The Interaction of HSV and HIV

Introduction

The prevalence of Herpes simplex virus type 2 (HSV-2) is increasing worldwide. HSV-2 is the most common cause of genital ulcers, and evidence indicates that it is a major cofactor for HIV infection. HSV-2 prevalence in developing countries, although very high, varies widely according to country, gender, and urban versus rural areas, ranging from 2–74%, and this could have a huge impact on the HIV epidemic.

There are two main treatment strategies for HSV-2: episodic and suppressive. The former involves treatment of primary and recurrent genital herpes. The latter is undertaken to prevent recurrences. Both strategies could be tested as potential HIV prevention strategies.

This newsletter reports on a workshop held in London in November 2003, providing an update on LSHTM-led research on various HSV-2 and HIV prevention strategies.

The Interaction Between HSV and HIV

Associations between HIV and HSV-2 have been found in epidemiological studies. Possible mechanisms for this are that HSV-2 increases the risk of HIV acquisition, HIV increases the risk of HSV-2 acquisition, HSV-2 increases HIV infectivity and/or HIV increases HSV-2 infectivity. There is strong evidence that HSV-2 infection enhances the risk of HIV acquisition: the evidence is stronger for men than for women. This effect is not necessarily related to herpetic lesions, but also to asymptomatic genital shedding.

Some issues are unresolved, such as gender differences in the effect of HSV-2 on HIV acquisition, differences in the effect between older HSV-2 infection and recent infection, and the effect of symptomatic vs. asymptomatic HSV-2 infection.

Evidence from observational studies that HSV-2 enhances HIV transmission is strong enough to warrant randomised controlled trials (RCTs) of HSV-2 specific interventions.

Anne Buvé, Institute of Tropical Medicine, Antwerp

Studies of Episodic Therapy

The effects of episodic HSV therapy on clinical course and HSV-2 transmission include decreased severity of lesions; faster healing process; reduced HSV shedding; no change in recurrence rate but reduction in duration of recurrence. Few data are available on the effects of episodic HSV therapy on HIV acquisition/transmission. There is evidence of decreased lesional shedding of HIV following treatment of HSV ulcers, but there are no results from RCTs yet.

The Role of Episodic Therapy in HSV-2 & HIV Control: the ANRS 12-12 Trial in Ghana & Central African Republic

The trial aims to determine whether antiviral therapy for genital herpes reduces HIV shedding in women both HSV-2+ and HIV+. The study, in Ghana and the Central African Republic (Bangui), will involve 600 women randomised to Aciclovir (ACV) or placebo, 400mg TID for 5 days. Enrolment started in March 2003 (Accra and Kumasi) and December 2003 (Bangui).

Study objectives

Study 1: Aetiological study of genital ulcer syndrome (GUS) – to determine the viral and bacterial aetiologies of GUS among women in the study sites, and the impact of syndromic management (SM) on cure rates.

Study 2: RCT of ACV vs. placebo in addition to SM – to...
determine the impact of ACV on HIV shedding among women HIV+/HSV+, the impact of ACV on HSV shedding among women HSV+/ (HIV+ & HSV+), and the impact of ACV on cure of HSV+ ulcers; and to evaluate the validity and feasibility of adding ACV to the GUS algorithm (compliance, side effects).

Helen Weiss & Philippe Mayaud, LSHTM

Collaborators: WAPCA & NACP, Ghana; CNR MST & PNLS, CAR; INSERM U430, HEGP & Institut Pasteur, Paris; LSHTM & PHLS, UK; University of Sherbrooke, Canada. Funding: ANRS (France), GSK (UK).

Effect of Symptomatic & Asymptomatic Genital Herpes on HIV Shedding in HIV/HSV Co-infected Women, Tanzania

This study is part of a Wellcome Trust funded research project on ulcerative STI being carried out among cohort participants of a study of female barworkers in Mbuya Region. This latter study is a collaboration of LSHTM with the University of Munich in EU-funded research on HIV superinfections with different HIV sub-types. An open cohort of 600 female barworkers was established in late 2000, with 3-monthly follow up. Serial cross-sectional data have been collected on: 1) socio-demographic and behavioural characteristics, medical history; 2) clinical STI and HIV related signs; 3) STI and HIV infection.

Objectives and design

Objectives are 1) to determine whether cervico-vaginal shedding of HIV in HSV/HSV-2 co-infected women occurs more frequently in the presence of herpetic lesions; and 2) whether HIV shedding occurs more frequently in women with or without HSV-2 infection in the absence of herpetic lesions.

The study is analytical cross sectional in design. For objective 1, exposure is determined by presence of a herpetic lesion; for objective 2, by HSV-2 infection. The study population are HIV+ female barworkers participating in an open cohort from October 2000 to March 2003.

Gabrielle Riedner, LSHTM

Acknowledgements: Colleagues at LSHTM and collaborators in Mbuya & Dar es Salaam, Tanzania, Munich, Germany, Manitoba, Canada and France.

Funding: Wellcome Trust, EU.

HSV-2 & HIV Genital Shedding, Bangkok, Thailand

This HSV-2 study is nested within an RCT of micronutrient supplementation. Objectives are to determine: the association between HSV-2 infection and HIV genital shedding; the rate of decline of HIV genital shedding up to 6 days following presentation with an HSV-2 genital ulcer; and variability of viral load measurements.

Findings

No association was found between HSV-2 serology and quantity of HIV-1 genital shedding, and between HSV-2 genital shedding and quantity of HIV-1 shedding. The quantity of HIV-1 viraemia in semen and cervico-vaginal secretions was above detectable levels in everyone. However, numbers were small (men: n = 69, 26% with HSV-2 shedding, 13% with ulcers; women: n = 71, 8% with HSV-2 shedding, 15% with ulcers).

Repeated sampling from patients with ulcers

Ten men and 9 women were seen between 2 and 4 times following presentation with an ulcer. Follow-up was on average 6 days (range 4, 8) for men and 7.2 (range 5, 11) for women. There was no significant difference in mean percentage change in viraemia in either men or women.

Conclusion

No evidence was found that the quantity of HIV genital shedding declines immediately following presentation with an ulcer. There was high variability, particularly in HIV viral load measured from cervico-vaginal secretions.

Shabbar Jaffer, LSHTM


Impact of Episodic Aciclovir Therapy on Ulcer Duration & HIV Shedding Among Men in South Africa

The objectives of this proposed trial are to determine the efficacy of aciclovir (ACV) episodic therapy on reducing the duration and severity of an HSV-2 clinical breakout; to measure the effect of ACV on HIV and HSV-2 shedding from genital ulcers; to describe treatment-seeking behaviours among men; and to model the impact and estimate the cost-effectiveness of providing episodic herpes treatment as part of syndromic management (SM).

Methods

The study will take place in Johannesburg and a mining community in Carletonville, South Africa. Two government clinics located in Johannesburg and one clinic providing health care to miners in Carletonville will recruit men presenting with genital ulcer disease (GUD).

Study procedures

Consenting males presenting to the clinic with GUD will be treated with SM for GUD (penicillin and ceftriaxone) and randomized to ACV 400 mg or placebo TID for 5 days. At enrolment participants will be tested for HSV, HIV and syphilis serology, CD4 and STIs. Ulcer samples will be collected for HIV and HSV shedding, and blood and semen samples for HIV viral load. A questionnaire will be administered on sexual behaviour and demographics.

Outcomes will include: the effect of ACV on ulcer duration among those HIV+ and HIV--; the effect of ACV on ulcer HIV shedding, ulcer HSV, plasma HIV and semen HIV. The study will start in 2004.

Gabriela Paz-Bailey, LSHTM

Collaborators: Division of STD Prevention, US Centers for Disease Control & Prevention; National Institute of Communicable Diseases, South Africa; LSHTM.

RCT of Aciclovir Episodic Therapy in Addition to Syndromic Management of Genital Ulcer Disease in Malawi

Primary objectives are to determine the effect of routinely adding ACV to standard syndromic management in improving the cure rates of GUD, and to determine if HIV serostatus affects cure rates. Secondary objectives are: 1) to measure the effect of GUD management (with or without ACV) on frequency and quantity of HIV-RNA viral load in blood, ulcer lesions and genital secretions; 2) to determine GUD aetiologies; and 3) to evaluate the incremental cost benefit as GUD algorithms are revised.

Study design

The study is a randomised, double blind, placebo controlled trial of daily anti-herpetic episodic therapy with ACV (800 mg BID) for 5 days in addition to SM. Study site is an STD clinic at Lilongwe Central Hospital with male and female patients, HIV+ and HIV-. The study is targeting 500 patients, 250 patients in each arm, with a male and female randomisation. Patients will be followed up for 4 weeks.

Expected outcomes

The primary endpoint expected is an increase in the proportion of completely healed ulcers at D14, stratified by HIV serostatus. Secondary endpoints are baseline and D28 HIV-RNA levels in blood, ulcer lesions and genital secretions including semen in men.

Sam Phiri, LSHTM / Lighthouse Clinic, Lilongwe, Malawi & Philippe Mayaud, LSHTM

Collaborators: Lilongwe Central Hospital; MOH Malawi; UNC Project, Lilongwe; University of North Carolina; LSHTM. Funding: Fogarty International Centre (2004-06) and RDFD-Malawi.
**Studies of Suppressive Therapy**

**RCT of Suppressive Therapy with Aciclovir & Impact on HIV Shedding Among Dually Infected Women in South Africa**

**Objectives** are: 1) to measure the effect of daily ACV (400 mg BID) on the frequency and quantity of HIV RNA shedding in women who are HIV+/HSV-2+ with CD4+ >250; 2) to measure the effect on the frequency and quantity of clinical and sub-clinical HSV-2 shedding; 3) to evaluate HSV-2 (gG2 Elisa serological tests compared to gold standard tests; and 4) to determine factors associated with adherence to suppressive therapy.

**Study design**

Part I of the study is **formative research**: validate serological tests; explore and pilot adherence strategies; pilot specimen collection techniques and generate preliminary shedding data. Part II is a **clinical trial**: a randomised, double blind, placebo controlled trial of twice daily anti-herpetic suppressive therapy with ACV 400 mg for 3 months. The study population consists of family planning clients and female STD clients.

**Outcomes**

Expected outcomes are: 50% reduction in proportion of those shedding in the ACV group; 0.4 log reduction in the mean concentration of HIV RNA in genital tract among HIV shedders; 80% reduction in frequency of HSV shedding in the ACV group; and 0.5 log reduction in mean concentration of HSV DNA.

Additional outcomes should be: the relationship between CD4+ count, HIV plasma viral load and shedding of HIV and/or HSV-2; measure of adherence and suppression of HSV shedding; data to inform modelling and cost-effectiveness studies.

**Start date:** 2004.

**Sinead Delany-Moretwe**, LSHTM / RHRU, South Africa & **Philippe Mayaud**, LSHTM

**Collaborators:** RHRU, Johannesburg; Central Laboratory Services, JHG/ Witwatersrand University; HEGP, Paris; LSHTM. **Funding:** Wellcome Trust.

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**RCT of Suppressive Therapy with Valaciclovir & Impact on HIV Shedding in High-Risk Women in Burkina Faso**

**Objectives** are to measure the effect, in women both HIV+HSV2+ who are or are not taking ART, of once daily valaciclovir 1000 mg on the quantity and frequency of 1) HIV RNA shedding, and 2) clinical and sub-clinical HSV2 shedding; and also to determine factors associated with adherence to suppressive therapy.

**Study design**

Part I is **formative research**: Parts II and III are **clinical trial 1 (among women not requiring ARV)** and **clinical trial 2 (among women requiring ARV)**: randomised, double blind, placebo controlled trials of once daily anti-herpetic suppressive therapy with valaciclovir 1000 mg OD.

For **RCT2**, we will need 60 HIV shedders. For this, we need to recruit ~650 women for screening; 60 women eligible for ART will be entered into **RCT1**. Assuming 50% HIV shedding, the study will have 90% power to detect a decrease in quantity HIV of 0.4 log copies/ml and 75% power to detect a decrease in frequency from 50% to 15%.

**Outcomes**

Expected outcomes are a 0.4 log reduction in mean concentration of HIV RNA in genital tract; a 50% reduction in frequency of HIV shedding in the valaciclovir group; and an 80% reduction in frequency of HSV shedding in the valaciclovir group.

**Start date:** mid-2004

**Nicolas Nagot**, LSHTM / Centre Muraz, Burkina Faso & **Philippe Mayaud**, Helen Weiss, LSHTM

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**An HSV Suppressive Therapy Trial in High-Risk Women in Tanzania**

**Objectives** are to determine whether HSV-2 suppressive therapy with ACV can: 1) reduce HIV incidence, and 2) reduce HSV-2 and HIV viral shedding in high-risk women. A randomised, double-blind, placebo-controlled trial of oral ACV (400mg BID) versus placebo is underway, involving 1000 high-risk women (bar/guesthouse workers) in high transmission areas (HTAs) within the Lake Zone, NW Tanzania. For objective 2, participants are dual HIV/HSV infected women, nested within the main study cohort.

**Methods**

Screening of 1465 facility workers for HSV-2 and HIV took place in Nov-Dec 2003. In Jan-Mar 2004, 703 eligible HSV+ women were randomised to receive either ACV 400mg BID or placebo. Participants will be followed every 3 months for 24 months, with interim analysis at 12 months. All participants will receive HIV prevention education, condoms, STI syndromic management and family planning and VCT, with referral to appropriate services if necessary. A blood sample for HIV and syphilis serology is collected every 3 months; swabs for STI diagnosis and a cervico-vaginal lavage are collected every 6 months.

**Challenges**

The main initial challenges involved finding a pharmaceutical company prepared to make the placebo tablets, learning the Tanzania Pharmacy Board approval and clearance procedures, and developing tools to help clearly explain the aims of the trial and concepts of placebo, randomisation and blinding to potential study participants. Other challenges concern minimising losses to follow up and ensuring good adherence to therapy. Tools have been developed by the team to assist with these issues.

**Outcomes**

Study outcomes will be: HIV incidence by treatment arm; HSV episodes and shedding by treatment arm; lesion-healing time; acceptability and compliance; cost-effectiveness; HIV shedding by treatment arm.

**Debby Watson-Jones**, LSHTM / AMREF

**Collaborators:** AMREF Tanzania; NIMR, Tanzania; Kahama Mining Corporation Ltd; Geita Gold Mine Ltd; UCL Hospital, London; Institute of Tropical Medicine, Antwerp; INSERM U340 Paris; University of Laval, Quebec; LSHTM. **Funding:** Wellcome Trust, London.

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**The Effect of Herpes Suppressive Therapy on Genital Shedding of HIV-1 & HSV-2 in High-Risk Tanzanian Women**

This research is planned as a nested study within the above RCT of suppressive therapy in Tanzania. **Objectives** are to measure the effect of HSV suppressive therapy on the prevalence and quantity of HIV-1 shedding and HSV-2 shedding, in dually HIV-1/HSV-2 positive women; and to determine the association between clinical and sub-clinical HSV-2 shedding and the prevalence and quantity of HIV-1 shedding.

**Methods**

Individuals will be randomised to 3-monthly STI syndromic management and either placebo or ACV (400mg BID). Data for this nested study will be collected within the first 12 months of the main trial. Participants will be seen every 3 months, receiving STI syndromic management; a supply of study drugs; and free contraceptives and VCT. Every 6 months, samples will be collected for plasma HIV-1 RNA load measurement, genital swabs will be taken for STI testing and a cervico-vaginal lavage will be taken to measure HIV-1 (RNA and proviral DNA) shedding and HSV-2 DNA shedding.
Outcomes
Main outcomes will be the prevalence and the quantity of genital HIV-1 RNA shedding. Other outcomes include the prevalence and the quantity of genital HSV-2 DNA shedding, and proviral HIV-1 DNA shedding.

Claire Tanton, LSHTM / NIMR

Collaborators: LSHTM; AMREF, Tanzania; NIMR, Tanzania; INSERM U430, Paris.

Other HSV-2 Studies

Herpes Vaccines to Prevent HIV Transmission
Current HIV control strategies are not working and HIV vaccines are not imminent. Even with an HIV vaccine, additional approaches will be needed. 20–50% of HIV infections are attributable to HSV-2, but HSV-2 suppressive therapy is probably not suitable for a population approach.

Several HSV-2 vaccines have been developed. Chiron (recombinant glycoprotein) was found to have no effect (JAMA 1999; 281: 331-40). In two phase III double-blind RCTs, GSK (recombinant glycoprotein) was found to provide no protection in men or in HSV-1 positive subjects, but did give some protection in HSV-1 negative women (NEJM 2002; 347: 1652–61). A new study is now underway on HSV-1 negative women. On Xenova (DISC), phase III trials found no effect as a therapeutic vaccine, but it has potential as a prophylactic vaccine.

Collaborative proposal
The goal is to reduce HIV incidence by developing, testing, and making available an HSV-2 vaccine as an HIV control intervention in developing countries.

Components include: 1) Modelling impact and vaccination strategies; 2) Preparing field sites in Africa; 3) Further developing DISC vaccine; 4) Phase I and phase IIa studies in UK; 5) Repeat phase I in Africa; 6) Studying correlates of protective immunity; 7) Conducting phase Ib trial of DISC vaccine vs HSV-2; 8) (Depending on efficacy) Conducting trials with an HIV endpoint.

Judith Glynn, LSHTM

Collaborators: Institute of Tropical Medicine, Antwerp; LSHTM; Industry: Xenova (DISC vaccine). Funding: not obtained.

The Four Cities Modelling Project
The four-cities project was a large multi-centre study conducted in 1997 in Kisumu (Kenya) and Ndola (Zambia) – both high HIV prevalence – and Cotonou (Benin) and Yaounde (Cameroon) – both lower HIV prevalence. The overall objective of the modelling study is to explore which factors may have contributed to the different epidemics observed in the 4 different sites. From analysis undertaken, the 3 most important topics we are planning to investigate are HSV-2, circumcision and behaviour change. Specific questions are: What role does HSV-2 play in each epidemic? How will HSV-2 control affect HIV transmission? How will this vary across the 4 cities?

The STDSIM model, a very flexible micro-simulation model developed at Erasmus University Rotterdam, will be used for this project. It will allow us to closely model a specific population at a specific time. The first fit of the model to data has been carried out. Next steps are to improve the fit of the model to the data; to explore the role of HSV-2 in the HIV epidemics in the 4 cities (changing what we assume about the interactions between the two diseases); and finally… modelling interventions!

Possible interventions to be modelled are prophylactic (preventing HSV-2) vs. therapeutic (prevent symptoms, reduce transmission with lack of ulcers); HSV-2 treatment (e.g. periodic mass, episodic or suppressive; target groups); HSV-2 vaccines (e.g. mass, annual, combo; prophylactic vs. therapeutic). Overall, we want to better understand the role of herpes in epidemics, see where herpes control is useful – in some places, not others?

Esther Freeman, Wellcome Trust Modelling Project

Collaborators for Wellcome Four Cities Modelling Project: Institute of Tropical Medicine, Antwerp; LSHTM; Imperial College London and University of Quebec; Erasmus University, Rotterdam; Members of the Study Group on Heterogeneity of HIV Epidemics in African Cities.

Modelling HSV-2: Initial Ideas

Existing modelling
There are several existing models of HSV-2, but they have various limitations. Two assume HSV-2 is always infectious (White & Garnett 1999; Newton & Kuder 2000); none incorporate the per sex act transmission probability and factors influencing this in the basic reproductive rate; all except two (Korenromp 2002; Garnett 2004) look at the infectiousness of HSV-2 per sex partnership; only one looks at interaction with HIV (Korenromp 2002); and none have looked at implications of feedback between HIV and HSV2.

Simple HSV-2 and HSV-2/HIV model
We are therefore proposing to develop a simple deterministic and/or stochastic model that includes: per sex act transmission of HSV-2; distinct instances of symptomatic and asymptomatic virus shedding and non-infectious stages; simple portrayal of the effect of HIV infection status on HSV-2 virus shedding frequencies; and the effect of HSV-2 virus shedding instances on the per sex act transmission of HSV-2.

We would then incorporate the HIV dynamic into the developed HSV-2 model, and factor in feedback between the diseases to allow for: HSV-2 infection to increase the risk of HIV acquisition; HIV infection to increase the risk of HSV-2 acquisition; HSV-2/HIV co-infection to increase both HIV and HSV-2 infectiousness; gender differences; and differences between the effect of HSV-2 incident/prevalent infections.

The model could be used to better understand the magnitude of HSV-2/HIV feedback effect; the extent to which key behavioural/epidemiological factors influence patterns of transmission; key determinants of the HIV impact of different HSV-2 treatment strategies; and factors affecting the potential impact of an HSV-2 vaccine.

The group is currently seeking funds to develop a body of modelling analysis on HSV-2 and HIV.

Peter Vickerman, Charlotte Watts & Anna Foss, LSHTM

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