 RNA among patients with genital ulcer disease in Malawi. *Sex Transm Infect.* 2010;86(5):345–52. doi:10.1136/sti.2009.041814.
 - c. Paz-Bailey G, Sternberg M, Puren AJ, Markowitz LE, Ballard R, Delany S et al. Improvement in healing and reduction in HIV shedding with episodic acyclovir therapy as part of syndromic management among men: a randomized, controlled trial. *J Infect Dis.* 2009;200(7):1039–49. doi:10.1086/605647.

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1. Scalone L, Ryan M, Kotsopoulos N, Patel R. Evaluation of patients' preferences for genital herpes treatment. *Sex Transm Dis.* 2011;38:9,802–7. doi:10.1097/OLQ.0b013e318218702c.
2. International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 (http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2014.pdf, accessed 6 September 2016).

Patient values and preferences, acceptability and cost: other sexually transmitted infections and conditions

1. Nagarkar A, Mhaskar P. A systematic review on the prevalence and utilization of health care services for reproductive tract infections/sexually transmitted infections: evidence from India. *Indian J Sex Transm Dis.* 2015;36(1):18–25. doi:10.4103/0253-7184.156690.
2. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. *Cochrane Database Syst Rev.* 2014;(4):CD007768.

Additional references

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386(9995):743–800. doi:10.1016/S0140-6736(15)60692-4.
2. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One.* 2015;10(12):e0143304. doi:10.1371/journal.pone.0143304.

RECOMMENDATION 2

Question 2: How should we treat first clinical episodes of genital HSV infection?

Question 7: How should we treat severe clinical episodes of genital or anorectal HSV infection?

Included studies

1. Lai WH. Valaciclovir hydrochloride versus aciclovir in the treatment of first-episode genital herpes: a controlled, randomized open trial. *Chinese J Dermatovenereol.* 2000;14(1):34–6 (in Chinese).
2. Wald A, Benedetti J, Davis G, Remington M, Winter C, Corey L. A randomized, double-blind, comparative trial comparing high- and standard-dose oral acyclovir for first-episode genital herpes infections. *Antimicrob Agents Chemother.* 1994;38(2):174–6.
3. Fife KH, Barbarash RA, Rudolph T, Degregorio B, Roth R, Cameron WB et al. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection: results of an international, multicenter, double-blind, randomized clinical trial. *Sex Transm Dis.* 1997;24(8):481–6.

- Loveless M, Sacks SI, Harris JRW. Famciclovir in the management of first-episodic genital herpes. *Infect Dis Clin Pract*. 1997;691(suppl):S12–S16.

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- Nagarkar A, Mhaskar P. A systematic review on the prevalence and utilization of health care services for reproductive tract infections/sexually transmitted infections: evidence from India. *Indian J Sex Transm Dis*. 2015;36(1):18–25. doi:10.4103/0253-7184.156690.
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Additional references

- Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743–800. doi:10.1016/S0140-6736(15)60692-4.
- Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One*. 2015;10(12):e0143304. doi:10.1371/journal.pone.0143304.

Recurrent clinical episode of genital HSV infection (episodic therapy)

RECOMMENDATION 3

Question 3: Should we treat or not treat recurrent (not frequent) genital HSV infection with episodic therapy?

Systematic review

- Le Cleach L, Trinquart L, Do G, Maruani A, Lebrun-Vignes B, Ravaud P, Chosidow O. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. *Cochrane Database Syst Rev*. 2014;(8):CD009036.

Included studies

- Aoki FY, Tying S, Diaz-Mitoma F, Gross G, Gao J, Hamed K. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2006;42(1):8–13. doi:10.1086/498521.

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- Tying SK, Douglas JM Jr, Corey L, Spruance SL, Esmann J. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. *Arch Dermatol*. 1998;134(2):185–91.
- Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis*. 2002;34(7):944–8. doi:10.1086/339325.

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1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386(9995):743–800. doi:10.1016/S0140-6736(15)60692-4.
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RECOMMENDATION 4

Question 4: How should we treat recurrent (not frequent) genital HSV infection with episodic therapy?

Systematic review

1. Le Cleach L, Trinquart L, Do G, Maruani A, Lebrun-Vignes B, Ravaud P, Chosidow O. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. *Cochrane Database Syst Rev.* 2014;(8):CD009036.

Included studies

1. Abudalu M, Tyring S, Koltun W, Bodsworth N, Hamed K. Single-day, patient-initiated famciclovir therapy versus 3-day valacyclovir regimen for recurrent genital herpes: a randomized, double-blind, comparative trial. *Clin Infect Dis.* 2008;47(5):651–8. doi:10.1086/590561.
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Recurrent clinical episodes of genital HSV infections that are frequent, severe or cause distress (suppressive therapy)

RECOMMENDATION 5

Question 5: Should we treat recurrent, frequent genital HSV infection with suppressive or episodic therapy?

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RECOMMENDATION 6

Question 6: How should we treat recurrent, frequent genital HSV infection with suppressive therapy?

Systematic review

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