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# HERPES SIMPLEX VIRUS TYPE 2 PROGRAMMATIC AND RESEARCH PRIORITIES IN DEVELOPING COUNTRIES

REPORT OF A WHO/UNAIDS/LSHTM WORKSHOP (LONDON, 14-16 FEBRUARY 2001)



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## ABBREVIATIONS

<b>ANC</b>	Antenatal Clinics
<b>CMI</b>	Cell Mediated Immunity
<b>DISC</b>	Disabled Infectious Single Cycle
<b>GUD</b>	Genital Ulcer Disease
<b>HIV</b>	Human Immunodeficiency Virus
<b>HSV2</b>	Herpes Simplex Virus Type 2
<b>Ig</b>	Immunoglobulin
<b>LGV</b>	Lymphogranuloma venereum
<b>NNRTI</b>	Non-nucleoside Reverse Transcriptase Inhibitors
<b>PAF</b>	Population Attributable Fraction
<b>PCR</b>	Polymerase Chain Reaction
<b>RCT</b>	Randomized Controlled Trial
<b>RNA</b>	Ribonucleic Acid
<b>RPR</b>	Rapid Plasma Reagin
<b>STD</b>	Sexually Transmitted Disease
<b>STI</b>	Sexually Transmitted Infection
<b>UN</b>	United Nations
<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>WHO</b>	World Health Organization



## EXECUTIVE SUMMARY

*Herpes simplex virus type 2 (HSV2)* infection is the primary cause of genital herpes. It is highly prevalent in human populations in many parts of the world, and is the most common cause of genital ulcer disease worldwide.

In developing countries, the major public health importance of HSV2 relates to its potential role in facilitating HIV transmission. HSV2 is highly prevalent in most regions experiencing severe HIV epidemics, with infection rates rising steeply with age to reach levels of 70% or more among adult women and men in some African countries. Genital ulcer disease enhances the infectiousness of HIV-positive subjects and the susceptibility of HIV-negative subjects, and clinical research has shown effects of HSV2 infection on genital HIV shedding. The reciprocal effect of HIV immune suppression on the exacerbation of HSV2 symptoms implies that there is a positive feedback loop, with HIV enhancing HSV2 expression, which in turn may enhance HIV infectiousness and its spread. Accumulating data suggest that HSV2 may be responsible for a substantial proportion of new HIV infections in some parts of Africa.

Given the increasing awareness of the link between HSV2 and HIV, an international technical workshop was held in February 2001 to review existing knowledge concerning the epidemiology and control of HSV2 in developing countries and its interaction with HIV. The main aim of the workshop was to establish future research and operational priorities for genital herpes control. While the main focus was on developing countries, where the public health burden of HSV2 is greatest, experts from industrialized countries were also invited to share perspectives from these countries, where much previous research has been conducted.

This report covers the topics that were discussed during the workshop. In the epidemiology of HSV2 it was noted that the prevalence varies widely in developed countries. In the USA 22% of adults are noted to be HSV2-positive and in Europe the figure is around 15%. In developing countries rates are higher, with prevalences around 50% in some countries of sub-Saharan Africa. However, there are currently few data on HSV2 from many parts of the world, including Asia, South America and many parts of Africa.



The report also touches on the natural history of HSV2, including the aspect of subclinical or 'asymptomatic' nature of HSV2 manifestations. The amount of shedding required for HSV2 transmission to occur is not fully known, and neither is the relationship between clinical and subclinical HSV2 and HIV transmission. Recommendations for future research are, thus, highlighted in the report.

The report looks further into the epidemiological trends of genital ulcer diseases in Africa and discusses the evidence indicating that the aetiology of genital ulcers has changed in recent years. With this in mind the workshop discussed the implications thereof, and the appropriateness of the current syndromic management of genital ulcer disease. Country experiences of the aetiology of genital ulcer disease from South Africa are illustrated.

Under HSV2 control measures for developing countries, current practice and recommendations are made. The report further explores the role of episodic and suppressive therapy in HSV2 and HIV control and concern related to issues of resistance with the widespread use of antiviral therapy. Within the area of prevention discussions and recommendations were made on HSV2 vaccines and vaccine trials.

Finally, the report tackles research and control programme priorities in terms of epidemiological studies and natural history, HSV2 and its interactions with HIV, episodic and suppressive therapy, vaccines and behavioural and microbicide studies.



# 1. INTRODUCTION

*Herpes simplex virus type 2 (HSV2)* infection is the primary cause of genital herpes. It is highly prevalent in human populations in many parts of the world, and is the most common cause of genital ulcer disease worldwide.

In developing countries, the major public health importance of HSV2 relates to its potential role in facilitating HIV transmission. HSV2 is highly prevalent in most regions experiencing severe HIV epidemics, with infection rates rising steeply with age to reach levels of 70% or more among adult women and men in some African countries. Genital ulcer disease enhances the infectiousness of HIV-positive subjects and the susceptibility of HIV-negative subjects, and clinical research has shown effects of HSV2 infection on genital HIV shedding. The reciprocal effect of HIV immune suppression on the exacerbation of HSV2 symptoms implies that there is a positive feedback loop, with HIV enhancing HSV2 expression, which in turn may enhance HIV infectiousness and its spread. Accumulating data suggest that HSV2 may be responsible for a substantial proportion of new HIV infections in some parts of Africa.

There is an urgent need to consider potential control measures for HSV2 that might be applied in an effort to curb HIV transmission. These might include episodic or suppressive antiviral therapy, for example among high-risk groups, and behavioural interventions designed to reduce herpes transmission. Candidate HSV2 vaccines and vaginal microbicides are also under development. An increasing proportion of genital ulcer cases in Africa are now attributable to HSV2, and the implications for treatment algorithms also need to be considered.

Given the increasing awareness of the link between HSV2 and HIV, an international technical workshop was held in February 2001 to review existing knowledge concerning the epidemiology and control of HSV2 in developing countries and its interaction with HIV. The main aim of the workshop was to establish future research and operational priorities for genital herpes control. While the main focus was on developing countries, where the public health burden of HSV2 is greatest, experts from industrialized countries were also invited to share perspectives from these countries, where much previous research has been conducted.



## 2. OBJECTIVES

The objectives of the workshop were:

1. To review existing knowledge in the following four areas, with a particular focus on developing countries:
  - The epidemiology and natural history of HSV2
  - The interaction between HSV2 and HIV
  - HSV2 control measures
  - HSV2 diagnostics.
2. To identify important gaps in knowledge in each of these areas requiring further study.
3. To establish priorities for future research and control programmes.



### 3. PARTICIPANTS AND METHODOLOGY

Forty participants attended the workshop (Annex 1), and areas of expertise included virology, epidemiology, surveillance, behavioural science, clinical medicine, mathematical modelling and STI programme development and implementation in developing countries. Participants came from Africa (10), Asia (1), Europe (18) and North America (7). In addition, three representatives of UN agencies were present, and one from GlaxoSmithKline.

The workshop was organised around the four topic areas listed above, with a session devoted to each topic. The workshop included presentations by invited speakers, breakout discussion groups, and plenary discussions.

A list of discussion questions for each topic was circulated at the beginning of the meeting. In the final session, a list of research and programmatic recommendations arising during the workshop was discussed and prioritized.



## 4. EPIDEMIOLOGY AND NATURAL HISTORY OF HSV2

### 4.1. EPIDEMIOLOGY OF HSV2

HSV2 prevalence is increasing worldwide [Fleming *et al.*, 1997; Halioua and Malkin, 1999; O'Farrell, 1999], and HSV2 is the major cause of genital ulcer disease (GUD) in the developed world. In the developing world, the major public health importance of HSV2 lies in its potential role as a co-factor for HIV transmission.

The high prevalence of HSV2 in many populations results from the fact that it is a lifelong infection, which is highly infectious and often transmitted in the absence of symptoms. There have been few data on HSV2 prevalence until recent years, when type-specific serology became available, enabling researchers to estimate HSV prevalence and incidence. However, there is currently concern about the specificity of some of these serological assays when used to analyse sera from African countries (see Section 8).

### GLOBAL EPIDEMIOLOGY OF HSV2

HSV2 prevalence varies widely, with generally higher rates in developing than in developed countries and in urban than in rural areas. Prevalence is higher in the USA (22% in adults) [Krone *et al.*, 2000] compared with Europe (generally less than 15%). However, substantially higher rates are seen in Sub-Saharan Africa and the Caribbean, with prevalences in adults of around 50% in many countries (Table 1). Overall, prevalence is higher in women compared with men, especially among the young [Kamali *et al.*, 1999; Fleming *et al.*, 1997; Obasi *et al.*, 1999], and rates of up to 40% have been recorded among women aged 15-19 in Kisumu, Kenya [Weiss *et al.*, 2001]. Infection has been associated with younger age at first sex [Austin *et al.*, 1999], increased years of sexual activity [Cowan *et al.*, 1994], increasing number of lifetime partners [Austin *et al.*, 1999, Cowan *et al.*, 1994; Fleming *et al.*, 1997; Kamali *et al.*, 1999; Obasi *et al.*, 1999; Wald *et al.*, 1997], lack of circumcision (in men) [Weiss *et al.*, 2001] and current or recent other STIs [Cowan *et al.*, 1994; Obasi *et al.*, 1999].

**Table 1: HSV2 seroprevalence in general populations in developing countries**

Country	Population	Year	Prevalence <sup>1</sup>	Reference
Uganda	Adults (rural)	1989	74% (f); 57% (m)	Wagner <i>et al</i> , 1994
Congo	Adults (urban)	1982	71%	Nahmias <i>et al</i> , 1990
Kenya	Adults (urban)	1997	68% (f); 35% (m)	Weiss <i>et al</i> , 2001
Zambia	Adults (urban)	1997	55% (f); 36% (m)	Weiss <i>et al</i> , 2001
Rwanda	Hospital workers (rural)	1985	51%	Nahmias <i>et al</i> , 1990
Cameroon	Adults (urban)	1997	51% (f); 27% (m)	Weiss <i>et al</i> , 2001
Costa Rica	Adult women	1985	43% (f)	Nahmias <i>et al</i> , 1990
Tanzania	Adults (rural)	1993	42%(f);19%(m) <sup>2</sup>	Obasi <i>et al</i> , 1999
Brazil	Adults (urban)	1990/91	42%	Smith <i>et al</i> , 2001
Zaire	Adults (urban)	1985	41%	Nahmias <i>et al</i> , 1990
Rwanda	Adults (rural)	1985	33%	Nahmias <i>et al</i> , 1990
Benin	Adults (urban)	1997	30% (f); 12% (m)	Weiss <i>et al</i> , 2001
Brazil	Blood donors (urban)	1994	29%	Da Rosa-Santos <i>et al</i> , 1996
Rwanda	Army Recruits (rural)	1985	28% (m)	Nahmias <i>et al</i> , 1990
Senegal	Surgical patients (urban)	1985	20%	Nahmias <i>et al</i> , 1990
Philippines	Adults (urban)	1991/93	9%	Smith <i>et al</i> , 2001
China	Gynaecology clinic (urban)	1984-5	2% (f)	Nahmias <i>et al</i> , 1990

<sup>1</sup> (f) females; (m) males

<sup>2</sup> Age-weighted sample: younger age-groups were over-represented

### HSV2 AS A MARKER FOR SEXUAL BEHAVIOUR

As HSV2 is more readily transmitted sexually than HIV, HSV2 serology may be a useful marker for changes in sexual behaviour in HIV intervention studies. However, the persistent nature of the infection implies that seroprevalence may not be a sensitive marker of behaviour change, although it will be more discriminating at the lower prevalences seen in younger age groups [Obasi *et al.*, 1999]. HSV2 seroincidence would be a preferable marker of behaviour change, especially in countries in sub-Saharan Africa where there is high incidence among young people.

### IDENTIFIED GAPS IN KNOWLEDGE

There are currently few data on HSV2 prevalence from many parts of the world, including Asia, South America and many parts of Africa. HSV2 incidence data are also scarce [Kamali *et al.*, 1999; McFarland *et al.*, 1999; Hayes *et al.*, 2001]. Prevalence and incidence data are necessary: i) to estimate population attributable fractions (PAFs) for HIV; ii) as background data to inform future intervention studies, such as HSV2



treatment and vaccine trials; iii) to evaluate the need for changes in syndromic management of GUD due to presence of genital herpes; and iv) to evaluate the need for regular HSV2 seroprevalence surveys.

Genital herpes can also be due to HSV1 infection, and a study in Scotland found that 40% of genital herpes was due to HSV1 in 1991 [Ross *et al.*, 1993]. Both HSV1 and HSV2 are able to infect and reactivate in the same anatomic area, although the natural history of these infections is markedly different, with HSV2 recurring more frequently than HSV1, so most clinical reactivations are likely to be due to HSV2 [Sucato *et al.*, 1998]. In developing countries, the proportion of genital herpes caused by HSV1 is unknown, although assumed to be low.

Among HIV-negative pregnant women living in developed countries, the risk of neonatal herpes is very low (<3% among women who seroconverted during pregnancy in a study in Washington State, USA) unless primary HSV2 infection occurs during the third trimester of pregnancy, when the risk of transmission is estimated to be 30% to 50% [Brown *et al.*, 1997]. There are few data on the burden of neonatal herpes in developing countries.

## RECOMMENDATIONS

### ■ Analysis of sera from past and present studies for HSV2 prevalence

HSV2 testing of stored sera from existing cohorts was recommended as a source of additional data to understand past as well as current prevalence and trends. However, there are currently problems with specificity of serological tests on African sera.

### ■ Use of sentinel surveillance sera to obtain HSV2 prevalence data in different populations, especially in Asia and South America

Analysis of sera collected through routine sentinel surveillance would allow estimation of HSV2 prevalence in populations in which few data are available. Suitable sentinel populations may follow the HIV surveillance model: in areas of low prevalence, the focus would be on core groups, whereas in areas of high prevalence, data for the general population would be more relevant. Antenatal clinic (ANC) surveillance systems established to monitor HIV could also be used to record HSV2 prevalence. Possible sources of bias in using ANC data to represent the general population may differ from those reported for HIV.



Consideration could be given to the routine inclusion of HSV2 serology in established sentinel surveillance systems, particularly in populations where HSV2 is thought to account for a substantial proportion of HIV infections.

Estimation of seroprevalence should include young age-groups. As they are more sensitive to changes in behaviour patterns than are older age groups, such data should be more informative of the current situation.

#### ■ Estimating the proportion of genital herpes caused by HSV1 in developing countries

Little is known about the proportion of genital herpes caused by HSV1 in developing countries. Aetiological studies of ulcers performed in areas of high HIV prevalence should also include specific HSV1 testing.

#### ■ Estimating the burden of neonatal herpes in developing countries

Anecdotal reports suggest that neonatal herpes is rarely seen in Africa. However, the frequency of this outcome may be increased in areas of high HIV prevalence because of the increased risk of HSV2 genital shedding in HIV infected women.

An indication of the potential for vertical transmission of HSV2 could be obtained by measuring HSV2 incidence during pregnancy in existing studies, e.g.:

- the Rakai sub-study on pregnant women
- seroincidence studies in pregnant women participating in programmes to prevent perinatal transmission of HIV.

## 4.2. NATURAL HISTORY OF HSV2

### CLINICAL COURSE OF HSV2 INFECTION

The clinical spectrum of HSV2 includes primary infection with the virus (either HSV1 or HSV2), the first clinical episode of genital herpes, and recurrent episodes of clinical disease. The median recurrence rate after a symptomatic first episode of genital herpes is four to five episodes per year, and severe first episodes are associated with even higher recurrence rates [Benedetti *et al.*, 1994; Benedetti *et al.*, 1999]. In addition, subclinical or 'asymptomatic' infection may be associated with infectious viral shedding [Wald *et al.*,



1995]. The proportion of infections that are both symptomatic and recognized (by patient and clinician) is estimated to vary between 13% and 37%, although this is higher among HIV-positive individuals. This proportion may increase with provision of health education regarding signs and symptoms of herpes. For example, 50-75% of HSV2 seropositive subjects without a history of genital herpes have reported subsequent symptomatic episodes after receiving health education on genital herpes [Frenkel *et al.*, 1993; Langenberg *et al.*, 1989].

The natural history of herpes infection is poorly documented in low-income countries, and, to our knowledge, no long-term prospective studies of HSV2 shedding have been carried out in developing countries.

### **TRANSMISSION AND ACQUISITION OF HSV2 INFECTION**

The amount of shedding required for HSV2 transmission to occur is unknown. In a prospective study of HSV2-discordant partners, most transmission events were not associated with a clinically recognized HSV2 recurrence in the infected partner [Mertz *et al.*, 1992; Koelle *et al.*, 2000]. As for other STIs, the risk of acquisition of HSV2 seems to be higher in women than in men [Koelle *et al.*, 2000; Mertz *et al.*, 1992; Mertz, 1993]. This may relate to the higher number of HSV2 recurrences in infected men (about 20% higher than in women) [Benedetti *et al.*, 1994], to biological factors such as the larger and more vulnerable mucosal surface of women [Carpenter *et al.*, 1999; Nicolosi *et al.*, 1994, European Study Group of HIV Heterosexual Transmission, 1992], or possibly to differences in awareness and reporting of symptoms between women and men.

### **INTERACTION BETWEEN HSV1 AND HSV2**

In developed countries, acquisition of HSV1 in childhood has decreased as HSV2 seroprevalence has increased [Kinghorn, 1994], suggesting a possible protective effect of HSV1 against HSV2 acquisition. However, studies have shown discrepant results in this respect. Although HSV1 does not seem to modify the risk of HSV2 acquisition [Corey *et al.*, 1999; Brown *et al.*, 1997], it seems to increase the proportion of asymptomatic seroconversions [Langenberg *et al.*, 1999] and, in one study, to increase the rate of HSV2 shedding [Krone *et al.*, 2000]. Infection with HSV1 in childhood is almost universal in many developing countries, where HSV2 prevalence is also very high, and this confirms that HSV1 provides limited protection against infection with HSV2.



## RECOMMENDATIONS

### ■ Studies on the natural history of HSV2 nested within intervention studies

More information is needed on the natural history of HSV2 in developing countries. Such studies could be nested within HIV intervention studies, and could examine the effect of HIV infection on natural history of HSV2. These studies should be conducted in countries with high rates of HIV and HSV2 infection. The prospective nature of intervention studies will allow: i) estimation of the duration of primary infection, which determines frequency of shedding and recurrence rates; ii) assessment of differences in recurrence and shedding according to HIV and circumcision status; and iii) assessment of the effects of other factors, such as nutritional status and poor hygiene.

There are several issues to consider in the design of such cohort studies: i) the need to include young age-groups, not yet sexually active, in order to obtain data on primary infection; ii) losses to follow-up; iii) ethical issues, such as provision of voluntary counselling and testing services for HIV, antiretroviral therapy and aciclovir for severe herpetic episodes; iv) identification of cases will require regular serological surveys (probably six-monthly); v) the overall duration of follow-up required is unclear; vi) such studies should be performed in a site allowing good clinical follow-up.

### ■ Use of existing data from trials and cohort studies to estimate HSV2 transmission rates and to identify factors affecting transmission.

More data are needed on transmission rates of HSV2 and factors influencing transmission. There is an urgent need to analyse existing data generated in studies performed by different research groups. Current data may help to address the problem of unrecognized infection and subclinical viral shedding, which appear to be major factors in transmission. Transmission should be examined according to stage of infection, symptom status, sex, HIV status and condom use.

### ■ New studies to examine HSV2 transmission

Two types of study were recommended to examine HSV2 transmission: studies designed to identify and interview partners of patients with newly-diagnosed genital herpes and studies of discordant couples for HSV2. In both cases careful consideration should be given to appropriate counselling and treatment.



## 5. INTERACTION BETWEEN HSV2 AND HIV

### 5.1. BIOLOGICAL AND CLINICAL RESEARCH

HIV and HSV2 manifest a bi-directional interaction. HSV2 increases the efficiency of HIV acquisition and transmission whereas HIV may increase susceptibility to HSV2 and increase HSV2 shedding, HSV2 recurrence rate and severity of clinical manifestations.

#### EFFECT OF HIV INFECTION ON NATURAL HISTORY OF HSV2

HSV2 reactivation and duration of recurrences are significantly increased in HIV infected individuals [Augenbraun *et al.*, 1995; Fennema *et al.*, 1995]. The frequency and severity of recurrences increases as CD4 cell count decreases [Augenbraun *et al.*, 1995; Fennema *et al.*, 1995; Pannuti *et al.*, 1997; Schacker *et al.*, 1998b].

#### EFFECT OF HIV INFECTION ON HSV2 TRANSMISSION

HIV infection is also likely to increase transmission of HSV2, as there is evidence that the prevalence and quantity of genital HSV2 shedding is significantly increased among HIV seropositive individuals. [Mbopi-Keou *et al.*, 2000, Augenbraun *et al.*, 1995].

#### EFFECT OF HSV2 ON NATURAL HISTORY OF HIV DISEASE

There is some evidence that inclusion of aciclovir in antiretroviral therapy may prolong survival in HIV seropositive individuals [Ionnidis *et al.*, 1998]. One study has shown that HSV2 reactivation is associated with increases in plasma HIV1 RNA and intracellular gag mRNA and that plasma HIV1 RNA level decreases significantly during treatment with aciclovir [Mole *et al.*, 1997]. As a result, it is possible that HIV progresses more rapidly in untreated HSV2 positive individuals. However, evidence is inconclusive and more studies of the effect of episodic HSV2 therapy on HIV are needed, especially in developing countries.

#### EFFECT OF HSV2 ON HIV TRANSMISSION

A study of 12 men in the US infected with both HSV2 and HIV showed that HIV RNA was present in almost all HSV2 lesions, suggesting that HIV transmission is enhanced in the presence of HSV2 lesions [Schacker *et al.*, 1998a]. Another study among women who were mainly asymptomatic in Bangui (Central African Republic) found no overall



association between genital HIV RNA and HSV2 DNA levels, but some association of quantity of HIV and HSV2 shedding among dually shedding women [Mbopi-Keou *et al.*, 2000]. HIV RNA is often present at high titres in genital lesions (independent of plasma RNA levels), but titres of both HIV1 and HSV2 fall rapidly on treatment with aciclovir, supporting the hypothesis that HSV2 reactivation may play an important role in up-regulation of HIV1 on mucosal surfaces.

Few data are available on the effect of subclinical HSV2 on HIV shedding and viral load, or on the relative effects of symptomatic and subclinical infection.

It is plausible that the interaction between the two viruses differs in developed and developing countries, as well as between developing countries, due to the role of other factors (such as circumcision, prevalence of other STIs and other tropical conditions or infections), and similar prospective studies of dually-infected individuals are needed in developing countries. Further biological studies are also needed to define the mechanism by which HIV is secreted on the mucosal surface.

## RECOMMENDATIONS

The following priorities were identified:

- Assess the impact of aciclovir treatment on HIV shedding and viral load.
- Study the relative quantity of HIV viral shedding from genital lesions and in semen of HSV2 infected individuals. Compare rates of genital shedding of HIV during clinical episodes of herpes, during subclinical recurrences, and between recurrences.
- Study whether the effect of HSV2 on HIV transmission differs in Africa, due perhaps to concomitant infections (malaria, malnutrition, other STIs).

Such studies could be incorporated within randomized controlled trials (RCTs) of HIV or HSV2 interventions.

## 5.2. EPIDEMIOLOGICAL RESEARCH

### EFFECT OF HSV2 ON HIV ACQUISITION

Evidence for the effect of HSV2 on acquisition of HIV comes from epidemiological studies, and results of a meta-analysis of the relationships between the two infections were presented [Wald and Link, unpublished]. Nine prospective studies (four cohort



studies and five nested case-control studies) were identified. Studies in men showed a consistent two-fold increase in the risk of HIV acquisition. In contrast, the study in women did not show a significant increase in the risk of HIV infection (RR=0.5; 95% CI=0.2-1.1 for female sex workers in Thailand) [Kilmarx *et al.*, 1998]. A recent publication of incident HIV infection in women also found no significant association (OR=1.31; 95% CI=0.6-2.8 in Mwanza, Tanzania) [Hayes *et al.*, 2001].

A further 16 cross-sectional and case-control studies were identified, and these tended to show stronger associations (heterosexual men: OR=5.1, 95% CI 3.2-8.4; heterosexual women: OR=4.5, 95% CI 3.1-6.5). This stronger association is likely to be due to the synergy between the two infections, with HIV infection also increasing transmission of HSV2. In addition, it may be more difficult to control for confounding in cross-sectional studies.

The meta-analysis estimated the proportion of HIV infection attributable to HSV2 among HSV2-infected individuals at around 50%. This means that, if the prevalence of HSV2 in a population is 50%, the population attributable fraction (PAF) would be around 35%, increasing to around 50% in very high prevalence populations. PAF estimates are likely to be higher in young people with first episode or recent HSV2 infection.

Further data are needed from prospective studies to quantify the contribution of HSV2 to incident HIV infections, and to confirm whether PAFs are different in males and females. Such data are needed to explore the role of HSV2 in explaining the high incidence of HIV in specific populations, particularly among young women in some areas, and to determine appropriate target groups for interventions.

The PAF is a good measure of the effect of HSV2 on HIV susceptibility at individual level, but does not fully capture the population level effect of one virus on the transmission of the other. In addition, the relative contribution of recognized and unrecognized HSV2 disease to HIV spread is unknown.

### **EFFECT OF HIV ON HSV2 ACQUISITION**

Fewer studies have examined the risk of HSV2 by HIV status. In a cohort of drug-using sex workers in Amsterdam, HIV-positive women were at significantly increased risk of primary genital herpes (adjusted RR=7.64; 95% CI=2.84-20.50) [Fennema *et al.*, 1995]. Two other prospective studies were identified, both of which found a significantly



increased risk of HSV2 incidence among HIV-positive individuals, although adjustment for confounders may have been incomplete [Kamali *et al.*, 1999; McFarland *et al.*, 1999]

## RECOMMENDATIONS

- More data are needed on risk ratios and PAFs by age and sex, and for prevalent and incident HSV2 infections. Further data from prospective studies would be particularly valuable.
- Current and past data from studies of HIV-discordant couples should be analysed, stratifying by HSV2 status, to estimate risk of HIV transmission in HSV2-positive and negative couples. Further studies of HIV-discordant couples, where one or both partners are HSV2-infected, will allow effects of HSV2 on both HIV transmission and acquisition to be estimated. They will also allow investigation of sex differences in transmission and acquisition rates. These studies should be performed in populations with high rates of HIV infection.
- Estimation of PAFs of HSV2 for HIV transmission and acquisition according to age, sex and symptom status will help to identify target groups for intervention studies.

## 5.3. GENITAL ULCER DISEASE IN AFRICA: EPIDEMIOLOGICAL TRENDS

Chancroid, syphilis and genital herpes are all common causes of genital ulcer disease (GUD) in developing countries. However, there is some evidence that there have been changes in the aetiology of GUD in recent years [O'Farrell, 1999], and this may influence the appropriateness of current syndromic management.

Table 2 shows data from a gold mine STI clinic in South Africa from 1986 to 1998 [Htun *et al.*, 2001]. The proportions of GUD due to chancroid and syphilis decreased during the study period. Of the 239 GUD diagnosed in 1986, 53% were chancroid and 12% syphilis. By 1998, 33% and 3% of 200 GUD cases were chancroid and syphilis respectively. In parallel, a rapid increase in the proportion of herpetic ulcers, in both HIV-positive and negative subjects, was noted in the same setting (3/239 (1%) in 1986 and 47/200 (24%) in 1998). As a result, the frequency of treatment failure when using syndromic management is increasing.

**Table 2. Aetiology of GUD in a gold mine STI clinic, South Africa 1986–98**

	1986	1990	1994	1998
	[n = 239]	[n = 213]	[n = 250]	[n = 200]
<b>Single aetiology</b>				
<b>Chancroid</b>	127 (53.1) <sup>1</sup>	107 (50.2)	94 (37.6)	65 (32.5)
<b>LGV</b>	8 (3.3)	2 (0.9)	8 (3.2)	9 (4.5)
<b>Genital herpes</b>	3 (1.3)	3 (1.4)	25 (10.0)	47 (23.5)
<b>RPR positive</b>	29 (12.1)	17 (8.0)	22 (8.8)	6 (3.0)
<b>Total</b>	<b>167 (69.8)</b>	<b>129 (60.6)</b>	<b>149 (59.6)</b>	<b>127 (63.5)</b>
<b>Mixed infection</b>				
<b>Chancroid + RPR</b>	28 (11.7)	18 (8.5)	13 (5.2)	10 (5.0)
<b>Chancroid + LGV</b>	6 (2.5)	3 (1.4)	3 (1.2)	1 (0.5)
<b>Chancroid + LGV + RPR</b>	0	1 (0.5)	1 (0.4)	0
<b>LGV + RPR</b>	2 (0.8)	0	2 (0.8)	2 (1.0)
<b>G. herpes + LGV + RPR</b>	0	1 (0.5)	0	0
<b>G. herpes + LGV</b>	0	0	1 (0.4)	0
<b>G. herpes + RPR</b>	2 (0.8)	0	4 (1.6)	4 (2.0)
<b>G. herpes + Chancroid + RPR</b>	1 (0.4)	0	2 (0.8)	0
<b>G. herpes + Chancroid</b>	2 (0.8)	4 (1.9)	4 (1.6)	19 (9.5)
<b>Total</b>	<b>41 (17.2)</b>	<b>27 (12.7)</b>	<b>30 (12.0)</b>	<b>36 (18.0)</b>
<b>Indeterminate</b>	<b>31 (13.0)</b>	<b>57 (26.7)</b>	<b>71 (28.4)</b>	<b>37 (18.5)</b>

<sup>1</sup> Percentage distribution shown in parentheses.

## RECOMMENDATIONS

There was a consensus regarding the high priority that should be given to studies of GUD aetiology because of the implications for current syndromic management and its credibility among health staff and patients. Such studies are particularly important in areas where the percentage of ulcers of “unknown aetiology” is high.

- There is a need for routine monitoring of GUD aetiology in different settings.
- Future studies of GUD aetiology should
  - use PCR techniques for diagnosis
  - stratify data according to gender and HIV status
  - be carried out for different risk groups (STI clinic patients, sex workers, family planning attenders).



## 6. HSV2 CONTROL MEASURES FOR DEVELOPING COUNTRIES

### 6.1. CASE MANAGEMENT OF HSV2 IN AREAS OF AFRICA WITH HIGH HIV PREVALENCE

Clinical diagnosis of GUD is unreliable, reflecting similarities between the clinical presentation of different GUDs, the presence of mixed infections and atypical ulceration due to longstanding disease (associated with delay in seeking health care). As mentioned in Section 5, HIV may alter the clinical presentation of HSV2. In areas of high HIV prevalence, herpetic ulcers are often necrotic and complicated with secondary bacterial infections. This atypical presentation, added to the high prevalence of co-infections, makes clinical diagnosis even more difficult.

The syndromic treatment approach was developed to manage STIs adequately and effectively at all levels of the health system, and without the need for laboratory tests and highly-qualified clinicians. The increase in absolute and relative numbers of herpes cases among GUD patients is likely to increase the frequency of treatment failure when using current STI syndromic algorithms.

#### RECOMMENDATIONS

##### ■ WHO to lobby for affordable aciclovir for developing countries

The main constraint to the widespread use of aciclovir in developing countries is likely to be the cost of antiviral drugs. Aciclovir should be made more readily available through an efficient procurement, distribution and prescribing policy.

##### ■ Identification of sites to monitor emergence of resistance to aciclovir in Africa

The possibility of resistance to aciclovir, as a result of its widespread use in developing countries and especially in areas with high prevalence of HIV, should be monitored. WHO should establish two or three reference laboratories in Africa to monitor the sensitivity of the drug regularly.



### ■ Aciclovir to be included for treatment of severe herpetic ulcers

There is an urgent need for treatment of severe cases of genital herpes, especially in HIV-infected individuals. This means that a clear definition of “severe ulcer” should be developed for use by health staff.

### ■ Revision and evaluation of syndromic case management for GUD in communities with high prevalence of HSV2

Consideration should be given to whether algorithms of syndromic management of genital ulcers should include aciclovir.

### ■ Operational research into addition of aciclovir into syndromic management of GUD

Use of aciclovir as a part of the syndromic management of GUD should be done in parallel with cost-effectiveness analysis and evaluation of clinical algorithms. Compliance with the therapeutic regimens should also be studied.

### ■ Intensification of health education campaigns, which could lead to prevention, early diagnosis and treatment.

## 6.2 THE ROLE OF EPISODIC AND SUPPRESSIVE THERAPY IN HSV2 AND HIV CONTROL

Two main treatment strategies are possible for herpes: *episodic* and *suppressive* treatment.

#### ■ Episodic therapy:

- Treatment of primary genital herpes
- Treatment of recurrent genital herpes

#### ■ Suppressive therapy:

- To prevent recurrences.

Aciclovir is an antiviral drug, which has been the standard treatment for genital herpes for the past decade in developed countries. Two new therapeutic agents (valaciclovir and famciclovir) have recently become available, and are also effective and safe treatments [Wald, 1999]. However, they are also more expensive than aciclovir.



The effects of therapy on the clinical course of a primary attack or a recurrent episode, and on HSV2 transmission are:

- **Episodic therapy** (e.g., 400mg aciclovir 3 times per day for 5 days or 500mg valaciclovir twice daily for 5 days) [Spruance *et al.*, 1996; Tyring *et al.*, 1998]
  - decrease in pain duration (2 against 3 days)
  - faster healing (~4 days against 5-6 days)
  - shorter duration of HSV shedding (stopping twice as fast)
  - no change in recurrence rate
  - reduced duration of recurrence (5 days against 6 days for valaciclovir, up to 50% shorter in recent trials)
  - 25% to 50% of herpetic episodes will not progress beyond the initial lesion
  
- **Suppressive therapy** (e.g. aciclovir 400mg 2 times daily or valaciclovir 500mg once a day) [Baker *et al.*, 1999; Goldberg *et al.*, 1993; Patel *et al.*, 1997]
  - prevention or delay of 80-85% of recurrences (1.7 to 0.8 per annum)
  - although 25% of HSV2-infected individuals still have a breakthrough recurrence each quarter over 20% of individuals had no recurrences during five years on therapy
  - subclinical HSV2 shedding reduced by 94% (5.9 to 0.4% of days positive by culture) in women with genital herpes of less than two years' duration [Wald *et al.*, 1996]
  - a study is in progress to assess the impact of suppressive therapy on HSV2 transmission rates among sero-discordant partners
  - psychological benefits.

### **EFFECTS OF HSV2 THERAPY ON HIV SHEDDING AND TRANSMISSION**

As mentioned above, HSV2 antiviral therapy during episodes has been shown to decrease HIV shedding from herpetic lesions in individuals co-infected with HSV2 and HIV. However, there are no epidemiological studies demonstrating a reduction in the rate of HIV transmission.

### **PROPHYLACTIC THERAPY TO PREVENT HERPETIC DISEASE**

Although there are no data currently available, there is a biological rationale for prophylactic therapy in HSV2-negatives based on results of AZT prophylactic therapy and animal models. This would aim at preventing herpetic disease rather than infection. Since the first episode of disease would be aborted, fewer viruses should in theory be present in the neurones for reactivation, and this should limit the frequency of recurrences.



However, RCTs of intravenous aciclovir provided during first episodes of genital herpes have shown no effect on the rate of subsequent recurrences [Corey *et al.*, 1985; Peacock *et al.*, 1988]. A further consideration is that the practicalities of prophylactic therapy make it unlikely to be feasible on a large scale in developing countries. However, their use could be considered in specific groups at high risk of HIV infection, such as HIV-negative members of discordant couples, sex workers and, possibly, young women.

### **INTERVENTION STUDIES OF ANTI-HERPETIC THERAPY**

It was emphasised that the impact of treatment on HSV2 does not need to be evaluated *per se*. The focus should be on the effect of therapy on HIV transmission. Although there is some evidence that herpetic treatment decreases HIV shedding, further studies in developing countries are needed to measure the impact of treatment on both HIV transmission and acquisition. In addition, evaluation of the effect of therapy on HIV is required before recommending the widespread use of therapy for mild herpetic ulcers.

Intervention studies of herpes treatment are, therefore, proposed in order to determine the potential of anti-herpetic therapy to reduce HIV shedding, and ultimately transmission. The objectives of intervention studies of HSV2 antiviral therapy would be:

#### **■ Episodic treatment**

- to determine the impact on HSV2 shedding (in developing countries)
- to determine the impact on HIV shedding
- to revise syndromic management guidelines.

In trials of episodic therapy, randomization could be carried out at either the individual or community level. Community randomization would allow measurement of effects on HIV transmission and acquisition. However, the substantial geographical variations in the epidemiology of HIV and STIs, and in access to health care services, may limit the generalizability of such trials.

#### **■ Suppressive therapy**

- to determine the impact on HIV shedding
- to study the natural history of HSV2 in treated and untreated patients.



## ACICLOVIR RESISTANCE

There has been some concern related to the widespread use of aciclovir, which could contribute to selection of resistance in individuals with HSV2 infection. In a study of long-term suppressive aciclovir therapy, HSV2 isolates from patients who had received up to six years of therapy showed no evidence of resistance to aciclovir [Baker, 1994]. In another study, in which suppressive aciclovir was stopped after six years, 3.5% of HSV2 isolates recovered from these subjects were resistant. These values are comparable to those of pre-therapy isolates and to reported values of isolates from aciclovir-naïve individuals [Fife *et al.*, 1994]. Unlike HIV, most HSV2 resistance to aciclovir is caused by mutations in the viral thymidine kinase or DNA polymerase genes and these strains tend to have reduced virulence and transmission. However, resistant HSV occurs much more frequently among HIV-infected patients, probably due to increased replication of HSV and decreased immunity in these patients [Severson and Tyring, 1999].

## RECOMMENDATIONS

The following studies are needed:

- Trials of episodic therapy, measuring the effect on HIV shedding
- Trials of episodic therapy, measuring the effect on HIV acquisition or transmission
- Trials of suppressive therapy in high-risk groups, measuring the effect on HIV acquisition among individuals at high risk of infection (e.g., HIV-negative partners in serodiscordant couples, HIV-negative sex workers)

In all cases the RCT is the preferred study design, and the development of drug resistance should be monitored.

## 6.3. VACCINE TRIALS

Given the high prevalence of HSV2 infection in many countries, and the fact that most infections are subclinical, the development of an effective HSV2 vaccine would provide a powerful control tool.

HSV2 vaccines can be divided into two main categories according to whether they target infected or uninfected individuals.

*Prophylactic vaccines:* aim at protecting against HSV infection or disease in the uninfected individual. Prophylactic vaccines have been shown to work in animal experiments.



*Therapeutic vaccines:* aim at reducing the frequency and/or severity of recurrences in the infected individual. The availability of an effective therapeutic vaccine would be useful in addition to prophylactic vaccines because of the high prevalence of HSV2 in many countries. Their main disadvantage is the likely need for frequent revaccination (6–12 monthly).

A vaccine should induce Th<sub>1</sub>-type cell mediated immune (CMI) responses as well as neutralizing antibody. In addition, mucosal CMI responses are desirable. Three HSV2 vaccines have recently been evaluated in clinical trials:

■ **Recombinant Glycoprotein Vaccine gB<sub>2</sub> and gD<sub>2</sub> with MF59 (Chiron)**

This subunit HSV vaccine is no longer in commercial development. Phase I studies showed that it was well tolerated and induced specific neutralizing antibody and T-cell lymphoproliferation responses comparable to or higher than those seen in HSV2-infected subjects. Two phase III trials have assessed effectiveness of the vaccine in prevention of HSV2 infection. Survival analysis showed a short-term efficacy of 50% for the first five months of follow-up but, thereafter, the effect disappeared. The overall efficacy was 9% (95% CI -29% to 36%), although substantial differences were observed in men and women (-4% in men and 26% in women). Vaccination had no significant influence on duration of the first clinical episode of genital HSV2, or on the subsequent frequency of recurrence. The authors concluded that efficient and sustained protection against sexual acquisition of HSV2 infection will require more than high titres of specific neutralizing antibodies and, as the vaccine provided only transient protection against HSV2 infection, work has been halted.

■ **Recombinant Glycoprotein Vaccine gD<sub>2</sub> with SBAS4 (GlaxoSmithKline)**

This subunit HSV vaccine is in commercial development and, again, induced HSV-specific antibody and cell mediated immune responses in phase I studies. Two phase III trials assessed vaccine efficacy in prevention of genital HSV disease with secondary assessment of prevention of HSV2 infection. The vaccine induced significant protection (approximately 70% efficacy) against genital herpes disease in women who were initially HSV1 and HSV2-seronegative. Trends towards protection in women against HSV infection were also seen in both studies (39-48% efficacy), although not statistically significant. In contrast, there was no evidence of protection in women who were initially HSV1-seropositive, or in men. The main disadvantages of this vaccine are



the apparent failure to improve on protection provided by HSV1 infection and the need for frequent vaccine administration to boost host immunity.

### ■ Disabled Infectious Single Cycle (DISC) HSV2 Vaccine

(Cantab (now Xenova)/GlaxoSmithKline)

Phase I studies have shown that this vaccine is well tolerated and induces neutralising antibody and lymphoproliferative responses comparable to those seen in HSV2 infected subjects. Eighty-three percent of vaccine recipients developed HSV-specific cytotoxic T-lymphocyte responses. Phase II efficacy trials are underway in US and UK to assess efficacy of DISC as a therapeutic vaccine, in the treatment of frequently-recurrent genital HSV2 infections. Because of its rich content of HSV2 virion, this product may improve on the natural protection provided by HSV1. However, its closeness to HSV2 means that it would not be possible to distinguish natural infection from vaccine-induced immunity. The most likely main disadvantage of the DISC therapeutic vaccine is that it may need to be administered frequently.

Differing vaccine efficacy in men and women may be explained by gender-specific immunological differences and/or gender differences in the pathogenesis of infection (at the dermo-epidermic surface). A vaccine which protects only women would be expected to: i) reduce HSV infection and disease in vaccinated women; ii) decrease the rate of neonatal HSV infection; iii) have an impact on the epidemic spread of genital herpes in men and women; and iv) possibly reduce acquisition and transmission of HIV infection.

Failure to protect HSV1 seropositive women may result if vaccination does not add to the natural protection provided by HSV1. In this case administration of vaccine to young children, before HSV1 infection occurs, would not be particularly helpful. Lack of efficacy of vaccines in HSV1-infected individuals would render the vaccine useless in developing countries, where HSV1 infection is almost universal.

An additional question is whether prevention of symptomatic HSV disease without prevention of asymptomatic HSV infection significantly reduces the risk of acquiring or transmitting HIV infection.

Finally, although subunit vaccines should be safe in HIV-infected individuals, it is unclear whether vaccine efficacy is reduced in such individuals.



## RECOMMENDATIONS

### ■ Lobby for investment in prophylactic vaccine development

There was a commitment to lobby for increased investment in the development and evaluation of prophylactic vaccines. This should include evaluation of the DISC vaccine for use as a prophylactic vaccine. A major priority is to ensure that any vaccine produced is available and affordable in the developing countries.

### ■ Work towards creating partnerships to enable DISC vaccine to be taken to next stage of development

Partnerships should be sought to enable the DISC vaccine to be taken to the next stage of development. Phase I studies in HIV-1 infected individuals are needed to check safety. It may be appropriate to move on to a combined phase II/III trial, using the first enrolled individuals for further studies of safety and immunogenicity and to measure antibodies in genital secretions.

### ■ Develop locally administered vaccines

It may be useful to develop a vaccine that could be administered locally to induce a local mucosal response. For example, intrarectal suppositories could be used and would cover the genital mucosa because they drain to the same lymph nodes. No phase I studies have been done on this. Trials would be needed in HSV1-positive and negative individuals, and HIV-positive and negative individuals to investigate immunogenicity and safety.

Vaccine trials should initially be conducted in HSV2-seronegative women. They would be stratified by HSV1 serostatus, though in some settings there may be few HSV1-negative individuals. Where HSV2 seronegative men are also studied, analysis should be stratified by both HSV1 and circumcision status. Individual randomization of young people would minimize sample size, because of the higher seroconversion rates in this age group. The primary endpoints would be prevention of HSV2 disease, because of the impossibility of distinguishing between natural infection and vaccine-induced immunity, with a secondary endpoint of HIV infection.



#### **6.4. OTHER PREVENTIVE STRATEGIES**

In the absence of a vaccine or feasible therapeutic strategy in many developing countries, other preventive strategies are needed for HSV2 (and HIV) control. Discussions focused on female-controlled methods and behavioural interventions.

#### **REDUCING EXPOSURE TO THE VIRUS**

As with other sexually transmitted infections, behavioural interventions are needed. The format of these interventions will depend on current HSV2 epidemiology. In countries with high HSV2 prevalence in the general population, such interventions will need to target the general population. In other countries with lower prevalence of HSV2, they may be focused on 'high-risk' groups. Behavioural interventions will include prevention messages with the aim of delaying sexual debut and reducing rates of partner change.

It is reported that male condoms protect against HSV2 less effectively than against HIV, although a recent study of discordant couples found that consistent condom use significantly protected women, but not men, from acquiring HSV2 infection [Wald, 2001]. Given the efficacy of condoms in protecting against HIV infection, promotion of condom use should always be included in any STI prevention intervention.

The acceptability and feasibility of HSV2 screening as a prevention measure was also discussed. However, raising awareness in the community does not seem acceptable unless treatment is available for symptomatic patients.

#### **REDUCING TRANSMISSION OF THE VIRUS**

Prevention strategies for herpes transmission should also focus on individuals with genital herpes lesions. These will be a small proportion of those who are HSV2-seropositive, but are likely to be the ones at highest risk of transmitting the virus. Health education for such patients should promote abstinence during symptomatic periods, and consistent condom use even with regular partners. The inclusion of antiviral therapy in a GUD treatment algorithm would also decrease the infectious period.

The availability of female-controlled methods to reduce HSV2 transmission is of primary importance because of the social, cultural and economic obstacles women face in negotiating safe sex.



Current methods include:

- **Female condoms:** these are likely to provide good protection against HSV2, although currently there are no data available on this. However, in some locations the female condom is thought to be of limited value because of the need to agree its use prior to sex [Hart et al., 1999].
- **Other cervical barriers** (such as the diaphragm and cervical cap) are unlikely to be effective except for cervical herpetic lesions.
- **Vaginal microbicides**
  - Spermicides (N-9, menfegol, benzalkonium chloride) have been shown to be active against HSV2 *in vitro* [Jennings and Clegg, 1993] and in mice [Whaley et al., 1993], but there has been no evidence of a protective effect *in vivo* [Vontver et al., 1979]. Trials of N-9 have shown unacceptable toxicity, and a possible increase in HIV risk, and attention is now turning to products with a better safety profile.
  - Sulphated polysaccharides (Pro-2000, dextrin sulphate, carrageenan): these have *in vitro* activity and have been shown to be protective in vaginal mouse models.
  - pH modifying products (Buffergel): there are no data available on their efficacy against HSV2.
  - Specific anti-HIV products (NNRTI): these are most likely ineffective against HSV2.

## RECOMMENDATIONS

In high prevalence areas the recommendations were to:

- **re-emphasize primary prevention: behaviour modification and condom use**
- **evaluate counselling strategies for HSV2 seropositive individuals**

This might involve developing community-based education on symptom recognition, temporary abstinence and condom use during symptomatic episodes. This could include health education in schools.

- **evaluate management of patients with genital herpes lesions in STI clinics**

This would be a package based on: enhancement of symptom recognition, care seeking and counselling on sexual behaviour during episodes. Inclusion of aciclovir for GUD



management would ensure credibility of the syndromic approach, but episodic treatment should first be evaluated and treatment is only recommended for severe cases. Addition of partner notification did not seem useful in the absence of treatment and testing facilities. Although presence of the partner may help in counselling, it was not considered a priority in developing countries.

#### ■ Include HSV2 as an outcome in microbicide trials

The importance of including HSV2 as an outcome variable in phase III trials of vaginal microbicides for HIV prevention was emphasized. It was also recommended that previous HIV microbicide studies could be re-analysed to evaluate their effect on HSV2 infection where this was measured.

Widespread HSV2 screening was not recommended at this stage.



## 7. MATHEMATICAL MODELLING

Mathematical modelling is being used to model HSV2 spread and control and the interactions between HSV2 and HIV. The modelling allows improved understanding of the mechanisms of STI spread by analysing, interpreting and identifying gaps in empirical data and guiding future field studies. However, as the validity of the output depends on the validity of the input, modelling does not usually provide quantitative certainty.

Modelling HSV2 spread has highlighted that sexual behaviour patterns, such as age mixing, and biomedical factors, such as the duration of the period with recurrences, are more important determinants of HSV2 incidence and prevalence than the frequency and duration of individual recurrences.

Models of HSV2 control have assessed the impact of antiviral therapy on HSV2 morbidity and seroprevalence, the impact of behavioural risk reduction, and a comparison of short-term and long-term controls. The main findings are:

- High levels of antiviral treatment (i.e., widespread use for a long duration) are needed to decrease seroprevalence and this treatment should also cover asymptomatic cases.
- Behaviour change interventions, such as reduction in partner change rates, induce a very slow change in HSV2 seroprevalence, mainly because HSV2 is a lifelong infection.

### RECOMMENDATIONS

- Modelling work on the transmission and control of HSV2, and its interaction with HIV, needs to continue
- Future challenges include modelling:
  - the risk of development of drug resistance
  - cost-effectiveness of treatment strategies
  - vaccine coverage and efficacy, including the potential indirect effect of HSV2 vaccination on HIV incidence.



## 8. HSV2 DIAGNOSIS

Evaluation of HSV2 assays is based on sensitivity, specificity and reproducibility, and independent blinded comparison.

### SEROLOGY AND DIRECT TECHNIQUES TO DETECT HSV2 INFECTION

The gold standards for HSV2 serology include Western blot and immunoblot enzyme assays. These assays are based on detecting type-specific epitopes present within glycoproteins G and C (gG and gC). Western Blot is time consuming, expensive and technically difficult to replicate on a large scale, whereas ELISA tests are more widely available and have been developed into commercial assays [Cowan, 2000].

Several approaches allow measuring incidence: pre and post-sample comparison, detection of IgM response (which is possible during 6-12 weeks following infection and can be detected in recurrent HSV disease), detection of low avidity antibody (limited to 30 days after infection) and measurement of antibody titre. In addition, quantification of weak virus is possible by culture or quantitative PCR.

PCR is more sensitive for HSV detection than culture. A quantitative PCR assay to detect and type HSV DNA in clinical samples has been developed [Ryncarz *et al.*, 1999]. This assay has been shown to detect 10 to  $10^8$  copies of HSV DNA/20  $\mu$ l of sample and a variability of less than 5% among duplicate samples.

A further important issue is that different serological assays have been shown to produce conflicting results in sera from African countries. Further studies to try to explain reasons for these discrepancies and to determine the performance of alternative commercial assays on African sera are being planned.

Advantages and disadvantages of fluid specimens other than blood (e.g., saliva and urine) for diagnosis and surveillance are:



## ADVANTAGES

- more acceptable because they are not invasive
- more convenient: inexpensive, rapid, simple, sterile precautions not needed
- less hazardous.

## DISADVANTAGES

- lower IgG/IgM levels, which may reduce the sensitivity of the assay compared to the results obtained with blood samples. Samples should be taken at crevicular and gingival locations, where Igs are more concentrated. Urine contains even less Ig than saliva.
- less well characterized
- likely to present higher subject-to-subject variability
- limited markers available.

Saliva may be frozen for years whereas urine must be tested fresh within about six months.

## DIAGNOSIS OF CLINICAL EPISODES

Available commercial kits based on crude antigen are inaccurate in comparison with culture. Approximately 46% of cases of primary infection and 62% of recurrent HSV2 episodes are correctly diagnosed using the Sigma kit, whereas Incstar (now Diasorin) allows diagnosis of 75% and 69% of cases respectively [Ashley et al., 1991].

## RECOMMENDATIONS

Four main recommendations were discussed and agreed:

- Standardized evaluation of current serological tests using panels of African sera
- Standardization of sampling techniques for genital shedding studies
- Further work on quantification techniques for HSV-DNA
- Development of rapid diagnosis tests for herpetic ulcers.



## 9. RESEARCH AND CONTROL PROGRAMME PRIORITIES

Agreed priorities for control programmes and future research are summarized below.

### 9.1. EPIDEMIOLOGICAL STUDIES AND NATURAL HISTORY OF HSV2

#### ■ Analysis of sera from past and present studies to obtain HSV2 prevalence data

Limited data on HSV2 prevalence are available at present. It was recommended that stored sera from past and current studies be tested in order to increase data on HSV2 prevalence and incidence in different populations. Testing will also allow analysis of past prevalences and trends to gain insight into the relative timing of HSV2 and HIV epidemics.

#### ■ Use of sentinel surveillance sera to obtain HSV2 prevalence data in different populations, especially in Asia and South America

There are currently few data on HSV2 prevalence from many parts of the world, especially from Asia and South America. Routinely collected sentinel surveillance sera would allow estimation of HSV2 prevalence in some of these populations at minimal cost and inconvenience.

#### ■ Use of existing data from trials and cohort studies to document the natural history of HSV2 in developing countries and to identify factors affecting HSV2 transmission

The natural history of HSV2 infection is poorly documented in developing countries. Cohort studies and intervention trials could be used to study the natural history of HSV2 in developing countries.



### ■ Estimation of PAFs of HSV2 for HIV transmission and acquisition according to age, sex and symptom status

Estimates of the proportion of HIV infections attributable to HSV2 transmission are needed to help quantify the effect of HSV2 on the HIV epidemic in different populations. PAF estimates are needed by sex and age-group in order to explore possible differences in the effect of HSV2 on HIV acquisition between males and females and to determine target groups for interventions. The contribution of clinical and subclinical HSV2 infection to HIV spread also has implications for the choice of HSV2 control measures.

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## 9.2. BIOLOGICAL STUDIES: HSV2 AND ITS INTERACTION WITH HIV

### ■ Clinical studies to assess the effect of subclinical HSV2 infection on HIV shedding

There is strong evidence of the bi-directional interaction between HIV and HSV2 in co-infected subjects. However, there is insufficient evidence concerning the effect of asymptomatic HSV2 shedding on HIV transmission. Studies of HIV shedding in HSV2-infected subjects, and of the relative importance of unrecognized HSV2 infection and subclinical shedding for HIV transmission, are urgently needed. HIV shedding should be examined according to HSV2 shedding, HSV2 symptom status, stage of HIV infection and sex.

Shedding and transmission studies can be performed in parallel with interventions to prevent HIV and HSV2. To increase the efficiency of both types of study they should be performed in areas with high rates of both HIV and HSV2 infection

## 9.3. EPISODIC AND SUPPRESSIVE THERAPY

### ■ Monitoring GUD aetiology in STI clinic attenders by gender and HIV status

Changes in the aetiology of GUD in some countries has been associated with an increase in the frequency of treatment failure when using the syndromic approach to diagnose and treat STIs. High priority should be given to studies of GUD aetiology, especially in areas in which the proportion of ulcers of unknown aetiology is large and where HIV prevalence is high. These studies could be nested within studies of the impact of episodic treatment on HIV shedding and should be carried out in different groups of the population (STI patients, sex workers and family planning patients). They should also be examined according to HIV status and level of immunosuppression, since these factors



are associated with reactivation of chronic infections. Diagnosis of herpes should be performed using PCR techniques. These studies will help to re-evaluate and improve syndromic case management in specific populations.

#### ■ **Lobbying for affordable aciclovir for developing countries**

There is an urgent need for treatment of severe HSV2 ulcers, which are frequently associated with HIV infection. Treatment will require inclusion of aciclovir in current algorithms of syndromic management of GUD in countries with high HIV prevalence, as well as improvements in the differential diagnosis of herpetic and bacterial ulcers. Although aciclovir is already recognized as an essential drug, it is expensive in most developing countries. WHO should negotiate with drug companies to ensure that this drug becomes available and affordable in developing countries.

Further evaluation of the effect of therapy on HIV transmission is required before recommending the widespread use of aciclovir for minor herpetic lesions.

#### ■ **Identification of sites to monitor the emergence of resistance to aciclovir in Africa**

The widespread use of aciclovir may be associated with an increase in the level of resistance to aciclovir, particularly in countries where HIV prevalence is high. WHO should establish two or three sites in Africa to monitor the emergence of resistance to aciclovir .

#### ■ **Operational research on incorporation of aciclovir in syndromic management**

The potential incorporation of aciclovir in syndromic management should be assessed using cost-effectiveness analysis based on different scenarios (including differences in HIV prevalence). Research is also needed on compliance with therapeutic regimens.

#### ■ **Episodic therapy intervention trials - effect on HIV shedding**

Further data are needed on the effect of episodic herpes therapy on HIV shedding and transmission of HIV infection.



### ■ Episodic therapy intervention trials - effect on HIV acquisition and transmission

The effect of episodic herpes therapy on HIV transmission and acquisition could be assessed in RCTs. Studies targeting HIV discordant couples would allow examination of effects on HIV transmission, whereas those performed within high-risk groups, such as sex workers, would measure effects on HIV acquisition.

### ■ Suppressive therapy trials in high risk groups - effect on HIV transmission

While continuous suppressive therapy in the general population may not be a practical intervention, it may be feasible and appropriate in groups at high risk of HIV infection. RCTs should be carried out to measure the effect of suppressive therapy on HIV incidence in HIV-negative partners in discordant couples and in HIV-negative sex workers.

## 9.4. VACCINATION

It was agreed to form a working group to establish a dialogue with commercial companies involved in HSV2 vaccine development and production. The group should engage these companies in discussions regarding further development and testing of the two types of HSV2 vaccine, prophylactic and therapeutic. Specifically, the group would:

- Lobby for further investment in prophylactic vaccine development, including development and testing of the DISC vaccine for prophylactic use
- Lobby to ensure availability and affordability of vaccine products in developing countries
- Work towards creating partnerships to enable the DISC vaccine to be taken to the next stage of development (phase II/III trials)
- Consider studies of locally administered vaccine products.



## 9.5. BEHAVIOURAL AND MICROBICIDE STUDIES

### ■ Re-emphasis on primary prevention: behaviour modification and condom use

Continued emphasis must be placed on reducing exposure to HSV2 and HIV through behavioural modification and condom use. These messages are particularly important for young people, who are at very high risk of HSV2 infection in many developing countries.

### ■ Evaluate counselling strategies for HSV2 in seropositive individuals

Evaluation of HSV2 counselling strategies is urgently needed, focusing on newly-acquired HSV2 infections, particularly among young people. There is a need to define effective strategies using community-based education in developing countries.

### ■ Evaluate management of patients with genital herpes lesions in STI clinics

Enhancement of symptom recognition (by both patient and clinician), care seeking and counselling on sexual behaviour during a herpetic episode.

### ■ Include HSV2 as an outcome in planned HIV microbicides studies

HSV2 infection should be included as an outcome in any phase III trials of vaginal microbicides. Previous HIV microbicide studies should be re-analysed where possible to evaluate the effect on HSV2.

## 9.6. MATHEMATICAL MODELLING

Work should continue on mathematical modelling allowing prediction of the impact of alternative control approaches on the HIV and HSV2 epidemics in a given population.

- Continue modelling the transmission and control of HSV2, and its interaction with HIV
- Model the risk of development of drug resistance
- Model cost-effectiveness of alternative treatment strategies
- Model the effects of vaccination, including indirect effects on HIV incidence.



## 9.7. DIAGNOSIS

### ■ Rapid diagnostic tests for herpes ulcers

Evaluation of algorithms for syndromic management of GUD is needed, with possible use of aciclovir for severe ulcers. To avoid over-treatment, development of rapid diagnostic assays for GUD should be a high priority.

### ■ Evaluation of current serological tests on panels of African sera

Studies of the performance of current serological assays are needed to investigate discrepant results in sera from African sites. Coordination and exchange of information between different laboratories using these tests in developing countries should be strengthened.



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