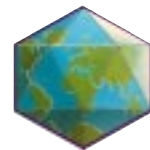


Recommendations from the
IHMF Management Strategies Workshop and
3rd Annual Meeting

Editors: Dr E Sandström
Professor RJ Whitley

GENITAL AND OROFACIAL HERPES SIMPLEX VIRUS INFECTIONS – CLINICAL IMPLICATIONS OF LATENCY

Jointly sponsored by the University of Alabama School of Medicine,
University of Alabama at Birmingham, USA and
the *International Herpes Management Forum* (IHMF)



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The above were participants in the *Management Strategies* Workshop.
The contribution of the participants at the 3rd Annual Meeting of the IHMF is also acknowledged.

The *International Herpes Management Forum* (IHMF) was established to improve the awareness, understanding, counselling and management of infections caused by herpesviruses. Steered by an IHMF Board of Professor Richard Whitley, Dr Martin Wood, Dr Larry Corey, Professor Paul Griffiths, Dr Susanne Kroon, Dr Antonio Volpi and Dr Koichi Yaminishi, the IHMF involves international Opinion Leaders in all aspects of medical management of herpesvirus infections including herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV) infections.

Two *Management Strategies* Workshops were held in 1995, leading up to the 3rd Annual Meeting of the IHMF in November 1995 when recommendations on specific issues affecting the management of herpesvirus infections were debated.

The seventh IHMF workshop was held on 3–4 April 1995 to discuss latency and its implications for the clinical management of herpesviruses. All herpesviruses can exist in a latent state, but the implications of reactivation depend on the virus involved, and the immune status of the host. Presentations highlighted populations at greatest risk of the consequences of latent herpesvirus infections and reviewed the strategies that have been implemented to reduce these risks. The aim of the seventh workshop was to improve understanding of the nature of latent herpesvirus infections so recommendations could be developed to limit the consequences for the affected individual in terms of discomfort and disease and for the population as a whole in terms of transmission.

The draft recommendations from the workshop were discussed at the 3rd Annual Meeting of the IHMF which took place on 17–19 November 1995. Following the Annual Meeting it was decided that the workshop topics were best illustrated in two separate *Management Strategies* publications entitled *Genital and Orofacial Herpes Simplex Virus Infections – Clinical Implications of Latency* and *The Increasing Importance of Cytomegalovirus, Epstein-Barr Virus and the Human Herpesviruses Types 6, 7 and 8*.

The editors would like to thank all the participants at the 3rd Annual Meeting for their contribution and especially the Co-Chairs of the working groups.

This series of monographs is jointly sponsored by the University of Alabama School of Medicine, Division of Continuing Medical Education and the IHMF. This publication is CME accredited for American and Canadian physicians (see inside back cover).

Objectives

The information contained in this publication should enable the physician to:

- ◆ Attain a basic understanding of the molecular basis of HSV latency
- ◆ Describe the pathophysiology of genital and orofacial HSV infections
- ◆ Recognize populations at greatest risk of HSV transmission and disease
- ◆ Appreciate the different therapeutic approaches to management of HSV infections
- ◆ Have a greater understanding of the educational and counselling issues associated with a sexually transmitted disease

Target Audience

The information contained in *Genital and Orofacial Herpes Simplex Virus Infections – Clinical Implications of Latency* is aimed at physicians, healthcare workers and other individuals involved in the management of herpesvirus infections.

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Viral and Host Factors Involved in Latency

Latent viral infections are defined as persistent infections in which the viral genome is present, but gene expression is limited and infectious virus is not produced.

Eight herpesviruses: herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus types 6A and 6B (HHV-6), human herpesvirus type 7 (HHV-7) and now human herpesvirus type 8 (HHV-8) – also referred to as Kaposi's sarcoma-associated herpesvirus¹ – are known to infect humans naturally. Latency is not unique to herpesviruses, but all herpesviruses depend on latency for their survival in nature.

In general, the herpesviruses are lytic pathogens, destroying most of the cells that they infect. However, during initial infection of the host, herpesviruses express latent functions, which restrict the expression of viral genes and enable the cell harbouring the virus to survive. To achieve this state, a fine balance exists between the virus and its host, involving viral and cellular factors, as well as components of the host immune response.

Within the confines of this chapter we cannot hope to achieve a complete overview of all the factors involved in the complex inter-relationships between virus and host, but will attempt to put forward the most current concepts on how HSV is able to establish, maintain and reactivate from the latent state.

The Molecular Basis of Latency

The mechanisms by which herpesviruses avoid elimination from the infected host after the acute phase of the infection are still poorly understood. Most available data on the mechanisms by which herpesviruses establish latency are derived from studies of HSV because of the availability of animal models.

Following primary infection, replication of HSV at the portal of entry (usually oral or genital mucosal tissue) results in infection of sensory nerve endings.² Viral nucleocapsids are then transported by retrograde axonal flow to the neuronal cell nuclei in the sensory ganglia where latency is established after a brief period of viral replication.³ There are no data which support the existence of HSV in peripheral skin tissue in a latent state.^{4,5} Latent virus does not multiply and consequently is not susceptible to drugs directed against viral enzymes associated with viral DNA replication.

An understanding of the molecular mechanisms that underlie the establishment, maintenance and reactivation of HSV latency will require a better understanding of the interplay between cellular and viral factors that mediate the repression and activation of viral genes. Because immediate early viral genes are the first to be activated, factors that affect the expression of these genes are of special significance to studies of latency.

The viral genome

The HSV viral genome consists of two stretches of unique sequences known as the unique long (U_L) and unique short (U_S) regions which are flanked by large inverted repeats (Figure 1).⁵ In the neuronal cell nuclei the linear genome becomes circularized to form an episome, or extrachromosomal element.

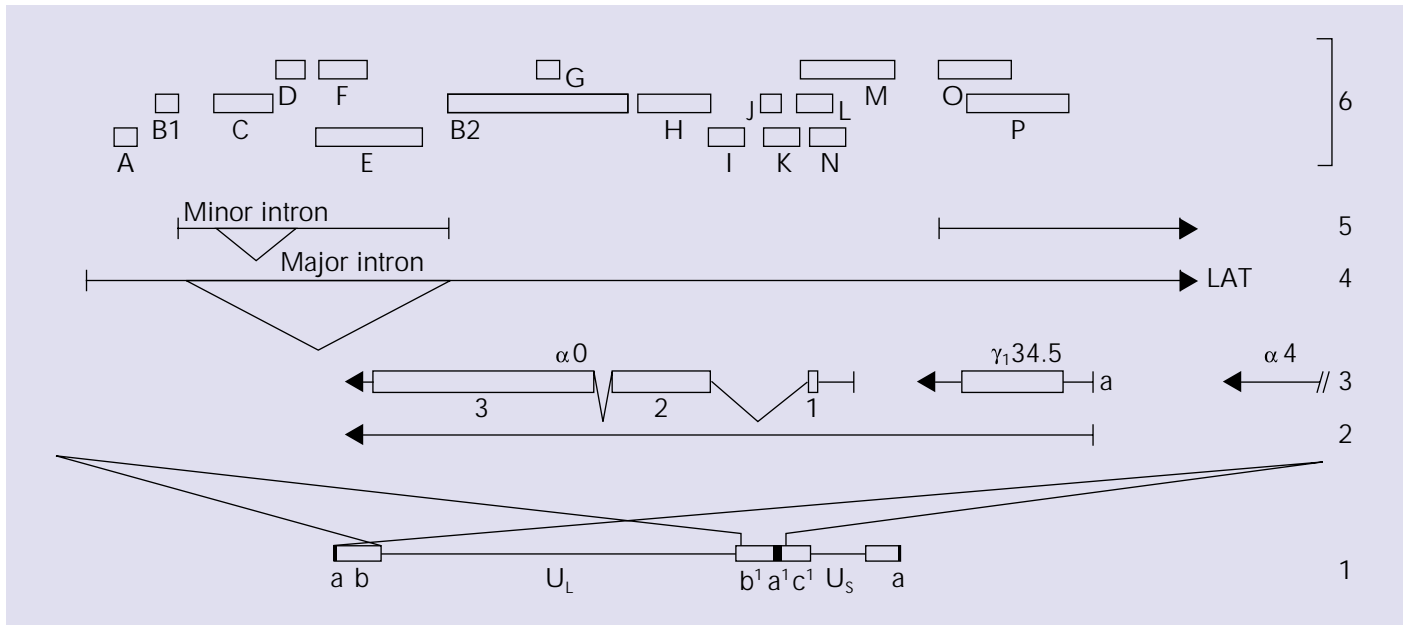


Figure 1: Schematic representation of the arrangements of transcripts and open reading frames (ORFs) in the latency-associated transcript (LAT) region. Line 1: orientation of HSV-1. Line 2: a transcript encompassing $\gamma_134.5$ and α_0 . Line 3: the 3' end of α_4 , $\gamma_134.5$ and α_0 transcripts and coding domains. Line 4: the 8.3 Kb unspliced LAT. Line 5: the major 2 Kb intron showing the position of the minor intron. Line 6: the 16 ORFs

Following HSV infection of cells, the virus encodes approximately 80 different genes, most of which are expressed during viral replication in a co-ordinated and temporally regulated cascade of gene expression, resulting in the production of infectious virus and the death of the cell.^{5,6} In general, replication involves the expression of three classes of gene, immediate early (α), early (β) and late (γ). The replication process begins when a component of the HSV virion, VP16 (also known as α transducing factor [α TIF]), through an interaction with the cellular transcription factor, Oct-1, induces the transcription of five immediate early viral genes: α_0 , α_4 , α_{22} , α_{27} , α_{47} . These in turn can activate the early or β genes and finally, with the onset of DNA replication, the late or γ genes are expressed.⁵

Available evidence suggests that HSV replication during the maintenance stage of latency is blocked at the level of viral immediate early gene expression and so a key question is: does HSV encode functions which enable the establishment of the latent state?

Latency-associated transcripts

Thorough analyses of sensory neurones have shown that the only detectable viral expression in these cells are RNAs referred to as latency-associated transcripts (LATs [Figure 1]), which are abundant in the nuclei of latently-infected cells (Figure 2).⁷

Neurones harbouring latent virus have been shown to contain several of these transcripts derived from the ab and $b'a'$ sequences flanking U_L (Figure 1). The longest transcript is 8.5 Kb in size and is present in relatively small amounts. This transcript is antisense

(transcribed in the opposite direction) to two genes, $\alpha 0$ and $\gamma_1 34.5$, expressed during the replicative cycle. Another set of transcripts, 2 Kb and 1.5 Kb in size, are much more abundant and are antisense to a small portion of the $\alpha 0$ gene, which is thought to play an important role in the reactivation of latent HSV by upregulating viral transcription at the onset of reactivation. Currently, it is thought that the abundant 2 Kb and 1.5 Kb transcripts are excised (introns) from the larger transcript (Figure 1).

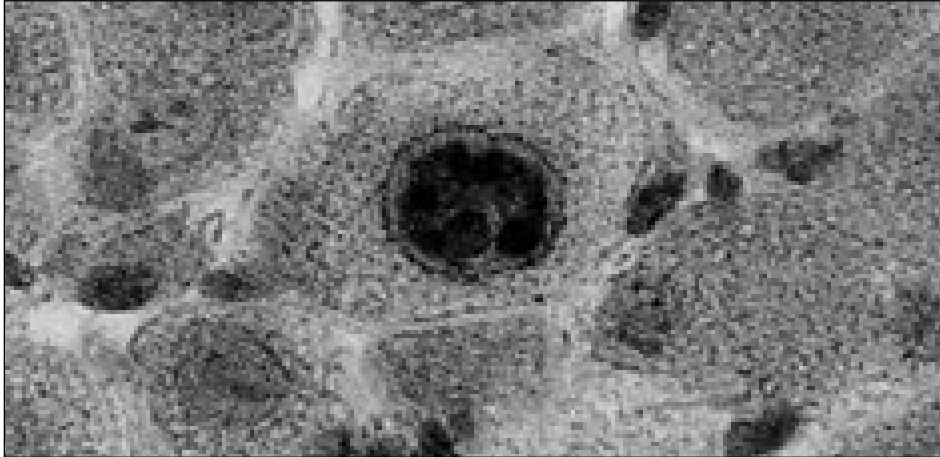


Figure 2: Detection of HSV LATs (brown staining) in the nucleus of a sensory neurone by in situ hybridization. The section is counterstained with haematoxylin

The observation that the LATs are antisense to and partially overlap the $\alpha 0$ gene led to speculation that the RNAs may interact with one another enabling the establishment of latency by suppressing the expression of the $\alpha 0$ gene and maintaining the HSV genome in its transcriptionally inert, latent state.⁸ However, this hypothesis fails to explain why mutants from which the sequence encoding the LAT or its promoter have been deleted can reactivate, albeit less well, from a latent state.⁹ It also fails to explain why mutants lacking the sequences encoding the 2 Kb and the 1.5 Kb transcripts are able to establish latency.

A definitive role for LATs in the establishment, maintenance or reactivation of latent virus remains to be determined. However, the most popular hypothesis for the mechanism by which HSV establishes latency is that there is a viral function which blocks the expression of the α genes. If this was the case, the viral gene product would have to be encoded within the domain of the viral genome expressed during latency, i.e. in the LAT. Current studies indicate that the 8.5 Kb DNA domain is transcribed to yield several RNAs.^{10,11} By inserting *tags* – small amino acid sequences that react with a monoclonal antibody – the expression of two proteins has been identified.^{10,11} One is referred to as open reading frame P (ORF-P) and the other as open reading frame O (ORF-O). Neither of these proteins are encoded during the replicative cycle of the virus, but are expressed when the major regulatory protein, ICP4, is absent.

ICP4 binds to specific sites on the DNA. If the binding site is at the transcription initiation site then ICP4 inhibits transcription. Deletion of the binding site results in increased transcription and large amounts of ORF-P and ORF-O protein. It is therefore hypothesized that these proteins are only expressed when ICP4 is absent, i.e. in latently-infected cells.

ORF-P and ORF-O overlap in part. Both ORFs are antisense completely (ORF-P) or partially (ORF-O) to $\gamma_1 34.5$. The latter gene is essential for virus multiplication. By removal of the ICP4 binding site at the transcription initiation site of ORF-P, it has

been possible to produce a virus which overexpresses ORF-P and has a diminished expression of the antisense $\gamma_134.5$ gene.

A current hypothesis to explain the latent state is that proteins encoded in ORF-P and ORF-O and possible other ORFs from the 8.5 Kb region of the viral genome transcribed during latency, bind alone or in combination with cellular proteins, to viral DNA and block transcription of α genes. Transcription is activated by as yet unidentified signals. Once α genes are transcribed and expressed, viral replication ensues and progeny virions are produced.

A model of HSV latency

- ◆ During latency, HSV does not replicate. In the simplest model for HSV latency, the balance between the latent state and viral gene expression rests on the copy number of viral DNA genomes per cell (approximately 10–100 per sensory neurone harbouring latent virus)^{6,7}
- ◆ To account for this high number of viral genomes, either more than one genome can enter and establish latency in the same neurone or viral genomes are amplified by cellular machinery during the latent state. Studies have shown that prior colonization of the ganglion with HSV appears to preclude its super-infection by another HSV strain¹⁵
- ◆ The hypothesis then proposes that both viral and cellular factors may cause the viral DNA copy number to be increased. Viral replication may occur when a critical copy number of genomes is attained. The effect of the stimulus, the increase in the viral copy number and the precise threshold may vary from cell to cell and would therefore account for the observation that not all latent virus is activated simultaneously. The fact that some individuals suffer no recurrences would be accounted for by their copy number not achieving the critical level required for viral replication

The Host Response

Viral factors are undoubtedly involved in the maintenance of the latent genome; however, *in vivo* the cell is not an isolated organism but is acutely sensitive to its immediate environment (Figure 3). For example, more frequent recurrences of HSV-1 from trigeminal ganglia as opposed to sacral ganglia, and *vice versa* for HSV-2, are evidence that even subtle viral and cellular differences can affect the latent state.¹²

The immune system has an important role in limiting the effect of primary herpesvirus infections and in constraining the infection to a latent state. Although host immunity does not prevent reactivation or even, in some instances, recrudescence, it

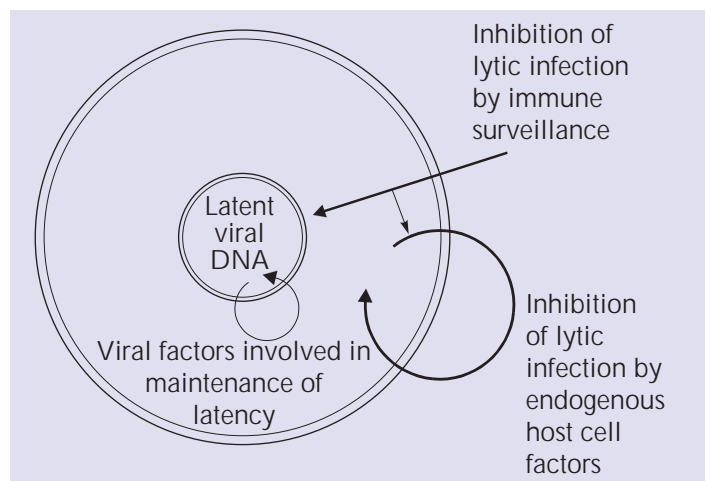


Figure 3: Host–virus relationships. The cell harbouring latent viral DNA is acutely sensitive to its immediate environment

is likely that the host response plays an important role in rapidly controlling these events. Therefore, immunocompromised patients are much more likely to have frequent and severe herpesvirus infections; the loss of cellular immune function allowing the latent viruses to reactivate and cause clinical disease.

The primary aims of the host response are to promote host survival, rescue infected cells and establish lifelong immunity to re-infection. In achieving these aims the virus may be contained or eliminated.

Elimination of the virus-infected cell

Antibody-dependent cell-mediated cytotoxicity (ADCC) is an important component of the host response to infection (Figure 4). Virally-encoded proteins are presented by major histocompatibility complex class I (MHC I) molecules to the T cell receptors of CD8⁺ cytotoxic T lymphocytes (CTLs), with subsequent lysis of the infected cell. Although neurones express low levels of MHC I molecules, recent data suggest that they can rapidly up-regulate the transcription of class I genes in response to HSV.¹³

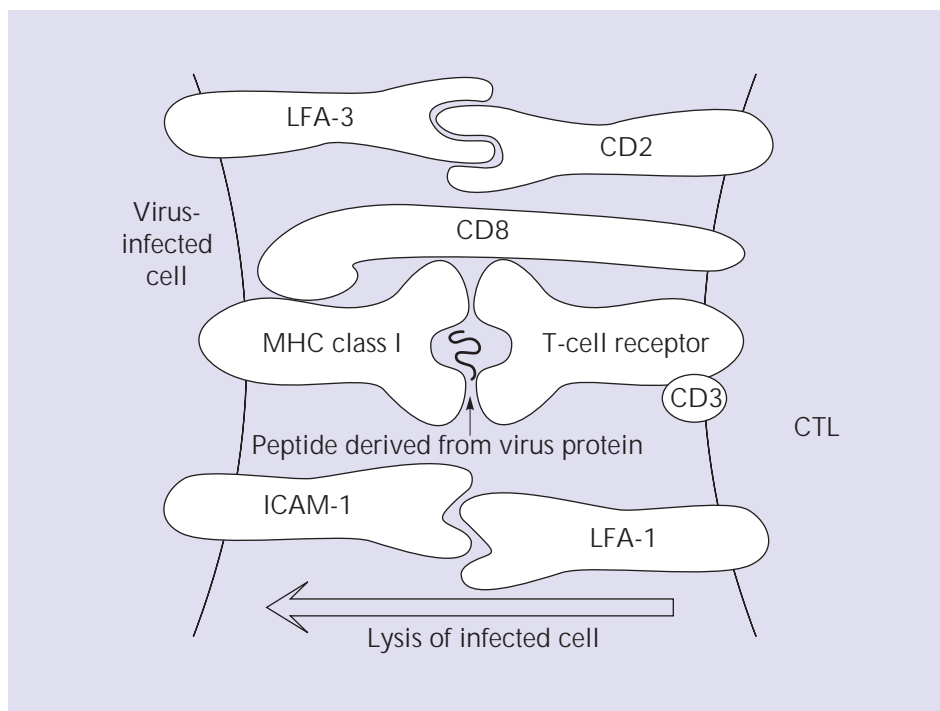


Figure 4: Interaction between the immune system and a virally-infected cell. CD8⁺ CTL recognition of a virus-infected cell. A short peptide fragment derived from a virus protein is presented to the T-cell receptor in association with a particular MHC class I molecule. The CTL – target cell interaction is stabilized by CD8 binding to the MHC class I molecule and by the specific binding of various adhesion molecules (only the LFA-1 – ICAM-1 and LFA3 – CD2 interactions are shown)

In theory, down-regulation of the MHC I molecules, which are vital for immune recognition, would be a valuable means of evading the immune response. A recent *in vitro* study has shown that HSV infection of human fibroblasts results in a decreased expression of the MHC I molecule on the cell surface and failure of CD8⁺ CTLs to recognize and lyse the virally-infected cells. It appears that the HSV α 47 gene product somehow retains the MHC I protein complexes in the endoplasmic reticulum allowing HSV to evade detection by CD8⁺ lymphocytes.¹⁴ It is not known if similar down-regulation occurs in humans following infection.

Containment of viral infection

The classic antiviral response, lysis of infected cells by CTLs, is essential when the host needs to destroy an infected cell, for instance when there is the possibility of tumour outgrowth with oncogenic viruses such as EBV (Figure 4). In general, herpesviruses and the human host are very well adapted to one another and it may not be in the interests of the host to eradicate latency. In the absence of recurrences, the persistence of virus in a latent state is of no consequence to the host, except for the risks of transmission via asymptomatic shedding, and it is not always in the interest of the host to kill the latently-infected cells. In this instance, a cytokine-mediated regulation of viral infection seems much more likely.

Numerous cytokines are secreted by cellular immune cells, e.g. γ -interferon, which can affect the transcriptional environment of neighbouring cells. In this way lytic infection may be prevented and cellular function maintained in a delicate balance with the latent state.

Clinical Implications of Genital Herpes Simplex Virus

The clinical manifestations of herpes simplex virus (HSV) infection are diverse, ranging from the common occurrence of vesicular lesions on the lip or genitals to more rare and severe conditions such as neonatal herpes, eczema herpeticum, erythema multiforme, herpetic keratitis, meningitis and encephalitis. Reactivation of HSV from latency can result in either subclinical or clinical recurrences with the implications of transmission and/or disease.

Seroprevalence

Until the late 1980s, seroepidemiological studies of HSV infections were hampered by cross-reactions to type-common antigenic determinants and could not identify patients who had been infected by both HSV-1 and HSV-2. In 1985, a test to detect type-specific glycoprotein G was first described allowing differentiation between HSV-1 and HSV-2 infection. Enzyme immunoassays are now available and a Western immunoblot of virus proteins has also been developed. These tests are sensitive and type-specific, but still have restricted availability.

Seroepidemiological studies, based on the detection of type-specific antibodies, have now been conducted in a wide range of countries. In all populations, the highest prevalence of HSV-2 antibodies, usually exceeding 75%, is seen in female prostitutes.

In the USA, the seroprevalence of HSV-2 increases at a rate of nearly 3% per year among women attending family planning clinics,¹ and now ranges from 20–50% in white men and women to 30–70% in African-American men and women (Figure 1).²⁻⁴

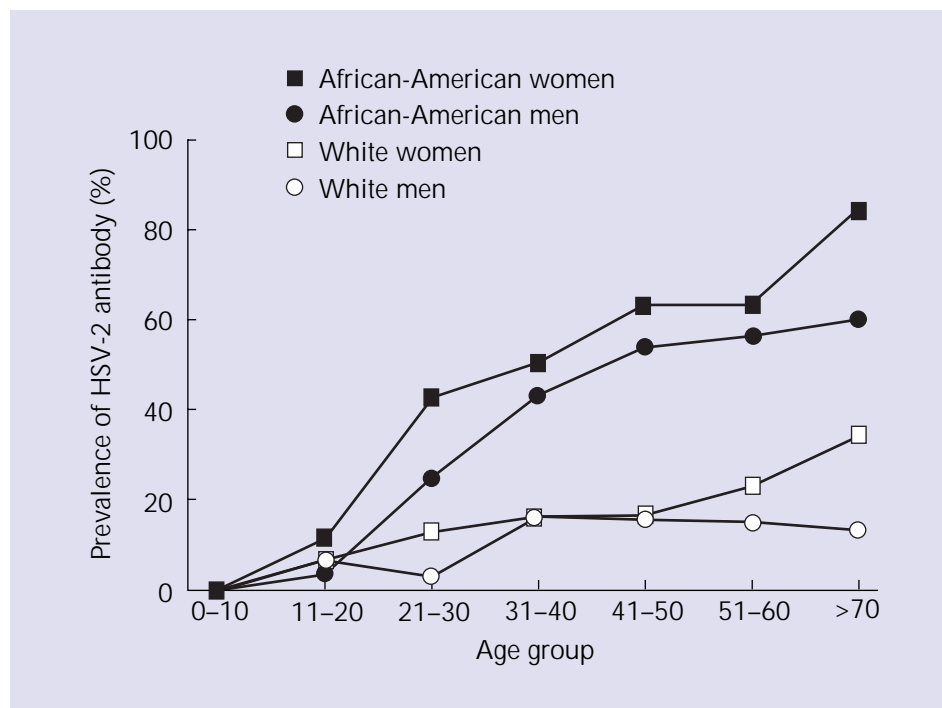


Figure 1: Prevalence of HSV-2 antibodies in the USA in 1978 by sex, age and race

Year	n	HSV-2+ n (%)	HSV-2 / HSV-1+ n (%)	HSV-1- n (%)
1969	941	164 (17)	536 (69)	241
1983	1759	559 (32)	759 (63)	441
1989	1000	330 (33)	465 (69)	205

Table 1: Results of testing for HSV-1 and HSV-2 antibodies in pregnant women in three different years in Sweden

Other areas of the world also exhibit high HSV-2 seroprevalence rates. A study of a rural population in Uganda showed a rate of 68%.⁵ In an Australian study comparing HSV-2 seroprevalence rates in patients attending antenatal or sexually transmitted disease (STD) clinics, antibody to HSV-2 was found in 15% of antenatal patients and 40% of STD patients with none of the antenatal patients and less than half of the seropositive STD patients reporting clinical genital herpes.⁶ In Sweden, studies on stored sera have shown a rising seroprevalence for HSV-2 amongst pregnant women from 19% in 1969 to 33% in 1989 (Table 1).⁷ Figures for the UK show a prevalence of approximately 23% in STD clinic attendees and a rate of 12% in female and 3% in male blood donors.⁸ Factors influencing the seroprevalence of HSV-2 include socioeconomic status, sexual history and number of partners, ethnic origin, patterns of sexual behaviour in different countries and pre-existing HSV-1 antibodies.³

Genital HSV-1 infection also appears to be increasing and in many geographical regions there is a growing incidence of first episodes caused by HSV-1 infection.³ The proportion of individuals who are HSV-1 seropositive and have genital HSV-1 infection is currently unknown.

The overall incidence of HSV-1 genital infection in the USA varies between 10% and 30% of new cases, but in countries such as the UK and Japan it can be as high as 50%.^{3,9}

Pathophysiology

The clinical impact of genital herpes varies between patients (Figure 2). Primary genital herpes is usually severe, characterized by extensive lesions and systemic illness (Figures 3 and 4). If genital herpes is diagnosed in pregnancy, particularly in the third trimester, the potentially fatal consequences of transmission to the neonate need to be considered and delivery carefully managed. Recurrent episodes of genital herpes are usually less severe, but may be frequent and troublesome.

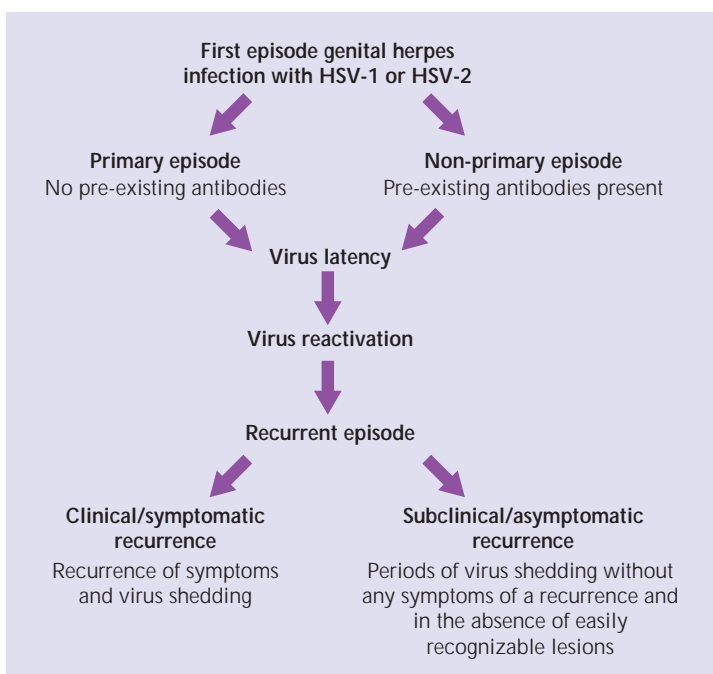


Figure 2: The natural history of genital herpes



Figure 3: Primary genital herpes in the female



Figure 4: Primary genital herpes in the male

The subclinical nature of HSV infection in a large proportion of those infected means that many individuals are unaware that they have the disease. This heightens the risk for transmission to susceptible individuals. Discordant serological status between monogamous sexual partners where the male is seropositive and the female is seronegative heightens the risk of the woman contracting primary genital herpes during pregnancy, which therefore increases the chances of neonatal HSV infection.

In the immunocompromised patient the natural history of HSV infections tends to be more severe, as a result of the impaired immune status of the host. If left untreated, lesions may persist and progress. The role of HSV, or herpesviruses in general, as co-factors for the progression of HIV has not been definitively established, but as the most common infective cause of genital ulceration, genital HSV infection increases the risk of acquiring the disease.^{10,11}

Frequency of recurrences

The implications of reactivation range from subclinical shedding to mild disease to more severe manifestations of infection in which the patient suffers considerable pain, discomfort and psychological morbidity. Reactivation also varies according to virus type and the site of infection, with genital HSV-2 infections showing the highest rate of recurrence (Table 2).¹²

		HSV-1	HSV-2
<p>● Recurrence rate per annum:</p>	Orolabial	42%	4%
	Genital	25%	89%
	<p>● Monthly rate per person:</p>	Orolabial	0.012
Genital		0.02	0.33

Table 2: Recurrence rates after primary HSV infection – influence of infection site and viral type

In many individuals, characteristic provoking factors have been identified for HSV-1 recurrences, which include physical or psychological stress, menstruation and skin trauma, including that associated with exposure to ultraviolet (UV) light.

The natural history of a recurrence differs from that of first episodes in that it is usually of shorter duration, the area of lesions is normally smaller and complications are unusual. This corresponds with the smaller amount and shorter duration of active viral replication. For the majority of individuals there will be a decrease in the rate of recurrences with time; although these changes appear to occur over many years.

Subclinical Viral Shedding

Periods of subclinical or asymptomatic viral shedding of HSV from the external genital skin and/or urethra or cervix occur with high frequency in many individuals.¹³⁻¹⁵ As the duration of subclinical shedding is often short and infrequent, frequent sampling is required to assess its presence. Wald *et al* studied a large cohort of women with a history of recurrent genital herpes who were asked to collect daily vaginal, cervical and rectal swabs which were then cultured for HSV.¹⁵ They collected samples first thing in the morning, thereby obtaining 6–8 hours sampling of pooled secretions. When analysed, the results showed that subclinical shedding of HSV is common and accounts for nearly one-third of the total days of reactivation of genital herpes (Table 3). Episodes occurred in clusters of days, similar to episodes of symptomatic reactivation, often involved more than one anatomical site and were most likely to occur shortly before or after a symptomatic reactivation.¹⁵ Recent acquisition of genital herpes (within the 12 months prior to enrolment) and a high frequency of symptomatic recurrences were independent predictors of an increased rate of subclinical reactivation. Results from a preliminary investigation in men by Wald and colleagues suggest that the frequency and pattern of subclinical shedding is similar to that observed in women.

	Without genital lesions	With genital lesions
Mean number of episodes/year*	3.8	6.5
Mean number of days of shedding/year*	5.5	11.7
Mean duration of episodes (days)	1.5	1.8
Days of shedding at ≥1 anatomical site (%)	17	22

* Calculated as 365 times the total number of episodes or days, divided by the total number of days with positive cultures

Table 3: Virological characteristics of subclinical and clinical episodes of HSV shedding among 110 women¹⁵

An earlier study has shown that subclinical shedding occurs more often after HSV-2 than HSV-1 infections (Table 4), more often in the first 3 months after acquisition of HSV-2 and becomes less frequent over time (Table 5).¹⁴

	Routine cultures positive (%)		
	Primary HSV-1	Primary HSV-2	Non-primary initial HSV-2
Any genital site	1.2	4.3	3.3
Cervix	0.6	3.1	2.6
Vulva	0.6	2.3	0.8
Cervix and vulva at same visit	0.0	1.1	0.5

Table 4: Subclinical shedding of HSV in women after first episode genital herpes

	Women shedding virus (%)		
	0–12 months	13–24 months	25–36 months
● Cervix	3.1	1.3	1.3
● Vulva	2.3	1.6	1.3
● Any genital site	4.3	2.3	2.1

Table 5: Time course of subclinical shedding of HSV-2 in women after first episode genital herpes

The consequences of subclinical shedding for horizontal transmission can be far reaching, as illustrated by a case reported in 1987, in which a woman who was shedding virus subclinically from her cervix infected two males; these two men then went on to infect four further partners over the next few weeks.¹⁶

Studies have shown that approximately two-thirds of individuals seropositive for HSV-2 have no history of genital herpes (Table 6).^{17,18} Up to 50% of these individuals have unrecognized symptomatic genital herpes, but after education regarding the signs and symptoms of disease, as many as half of these individuals become able to identify genital manifestations compatible with recurrent disease. This is of potential importance in helping to reduce transmission to new partners and infants.¹⁹

Study population	No history of genital herpes (%)	
	Women	Men
Obstetric patients and partners (Stanford) ²¹	65	54
STD clinic (Seattle) ¹⁸	82	–
Neighbourhood-based (San Francisco) ²⁸	87	81
Family planning (Western Pennsylvania) ¹	87	–

Table 6: Percentage of patients with no history of genital herpes among people with type-specific HSV-2 antibodies in the USA

Populations at Risk

The consequences of vertical transmission of HSV from mother to child, resulting in neonatal HSV infection, are severe and associated with high mortality if untreated.²⁰ The risk to the neonate is greatest if the mother experiences a primary infection during pregnancy. Virus is transmitted to the neonate in approximately 50% of cases and may result in neonatal HSV infection, compared with less than 3% of cases when the mother experiences a recurrent infection or subclinical shedding at the time of delivery.²⁰

The recent results of Wald *et al* on the frequency of subclinical shedding show genital herpes to be a chronic disease in which individuals who are seropositive for HSV are potentially infectious even during periods when they have no clinical symptoms.¹⁵ A large proportion of new cases of genital herpes are therefore the result of transmission by partners who were unaware that they had the disease.

Studies have shown that genital herpes appears to be transmitted more efficiently from men to women and that the annual risk of a seronegative woman acquiring the disease from a seropositive partner can be as high as 32%.¹³ Prior HSV-1 infection

appears to influence the rate of acquisition of genital HSV-2 infection as well as the severity of initial infection.¹³

Strategies for the Management of Infection

Prevention of transmission

Serological testing

HSV-2 seropositive individuals may have unrecognized or undetectable genital lesions. As such, it appears that serological detection of HSV-2 is the most efficient means of identifying those infected. This will require the widespread availability of type-specific serological assays. Once infected individuals have been identified, they can be counselled on prevention of transmission and warned about the potential of increased risk of HIV acquisition. Serological screening of pregnant women early in gestation and their partners would identify discordant couples who could then be educated about the risk of the woman acquiring primary genital herpes during pregnancy.^{20,21}

Barrier contraception

The association between subclinical viral shedding and transmission suggests that routine use of condoms can substantially reduce the risks of transmission of genital herpes and other STDs. However, data indicate that even highly motivated couples who are aware of the signs and symptoms of genital herpes, and attempt to avoid sexual contact when lesions are present, remain at risk of transmitting the disease to uninfected partners.¹³ Even if condoms are routinely used, they will have no effect on the transmission of virus as a result of subclinical shedding from ano-genital sites or on the transmission of HSV-1 as a result of orogenital sex.

Antiviral therapy

Effect on replicating virus: Antiviral therapy for genital herpes does not prevent either the establishment of latency or development of future recurrences but does appear to affect the amount of replicating virus. Confirmation that virus detected at mucosal surfaces as a result of subclinical shedding is replicating and, therefore, a risk for transmission has come from a study looking at the effect of aciclovir on the frequency of subclinical shedding.²² In this placebo-controlled study, 34 HSV-2 seropositive women were randomized to receive oral aciclovir 400 mg twice daily for 10 weeks, followed by a 14-day washout period and then 10 weeks of placebo (or *vice versa*). A comparison of HSV shedding rates among 26 women completing the study showed that aciclovir had a marked effect on subclinical shedding, reducing the number of culture-positive days from 5.8% on placebo to 0.37% of days (Table 7).²² Presumably,

	Placebo	Aciclovir	Reduction (%)	P
● Culture-positive days	83/1439 (5.8%)	6/1611 (0.37%)	94	<0.001
● Cervical shedding	38/1414 (2.7%)	2/1567 (0.13%)	95	0.005
● Vulval shedding	34/1422 (2.4%)	4/1581 (0.25%)	90	0.004
● Perirectal shedding	26/1435 (1.8%)	1/1607 (0.06%)	97	0.005

Table 7: Paired analysis of subclinical HSV shedding²²

when the virus reactivates and begins to replicate, aciclovir can act on viral DNA synthesis. In addition, any breakthrough isolates remained susceptible to aciclovir.¹⁶

There is no evidence that aciclovir has any impact on the transmission of HSV, but by reducing the incidence of both subclinical and symptomatic recurrences it is possible that suppressive antiviral therapy may reduce the risk of transmission.

Treatment and prevention of clinical symptoms: The use of oral aciclovir at a dose of 200 mg five times daily has proved effective in the treatment of genital herpes, particularly when it is initiated by the patient during the prodrome.²³ results in a significant reduction in the frequency of recurrences and has been well tolerated for periods of up to 10 years.^{24,25}

Two other antiviral agents, valaciclovir and famciclovir, are now available in some countries for the treatment of recurrent genital herpes. Valaciclovir is the L-valyl ester of aciclovir and achieves substantially higher plasma aciclovir concentrations than with oral aciclovir allowing simpler dosing regimens. Valaciclovir is as effective as aciclovir in resolving the symptoms of a genital herpes attack and also significantly increases the chances of vesicular lesions being prevented if treatment is initiated early. Famciclovir also offers a more convenient twice-daily dosing regimen and reduces the symptoms of recurrent genital herpes compared with placebo.

Suppressive aciclovir therapy has also been found to have a significant impact on the psychological morbidity associated with a diagnosis of genital herpes. A General Health Questionnaire was given to 102 patients with frequently recurring genital herpes. The results of the study show that approximately two-thirds of the patients who were initially classified as psychological cases were classified as non-cases after 3 months of aciclovir treatment.²⁵

Vaccines

Since genital herpes infections are caused by HSV-1 and HSV-2 – which are closely related at the genetic level – therapeutic trials of HSV vaccines must be designed to carefully control for type-specific differences in reactivation patterns.²⁷ Two recombinant, subunit vaccines, gD2 and gB2/gD2, are in clinical trials and use the gB and gD glycoproteins present on the envelope of HSV to induce neutralizing antibodies. The vaccines induce both cell-mediated and humoral immunity and the gB2/gD2 vaccine was able to generate neutralizing antibody titres equal to, and exceeding, the levels observed in individuals naturally infected with HSV-2. However, these vaccines contain no genetic components of HSV-1. Trials to assess the efficacy of these vaccines both as therapy and for prevention of disease are currently in progress. Genetically engineered HSV-2 vaccines which are attenuated are being developed.

If an effective prophylactic vaccine were developed, there would be a strong argument for vaccinating those at risk, for instance, those with a large number of sexual partners or seronegative women of child-bearing age.

Educational and Counselling Issues Regarding Genital Herpes Simplex Virus

It is estimated that more than 30 million people in the USA have genital herpes simplex virus (HSV) infection and that an additional 500 000–1 000 000 people become infected with HSV-2 each year.¹ Many of these people, perhaps up to 70%, may have subclinical infection.

In the early 1980s, genital herpes received widespread, alarming media attention. This, in combination with the social stigma associated with an incurable sexually transmitted disease (STD), and a lack of information on the subject, served to heighten concerns and fears about the disease and contributed to the serious emotional and psychosocial reactions that people often experience on diagnosis of genital herpes.

Although effective medical treatment to reduce the frequency and discomfort of genital herpes outbreaks is available, the impact of HSV infections on other aspects of patients' lives is dramatic and long-lasting.²

Genital Herpes Support Groups

American Social Health Association (ASHA)

In response to demand from infected individuals, ASHA began a programme in 1979 to educate the population about genital herpes (Table 1). This type of support is now being implemented in a number of countries.



- ◆ National herpes telephone hotline
- ◆ Network of local groups in cities around the country
- ◆ Publications/educational materials
- ◆ Work with media
- ◆ Support of HSV research

Table 1: Programmes run by ASHA to help people with genital herpes in the USA

As a result of the contact ASHA has had with large numbers of people with genital herpes, it has accumulated much information on patients' reactions when they are first diagnosed with this disease, and the type of care that should be provided to help them.

Patient Barriers

At the time of diagnosis, initial emotions may include anger, shock, denial, fear of rejection by partners and fear of discovery. Patients often show frustration toward healthcare providers at this time. Healthcare professionals should not underestimate the significance of a genital herpes diagnosis. In the beginning, the patients' distress at their diagnosis may lead to constraints in educating and counselling. They may not be prepared to listen to or retain the information they are being provided with and will require considerable emotional support. After a period of adjustment many people can cope better with their illness.

Education and Counselling

Education and counselling are of paramount importance to both patient and physician. By recognizing the impact on the personal as well as on the medical aspects of patients' lives, healthcare providers can adjust their counselling to meet the needs of their patients (Table 2).

As patients go through life they will encounter different situations for which they will continue to need help and advice, for instance, their pattern of recurrences may change, they may enter a new relationship or they may have plans to start a family.

Patients should be urged to overcome communication barriers and be honest with partners, so that strategies to reduce transmission can be adopted.³

Because of the nature of the disease, patients should be told that the virus can reactivate whether or not they are symptomatic. They should be informed about the transmission risks involved, particularly if the female partner in the relationship is seronegative and there are plans to start a family.

Education about genital herpes acquisition

It is generally agreed that sex education should begin at an early age, before the onset of sexual activity. The most effective campaigns combine education on STDs and HIV with advice on contraception. For HSV, education programmes should make individuals aware of the risks of person-to-person transmission of HSV, which should also include a warning about the risks of oral sex. Because of the variation in seroprevalence between populations, sex education should be relevant to different socioeconomic and ethnic groups.⁴

Condoms are helpful in preventing person-to-person transmission of HSV as well as other STDs. Infected individuals may be motivated to use condoms once they realize that not only do they pose a risk for transmission of genital herpes, but are at risk themselves from other STDs. Condom use will vary from country to country and be affected by factors such as religious beliefs, customs and cost. Condoms should be

- ◆ Educate patients in stages, taking care not to overload them with all the information at once
- ◆ Provide written information for reference
- ◆ Provide follow-up sessions for counselling so that after a period of weeks, patients can come back and clarify any questions they may have
- ◆ Offer advice about risk reduction
- ◆ Help patients improve communication skills
- ◆ Provide patients with resources for future questions

Table 2: Patient education and counselling

routinely recommended, but especially in discordant couples during pregnancy where the female is seronegative, and all patients should be warned about the risks of orogenital sex.

Antiviral therapy

Whether the routine use of aciclovir should be offered to all seropositive individuals is a controversial issue, but patients should be made aware of available data. Aciclovir can significantly reduce the discomfort associated with a symptomatic episode and, if used suppressively, can reduce the number of recurrences and give patients a sense of control over their disease.^{5,6} In addition, the results of a recent study have shown that aciclovir can significantly reduce subclinical viral shedding, decreasing HSV DNA detection in genital swabs by both culture and polymerase chain reaction techniques.⁷

Clinical Implications of Orofacial Herpes Simplex Virus

Seroprevalence

The incidence of primary herpes simplex virus type 1 (HSV-1) infection is greatest during childhood when there is a greater chance of contact with oral secretions and close person-to-person contact. Using type-specific serological assays, it has been possible to characterize the seroprevalence of HSV-1 infections with sera collected in the USA in 1978. These data indicate that by 5 years of age, over 35% of the African-American population, and 18% of the white population had been infected with HSV-1.¹

Geographical location, socioeconomic status and age have all been found to influence the frequency of HSV infection. Primary HSV-1 infections generally occur early in life, particularly in developing countries and in populations of low-socioeconomic status. During adolescence an increase in seroprevalence in all populations is associated with kissing. By adulthood there is a high prevalence of antibodies to HSV-1 worldwide, although there is significant country-to-country variation (Figure 1).

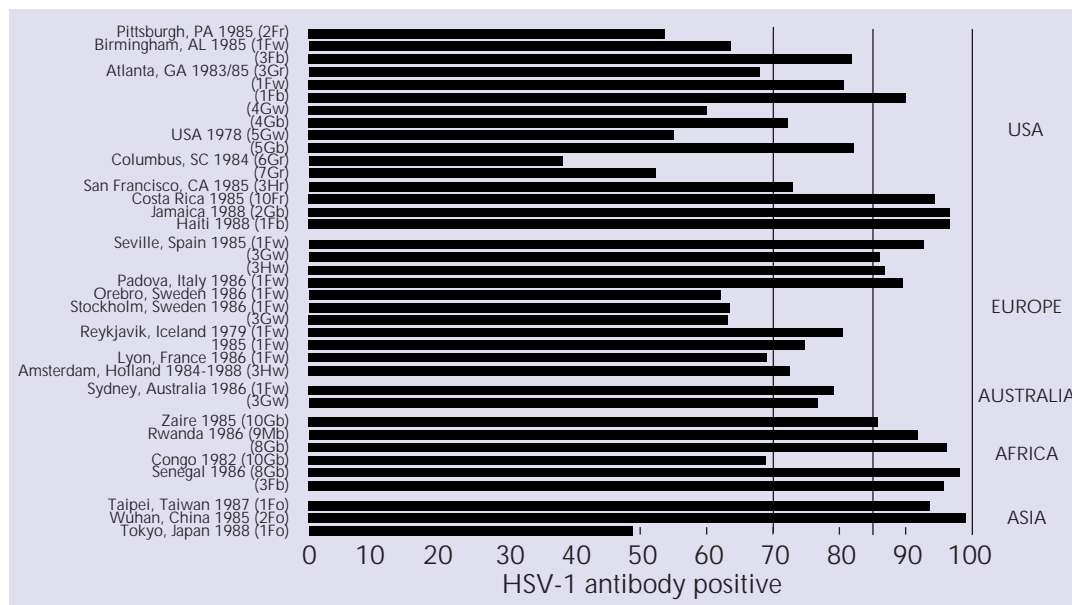


Figure 1: Prevalence of HSV-1 antibodies in different populations of the world. Serum source: (1) pre-natal clinics. (2) family planning or gynaecology clinic. (3) sexually transmitted disease (STD) clinic. (4) health maintenance organization. (5) National Health and Nutrition Examination Survey II (NHANES II) (USA population). (6) college students (freshmen). (7) college students (seniors). (8) hospital workers or patients. (9) army recruits. (10) general population. M, male. F, female. G, males and females. H, homosexual males. Race: w, white; b, African-American; r, white and African-American; o, oriental

Pathophysiology

Primary infections

Gingivostomatitis

Primary orofacial infection with HSV-1 usually occurs by viral inoculation of the oral mucosa. It may be subclinical or result in gingivostomatitis which is common in small



Figure 2: Child with primary gingivostomatitis

children and infants (Figure 2). Treatment with analgesics for pain relief, antiseptic mouthwashes to prevent secondary infection, and fluid intake will relieve the majority of symptoms. However, the results of a recent study by Aoki *et al* support the use of oral aciclovir for primary gingivostomatitis.² In a placebo-controlled trial, 68 children from 6 months to 12 years of age with acute primary gingivostomatitis of less than 96 hours duration were randomized to either an oral aciclovir suspension 600 mg/m² four times daily for 10 days, or placebo. Aciclovir reduced new lesion formation by 70% ($P=0.0001$) and reduced the median time to healing from 8 days on placebo to 6 days on aciclovir ($P=0.005$). The duration of viral shedding was reduced by 60% ($P=0.0001$).²

Eczema herpeticum

Eczema herpeticum is a potentially serious complication that may occur in patients with atopic dermatitis. Clinically it manifests as widespread painful cutaneous lesions. Occasional dissemination to visceral organs can occur, usually following primary HSV-1 infection.

The diagnosis of eczema herpeticum is primarily clinical, supported by isolation of HSV and rising antibody titres. It is therefore important to recognize the clinical features. The vesicles are found mainly on already eczematous skin, particularly over the face, arms and trunk and resemble those of chickenpox (Figure 3).³ The incidence of children with eczema contracting HSV is high. In most cases this leads to a mild disorder, which may go unrecognized. In some cases, however, it can rapidly progress to severe visceral dissemination.³ In approximately one-third of cases, the source of virus is a parent with herpes labialis.⁴ In addition to intensive circulatory support and relevant antibiotic therapy, several reports have documented successful treatment of eczema herpeticum with both oral and intravenous aciclovir.⁴⁻⁷



Figure 3: Patient with eczema herpeticum

Recurrent infections

Herpes labialis

Following primary infection the virus is thought to ascend through sensory nerve axons to establish chronic, latent infection in the ganglia of the trigeminal, facial and/or vagus nerves. Although 20–40% of the population suffer recurrent orolabial infection with HSV, recurrent infections are severe in only about 1% but can be associated with significant discomfort and transient cosmetic disfiguring. Prodromal symptoms include pain, itching and tingling with the subsequent development of vesicles (Figure 4). Recurrent infections tend to be labial rather than intra-oral. It is

thought that an enzyme in saliva may partially protect the oral mucosa. This protection does not seem to extend to immunocompromised patients in whom intra-oral recurrences are common,⁸ probably because of increased viral load.

Many patients with occasional recurrences of herpes labialis will not require treatment. Studies with topical aciclovir have produced varied results according to the formulation of the topical preparation. Initial trials with aciclovir ointment (5% aciclovir in polyethylene glycol base) showed no benefit in reducing the speed of lesion crusting and healing time.⁹ Subsequent trials with aciclovir in an aqueous cream base have yielded more positive results showing a modest reduction in healing time from 6 to 4 days.^{10,11} Another study, however, showed no significant difference between treatment and control groups with respect to lesion crusting and healing time.¹² Fiddian *et al* have shown that lesions can be aborted if treatment is started before vesicles occur, reducing the number of patients going on to develop lesions by one-third.¹⁰

Although routine treatment of herpes labialis is not indicated, oral aciclovir (400 mg five times daily for 5 days) has been shown to significantly reduce the duration of pain and lesion healing time in patients with herpes labialis.¹³ Continuous aciclovir therapy (400 mg twice daily) has also been used effectively to suppress recurrences of herpes labialis and may be indicated in the 1% of patients in whom recurrences are particularly severe.¹⁴ It may also be recommended as prophylactic therapy in individuals who are at short-term high risk of developing a recurrent attack, for instance due to a forthcoming wedding, ski-ing holiday, etc.



Figure 4: Patient with herpes labialis

Erythema multiforme

Erythema multiforme is thought to be the result of a host-specific immune response to a wide variety of antigenic stimuli. The association between infection with HSV and the subsequent development of erythema multiforme is well established, although the role that the virus plays in the pathogenesis of this disorder is not known.¹⁵ In a recent study of 82 patients with recurrent attacks of erythema multiforme, 70% of patients had painful oral ulcerative lesions. The buccal mucosa and tongue were the most frequently affected sites, but the entire oral mucosa was affected in over 20% and the lips in 13% of cases. Lesions generally lasted 1–3 weeks and in over 60% of cases were preceded by an episode of herpes labialis.¹⁶

A large study by Schofield *et al* found 71% of attacks to be precipitated by preceding HSV infection, usually labial.¹⁷ The mean number of attacks per year was six (range 1–24) and the average duration of the disease was 9.5 years (range 2–36), illustrating the chronic nature of the infection.¹⁷ A comparison of short-term aciclovir treatment (200 mg five times daily for 5 days) versus continuous therapy (400 mg twice daily for 6 months) has been conducted. Both strategies reduced the number of recurrences, but the latter was shown to be the more successful treatment. Out of 37 patients treated in this way, there was complete disease suppression in 15 patients and partial suppression in eight patients.¹⁷

Herpetic whitlow

This has been an occupational hazard of medical and dental workers who are exposed to oral secretions containing virus that can be inoculated through minor abrasions on the hands. Several well-documented cases have been described including a paper by Stern *et al* (1959), who described 54 cases of herpetic whitlow in nurses over a period of 5 years.¹⁸ The outbreaks appeared to occur in clusters, which suggested that there were point sources of infection. Following an operation, the nurses were suctioning the patients mouths without wearing gloves and were becoming infected by HSV-1, which was being excreted in the oral cavity. Now that the wearing of gloves has become mandatory, herpetic whitlow is rarely seen.

Further documentation for the risk of transmission of HSV infections to healthcare workers comes from a study by Adams *et al* who used endonuclease typing to define two outbreaks among healthcare workers caused by two different viruses.¹⁹ One case identified subclinical shedding of HSV-1 from a boy as the cause of herpetic whitlow in two nurses and primary gingivostomatitis in the husband of one of the nurses. In another outbreak, virus from a patient with primary gingivostomatitis was identified in the fingers of two nurses with herpetic whitlow.¹⁹

Autoinoculation of HSV to fingers or hands as a result of primary oral or genital HSV infection may also occur. Children with primary gingivostomatitis may infect multiple fingers. In contrast, healthcare workers with herpetic whitlow generally only have a single digit involved.²⁰ Recurrent herpetic whitlow infections are mostly due to HSV-2, with most cases occurring in women aged 20–40 years who also have recurrent genital herpes.²⁰ Aciclovir has shown efficacy in the treatment of herpetic whitlow. In one study, eight patients with recurrent disease had all attacks aborted by oral aciclovir given during the prodrome.²¹

Frequency of recurrences

Studies performed to assess the frequency and severity of recurrent orofacial HSV-1 infections are limited. However, in the immunocompetent, primary infection with HSV-1 leads to recurrent infections in approximately 20–40% of the population.²²

Studies have failed to define conclusively the intra-oral sites of virus replication, although the gingivae and hard palate are commonly implicated.²³ The rate of HSV excretion is significantly increased during infection with the common cold and after oral trauma,²³ and both surgical treatment and operations have been shown to lead to reactivation of latently infected HSV-1.²⁴ Other trigger factors include ultraviolet (UV) light and emotional stress.²²

Subclinical Viral Shedding

The frequency of subclinical shedding of HSV-1 is much less well studied than that of HSV-2. The studies that have been performed document that subclinical shedding does occur, however. Otherwise healthy individuals, seropositive for HSV-1, shed virus on approximately 8% of days compared with approximately 40% of days for HSV-1 seropositive patients who have undergone oral surgery or who are immunocompromised.^{23–25}

Populations at Risk

Nosocomial transmission

Nosocomial infections have been defined as infections originating in a hospital setting and include infections developing in both patients and hospital staff, where there is no apparent reason to suspect reactivation of an existing infection.²⁶

Excretion of HSV in the oral cavity in the absence of clinical symptoms is a risk factor for dental personnel and healthcare workers.^{22,27} Consequently, there may also be a risk for the patients that they come into contact with. HSV can be directly inoculated into the skin, and healthcare workers exposed to infected secretions may develop herpetic whitlow, which can become a recurrent infection. There are many cases of dental practitioners contracting HSV infection in this way and it is therefore essential that they wear surgical gloves, and that gloves are changed between patients and not worn for lengthy periods of time.

The risk of nosocomial HSV infection is greatest to those who have an immature immune system or those who are immunosuppressed as a result of drugs or disease.

Strategies for the Management of Infection

Although there are data documenting nosocomial HSV transmission, there are few data on how prevalent these cases of transmission are. The use of gloves will prevent most cases of transmission from staff to patients and *vice versa*, but horizontal transmission in the general population is much harder to prevent without causing unnecessary alarm. Most individuals are unaware that herpes labialis is caused by a virus. Patients presenting to a physician with herpes labialis should therefore be advised to avoid physical contact with others, e.g. kissing, when lesions are present, and to use high standards of hygiene. Sexually active individuals should be made aware that HSV-1 infection as a result of orogenital sex may result in genital herpes.

Parents of children with eczema should be warned of the risks of eczema herpeticum and taught to recognize the symptoms so that an early diagnosis can be made.

Summary and Recommendations

Viral and Host Factors Involved in Latency

Latency is required for the persistence of herpesviruses in the host and these viruses have evolved elaborate mechanisms to control the latent state. Research into the molecular biology of latency suggests that it is not a resting state, but extremely dynamic, and that it involves a complex inter-relationship between the virus, host cell and the immune system.

Numerous recent publications suggest that several factors are likely to be involved in the control of the latent state. These include the protein products of open reading frame P (ORF-P) and open reading frame O (ORF-O) and transcription factors which may be present in neuronal cells, but not in cells found at the portal of entry of the virus. Further research is now needed to determine whether virally-encoded proteins can suppress activation of α (immediate early genes) and the role of neurone-specific transcriptional factors in the maintenance of the latent state.

The host immune system plays an important role in preventing the spread of virus after reactivation. Only if the effectiveness of the immune system is reduced, will clinically significant reactivation result.

Strategies to control the latent state

Continued research into the mechanisms by which herpesviruses establish, maintain and reactivate from latency are important to provide insight into the development of new drugs to control it.

To eradicate latency, drugs would have to be developed which either block the establishment of latency or activate all latent viral genomes under controlled conditions (e.g. under medical supervision in a hospital environment) in the presence of potent antiviral drugs (Figure 1). However, this is probably not desirable given that re-infection with other strains could occur. The goal should therefore be to control or maintain the latent state to minimize the risks for transmission of disease.

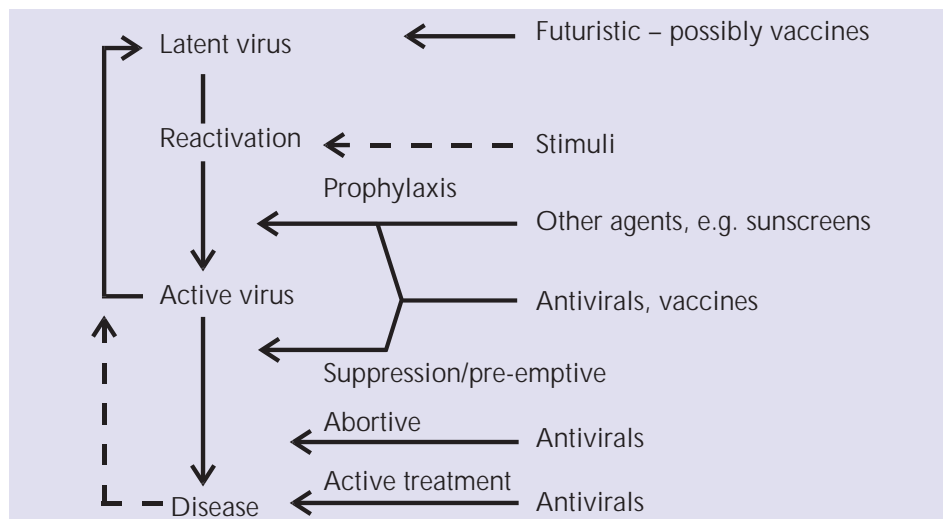


Figure 1: Strategies for the prevention and control of latent herpesvirus infections

Virus contained in the body may be important for the effectiveness of the immune system, maintaining antibody levels against disease throughout life. In this scenario, reactivation should be the prime target for intervention to minimize human discomfort and transmission. Further research should be carried out into the host immune mechanisms that maintain latency and the stimuli that result in reactivation in an effort to develop new drugs to control the latent state.

Reactivation of latent virus can be controlled to a certain extent by suppressive antiviral therapy. In the future, a wider availability of vaccines for the different herpesviruses may maintain the virus in a latent state.

Clinical Implications of Genital Herpes Simplex Virus

Recurrences of herpes simplex virus (HSV) serve a very distinct purpose for the continued spread of the virus, with seropositive individuals acting as potential reservoirs of infection. It is therefore desirable to limit the consequences for the individual in terms of discomfort and disease and for the population as a whole in terms of transmission.

Diagnosis of subclinical disease

It was agreed that type-specific serological tests should be made more widely available to identify discordant couples, where the woman is seronegative and may be at risk of contracting primary genital herpes during pregnancy. However, the issue of routine serological testing was controversial. The realization that genital herpes is a chronic infection with infected individuals shedding virus even when lesions are absent has presented physicians with a moral dilemma. On the one hand, any attempt to reduce the seroprevalence of HSV-2 in the population must focus on transmission from individuals who are unaware that they have the disease. On the other, a physician faced with a patient diagnosed HSV-2 seropositive must tell them that not only are they infected with the virus that causes genital herpes but also that, despite having no clinical symptoms, they represent a risk for the transmission of the disease to sexual partners. It was agreed that studies to examine the impact of HSV testing on behaviour and on transmission of virus to sexual partners are needed to assess the clinical and public benefit of routine serological testing in a general medical setting. No consensus was reached on who should be serologically tested, but it was agreed that an individual diagnosed HSV-2 seropositive should be made aware of all the facts, albeit not at first diagnosis.

Strategies for the management of infection and reducing transmission risks

Barrier contraception

While beneficial for the prevention of transmission of HSV, recommendations for the use of condoms will vary from country to country. They cannot prevent transmission in 100% of cases because of factors such as orogenital sex, manufacturing defects, improper use and extra-genital virus shedding, but should be recommended for routine use by discordant couples or when couples are not aware of their partner's serostatus. This is particularly important during pregnancy when the male partner is seropositive and the female seronegative.

Antiviral therapy

Treatment of first episode: A thorough clinical examination should be performed and history taken and if genital herpes is suspected, appropriate antiviral therapy should be started without delay. The patient should be advised of the clinical diagnosis but laboratory confirmation of the diagnosis is recommended, ideally by culture. This has the added benefit of determining virus type and providing information on the natural history of the disease. A follow-up visit should be scheduled to confirm the diagnosis, offer counselling (see page 19) and discuss the treatment options available. Patients should be asked to return to the physician on first recurrence.

Treatment of recurrent episode: The use of antiviral agents for the management of genital herpes is undoubtedly effective, with aciclovir able to be used for both the treatment and prevention of recurrent episodes. When aciclovir treatment is self-initiated in the prodrome, patients are able to abort a significant number of attacks. In respect to new treatments, trials of valaciclovir in recurrent genital herpes have shown some clinical advantage over aciclovir. To date only data on placebo controlled studies of famciclovir are available.

Suppressive therapy with aciclovir is effective for the treatment of recurrent genital herpes, increasing the number of patients who are recurrence-free. Preliminary data also demonstrate the benefit of suppressive aciclovir therapy on reducing subclinical shedding. The choice between use on a long-term, suppressive basis and as an episodic therapy may be influenced by a number of variables including the frequency and severity of episodes, the psychological state of the patient, the patient's lifestyle and cost implications (Figure 2).

The physician should do their best to ensure that the patient understands the diagnosis and participates in the treatment decision. In some cases when a patient is coping well with the disease and not experiencing undue suffering, they may decline antiviral therapy. Although not all recurrences require treatment, a large proportion of individuals experience relatively mild disease and in this case episodic therapy may be warranted if given early. Treatment initiated in the prodrome can be very effective at preventing lesions developing further and accelerating healing. Suppressive therapy is recommended when the patient is experiencing frequent and severe recurrences or when the disease is having a severe psychological impact. With all options the physician should ensure that the patient is involved in the decision-making process.

Risk of transmission: Recent studies have shown the benefits of aciclovir in significantly reducing subclinical viral shedding. While it may be argued that a reduction in virus would reduce the risk of transmission, it is not appropriate to make any recommendations regarding the use of suppressive aciclovir therapy for the prevention of transmission until formal studies have been completed.

Vaccines

Two subunit vaccines are in development, both for the treatment of recurrent genital herpes, as well as for prevention of disease, and are achieving antibody levels equivalent to those observed in individuals naturally infected with HSV-2. HSV vaccines offer the best hope for limiting the continued spread of genital HSV in a population.

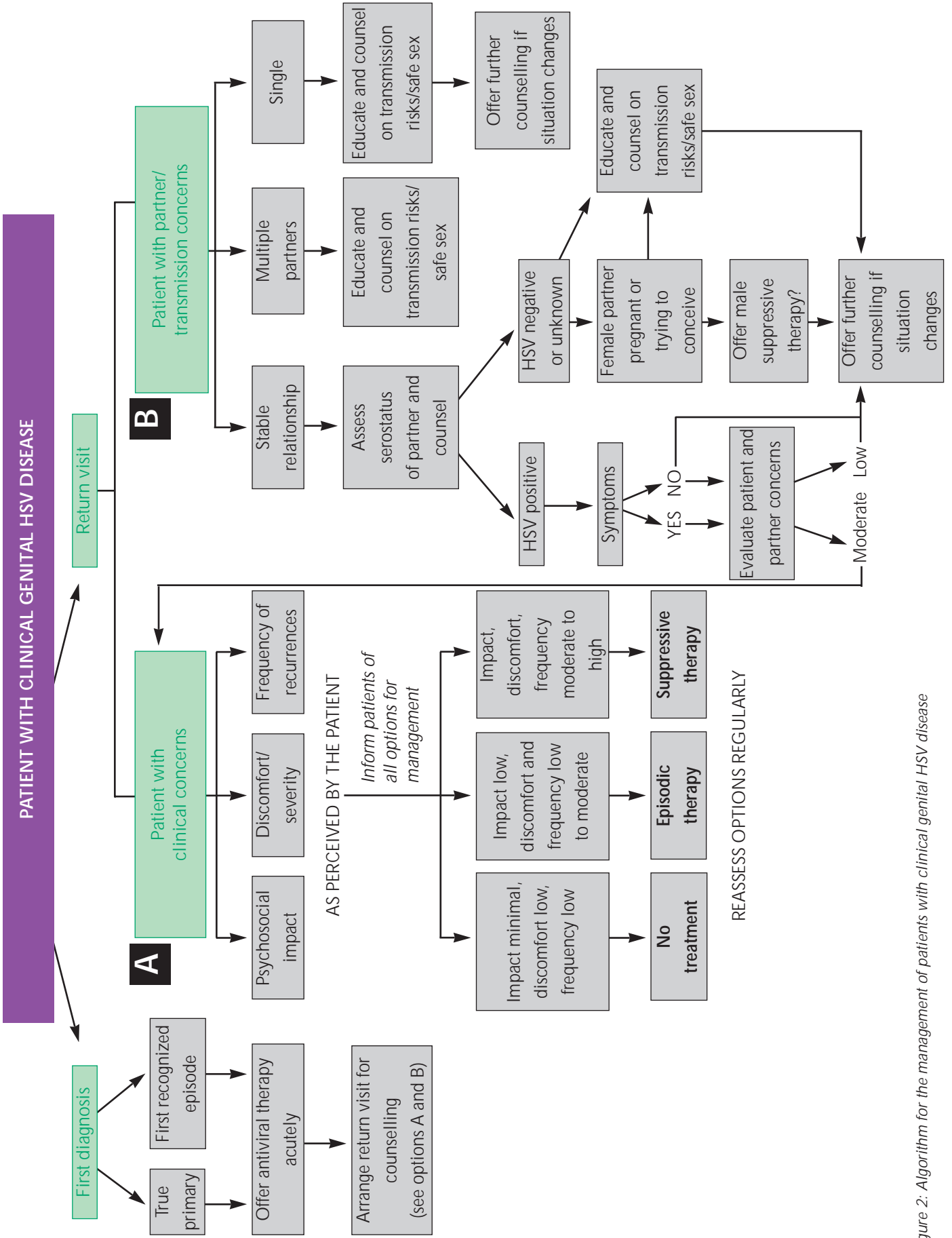


Figure 2: Algorithm for the management of patients with clinical genital HSV disease

Educational and Counselling Issues Regarding Genital Herpes Simplex Virus

Sex education

There is wide agreement that the most effective education on the risks of acquiring sexually transmitted diseases (STDs) should begin in early adolescence before an individual becomes sexually active. For HSV this should include messages about the risks of transmission associated with subclinical shedding, in which an infected partner may be unaware that they have the disease, and about orogenital sex as a route for acquisition of genital herpes. Sex education should include information about the benefits of barrier contraception for prevention of STDs in general, although it should be remembered that condom use will vary from country to country and be dependent on factors such as local religion, customs and cost.

First diagnosis

When given a diagnosis of genital herpes, a patient is likely to experience a certain amount of shock. At this stage the physician should focus on answering any immediate questions the patient may have as they are unlikely to be able to retain much other information (Figure 3). Written information for the patient to study at home can be given. Physicians should ensure that patients who present for treatment are well managed as this is critical for the patient's subsequent adjustment to the diagnosis.

Follow-up visit

A follow-up visit should be scheduled when laboratory confirmation of the diagnosis will be available. The physician will then be able to further explore the patient's questions and to counsel more extensively. At this stage the physician can discuss with the patient the treatment options available and which is most appropriate for the patient's needs. It is important for the physician to ensure that the patient understands the diagnosis and participates in any treatment decisions.

What patients want to know:

- ◆ An understanding of what the symptoms are and will be
- ◆ Information about transmission – how the infection was acquired and how it may be spread
- ◆ Information about the treatment options available
- ◆ Natural history, e.g. information about HSV types 1 and 2 and associated risks
- ◆ Information about recurrences and what to expect
- ◆ Strategies for risk reduction
- ◆ Advice and help on disclosing diagnosis to partner, e.g. with partner counselling
- ◆ Impact of disease on conception and pregnancy

Patient education and counselling

Education should be carried out in stages taking care not to overload the patient with information. As patients become more able to cope with the situation that is facing

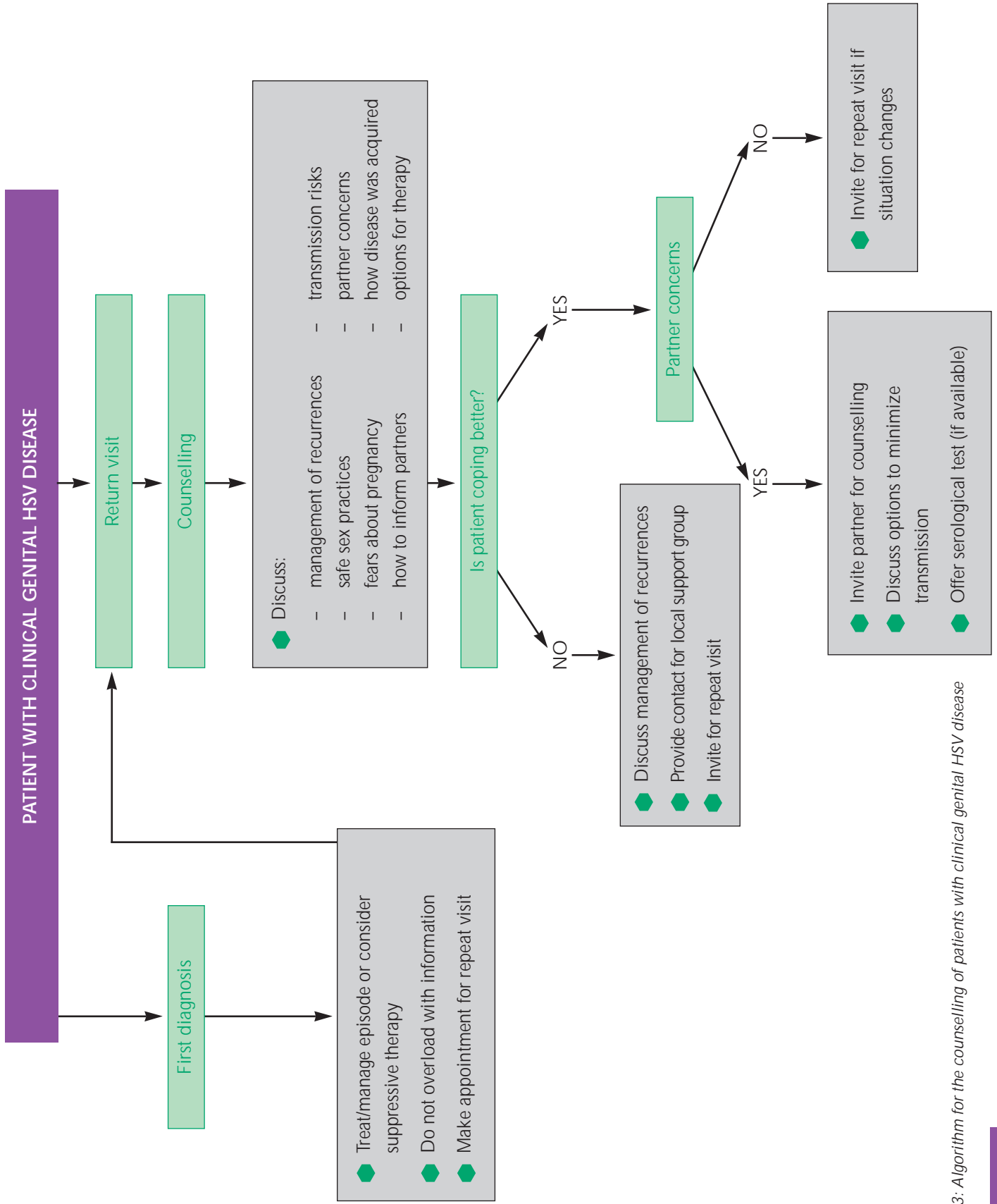


Figure 3: Algorithm for the counselling of patients with clinical genital HSV disease

them, they will want more information and this will vary according to their situation, i.e. starting a new relationship or starting a family.

Patients should be encouraged to talk about their illness and to be honest with their partners. This is particularly important in order to remove the social stigma that is associated with the disease and to enable patients to seek and receive emotional support from their partners – support that can play a key role in the adjustment process. Local groups, such as those initiated by the *American Social Health Association* (ASHA) in the USA, should help break down this barrier and help patients realize that they were by no means in the minority when they were given a diagnosis of genital herpes.

For HSV-seropositive individuals, the primary goal once they have come to terms with the disease must be to educate them about the risks of person-to-person transmission. At this stage it may also be appropriate to offer counselling and serology testing to partners. Once they are aware of the symptoms, partners are usually keen to avoid sexual contact during clinical episodes, but they should also be made aware of the risks of transmission associated with subclinical shedding between recurrent attacks. Prevention counselling should be tailored to the patient's circumstances, so that the patient and their partner can make an informed decision together. Condoms should be promoted to all patients at risk for other STDs and as a measure to reduce the risk of subclinical transmission of HSV in discordant couples. The potential preventative value of suppressive antiviral therapy is currently under study.

Increasing physician awareness

To increase physician awareness of genital herpes as a chronic infectious disease it is necessary to have guidelines, such as those drawn up by the *International Herpes Management Forum* (IHMF), available on a global level. Country-specific organizations, such as the network of national *Herpes Management Forums* (HMFs) and support groups like ASHA, are vital for the dissemination of this information. Strategies now need to be developed for adapting the information that is available so that it is appropriate for local healthcare delivery systems.

The amount and quality of counselling and support available to patients with genital herpes varies enormously and efforts to standardize this to guidelines set by ASHA are urgently required. A bare minimum would be to provide the patient with:

- ◆ a verbal overview of what the patient can expect in terms of the disease
- ◆ answers to questions they may have
- ◆ written material or other resource information, e.g. video for self-study

Counselling is a specialized skill and not an area where it was felt that medical students were particularly well trained. In the future training could be influenced better at the medical school level. For physicians and other healthcare workers already involved in clinical care, specialized training such as that carried out through the University of Alabama, Division of Continuing Medical Education in the USA could be instituted. This would involve distilling the scientific data into a more easily accessible and understandable format for training. In this way training could be targeted to physicians with a particular interest or involvement in the management of

patients with genital herpes infections. Patients could then be referred to local or regional centres where specialized support could be provided and which would also have appropriate diagnostic resources.

Physicians in general should be encouraged to liaise with local support groups and to take an active interest in the type of information they are distributing.

Clinical Implications of Orofacial Herpes Simplex Virus

The number of studies on orofacial HSV infection are limited and, consequently, so are the amount of data. It was agreed that more research was required into the frequency of recurrent HSV-1 infections and into the nature of subclinical shedding. This should include studies on other areas of orofacial viral shedding such as nasal and eye secretions.

Strategies for the management of infection

Primary gingivostomatitis

Primary infection with HSV-1 may pass unnoticed but in some cases can cause the individual considerable discomfort. Although not approved by any regulatory authority, recent results support the treatment of this condition in children with a suspension of oral aciclovir 600 mg/m² four times daily for 10 days.

Eczema herpeticum

Individuals with atopic eczema may be at risk of developing this potentially serious complication following a primary HSV-1 infection. In addition to intensive circulatory support and relevant antibiotics, aciclovir therapy is warranted, although the most beneficial dose and method of delivery have not been established.

Parents of children with atopic eczema should be advised to take extra care if they suffer recurrences of herpes labialis and be taught to recognize the symptoms of eczema herpeticum.

Recurrent herpes labialis

Although many patients do not require therapy, the literature supports treatment of this condition if it is initiated in the prodrome and topical aciclovir cream or ointment is available for this indication. It should be applied when the patient feels the characteristic tingling sensation and should be administered five times daily. In some countries aciclovir cream is available without a doctor's prescription.

A small percentage of patients experience frequent and severe recurrences and, in this instance, a short course of oral aciclovir 400 mg three times daily is recommended. Oral aciclovir may also be indicated as a short-term prophylaxis measure in patients whose recurrences are brought on by stressful situations or environmental factors, for instance a wedding, a new relationship or holiday.

Erythema multiforme

This is an uncommon but potentially serious disease and may require hospitalization. In patients in whom the disease is thought to be triggered by a prior herpetic infection, aciclovir treatment should be given at the first sign of a recurrent herpes infection.

Subsequent suppressive aciclovir therapy may be warranted to prevent further attacks. Supportive care should include analgesics and appropriate hydration. Steroids were not found to influence the course of the disease and were not recommended.

Nosocomial infections

Orofacial excretion of HSV, particularly when the infection is asymptomatic or subclinical, can be a risk for dental personnel and healthcare workers and is increased following oral trauma. Current strategies to reduce cross-infection, such as the wearing of rubber gloves, are effective and the number of cases of nosocomial transmission has greatly declined.

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