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Welcome

This is the newsletter of the **DFID Research Programme Consortium for Research and Capacity Building in Sexual & Reproductive Health and HIV in Developing Countries**. The RPC is a five-year research programme coordinated by the London School of Hygiene and Tropical Medicine (LSHTM) and is a collaboration with the following partner institutions:

- National Institute for Medical Research (NIMR), Mwanza, Tanzania;
- Navrongo Health Research Centre (NHRC), Ghana;
- School of Medical Sciences, Kwame Nkrumah University of Science and Technology (KNUST-SMS), Kumasi, Ghana;
- Reproductive Health and HIV Research Unit (RHRU), University of the Witwatersrand, Johannesburg, South Africa;
- Social and Public Health Sciences Unit of the Medical Research Council (MRC SPHSU), Glasgow, UK;
- International Planned Parenthood Federation (IPPF);
- Population Services International (PSI).

Further information on research by RPC members and partners can be found on our website: http://www.lshtm.ac.uk/dfid/aids/

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The Effect of Herpes Treatment on HIV

Introduction

In this issue of the SRH & HIV Bulletin, we discuss recent striking results and progress on a series of randomised placebo-controlled trials of herpes episodic or suppressive treatment to prevent transmission or acquisition of HIV in Africa conducted under the auspices of our Research Programme Consortium (RPC).

Herpes simplex virus type-2 (HSV-2), a sexually transmitted virus, is one of the most common pathogens worldwide. HSV-2 is a lifelong infection and is found in nearly 80% of HIV-infected patients. Once acquired, the virus cycles between latency (hidden in nerves), asymptomatic genital excretion of the virus ('shedding'), and clinical reactivations that can produce painful ulcers in and around the genitalia. The herpes virus can be targeted by specific HSV-2 antiviral drugs such as aciclovir, valaciclovir or famciclovir, which are medications with a good efficacy and safety profile, to which the herpes virus rarely becomes resistant, and which – in the case of aciclovir – are relatively inexpensive. These drugs are effective in preventing the recurrence of disease and in curbing the transmission of HSV-2 from infected to uninfected partners.

Epidemiological and biological data support a strong association between HSV-2 and HIV-1 infection. Observational studies have shown that HSV-2 enhances the risk of HIV-1 acquisition by at least 2 to 3-fold and that HSV-2 infection may increase HIV-1 infectiousness by increasing the quantity of genital (and plasma) HIV-1 RNA.

In 2001, an international workshop organised by the WHO, UNAIDS and the LSHTM called for randomised controlled trials of HSV-2 therapy to definitely establish a causal relationship between HSV-2 and HIV-1 infectivity and acquisition. A number of HSV-2 intervention trials are underway throughout Africa (and other parts of the world), evaluating both episodic and suppressive therapy approaches in various populations of HIV-negative or HIV-positive men and women, taking highly active antiretroviral therapy (HAART) or not, and measuring impact in terms of HIV acquisition or HIV transmission or transmissibility (as measured by genital shedding of HIV).

Results from trials conducted by RPC members in Burkina Faso, Ghana and South Africa are presented herein, whilst other results from trials conducted in Malawi, South Africa and Tanzania, are due out later this year.

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HSV-2 infection: a causal link with genital and plasma HIV-1 replication

Herpes simplex virus type 2 (HSV-2), responsible for most cases of genital herpes worldwide, is back in the spotlight for HIV prevention and control. In the early 1990s, studies showed that HIV-infected patients receiving long-term aciclovir for cytomegalovirus (CMV)-associated disease experienced a prolonged survival compared with untreated patients[1,2]. There was no clear explanation for such an effect since aciclovir is not known to be pharmacologically active against HIV. A meta-analysis of subsequent clinical trials, which had been conducted among patients with AIDS to measure the efficacy of the approach, concluded that there was some limited benefit of aciclovir on patient survival[3], but the strategy was not pursued following introduction of HAART.

Meanwhile, there is growing epidemiological evidence supporting the role of HSV-2 on HIV acquisition (a 2 to 3 fold increased risk)[4], and HIV transmissibility, as suggested by the increased frequency and quantity of HIV genital shedding in the presence of genital HSV-2[5,6]. These observations complemented earlier reports of biological interactions between the two viruses: HIV and HSV-2 could live together in the same cell[7], HSV-2 could induce changes in HIV cellular tropism, and HSV-2 proteins could up-regulate HIV replication in vitro[8]. Over 80% of HIV-infected individuals are also infected with HSV-2 in some studies from Africa[6,9], and it has been hypothesised that HSV-2 may considerably enhance the spread of HIV on the continent. Efforts to try and control HSV-2 may be worthwhile prevention strategies for HIV. Several trials assessing the impact of HSV-2 therapy in terms of HIV acquisition or HIV transmission (or transmissibility as assessed by impact on HIV plasma load and HIV genital shedding) have been started in the past few years (Table 1), many of which were launched under the auspices of the DFID Knowledge Programme on HIV/AIDS & STI (reported in *'HIV/AIDS & STI News'* Issue #7, September 2004).

The first completed trial was reported recently and its encouraging results have attracted considerable scientific and media attention[10]. The study, sponsored by the French Agence Nationale de Recherches sur le Sida et les Hepatites (ANRS) – with additional support from our former DFID Knowledge Programme on HIV/AIDS & STI, now the Research Programme Consortium on Sexual and Reproductive Health and HIV – was carried out in Burkina Faso in collaboration with Centre Muraz in Bobo Dioulasso, the Virology Department of the Montpellier University Hospital (France), and LSHTM. The study comprised two parallel randomised placebo-controlled trials (ANRS 1285a and 1285b) aiming at assessing the impact of valaciclovir 500mg given twice daily for 3 months ('suppressive therapy') on HIV-1 genital shedding and plasma viral load. Both of these trials have been published recently in the *New England Journal of Medicine*[10] and *AIDS*[11]. The ANRS 1285a trial enrolled 140 HIV-1/HSV-2 co-infected women not eligible for HAART. Women in the valaciclovir arm shed HIV-1 at the genital level less often (odds ratio=0.41, 95% confidence interval [CI]: 0.21 to 0.80; p=0.009), and in reduced quantities (mean reduction -0.29 $\log_{10}$ copies of HIV-1 RNA per mL of genital fluid, 95% CI: -0.44 to -0.15; p<0.001). Moreover, HIV-1 plasma viral load was reduced (mean reduction -0.58 $\log_{10}$ copies/mL, 95% CI: -0.72 to -0.35; p<0.001) among women treated with valaciclovir. These translated into approximately a 50% and 70% reduction of genital and plasma levels of HIV-1, respectively. As expected, the treatment was successful in reducing HSV-2 genital shedding and the occurrence of genital ulcer episodes.[10]

> "These exciting initial findings demonstrate why research into reducing HIV/AIDS transmission is such a vital element of the fight against the disease... We will follow the next stages of this research with interest."
>
> Gareth Thomas, UK Minister for International Development, LSHTM Press Release, February 2007

In the companion ANRS 1285b trial conducted among 60 women taking HAART for at least 4 months, valaciclovir had no overall significant impact on genital HIV-1 shedding.[11] Of note, HIV-1 plasma viral load was well controlled in the majority (83%) of participants at all visits, and this in turn decreased the likelihood of HIV-1 genital shedding. However, in the subgroup of women with detectable genital HIV-1 RNA shedding at baseline (the group most likely to benefit from the treatment, if the hypothesis of HSV-2/HIV-1 interaction was correct), a significant effect of valaciclovir on HIV-1 genital shedding was observed, of the same order of magnitude as in the ANRS 1285a trial, confirming the independent effect of HSV on HIV-1 replication in the genital compartment. Moreover, in women with detectable plasma HIV-1 RNA, viral load was decreased, although this was not statistically significant owing to the small number of women in this group (mean reduction -0.41 $\log_{10}$ copies/mL, 95% CI: -1.35 to 0.53; p=0.39). In addition, this trial showed for the first time that valaciclovir could reduce both the frequency and quantity of genital HSV-2 in women taking HAART. These findings suggest the possible use of anti-herpes treatment as an adjunct to HAART since, in addition to its beneficial effect on genital herpes, herpes treatment might help to prevent the emergence of resistant (and readily transmissible) HIV strains at the genital level, through its effect in reducing genital HIV replication which occurs despite antiretroviral treatment. This hypothesis, however, should be further tested in research.

The results of another trial, which used a different strategy to control HSV-2 – providing treatment to patients presenting with genital ulcers ('episodic therapy') – were presented at a satellite meeting organised by the sponsor of these trials (ANRS) at the 16th International AIDS Conference (IAC) in Toronto in July 2006, and at the IUSTI Conference in Versailles in October 2006. The ANRS 1212 trial, carried out in Ghana and the Central African Republic in collaboration with LSHTM, the INSERM Paris and the University of Sherbrooke in Canada, failed to demonstrate any impact of 400mg of aciclovir given 3 times daily for 5 days on HIV-1 genital shedding at day 7 and over 1 month, nor on HIV-1 plasma load at day 28. However, this study provided very useful information on the use of aciclovir for genital ulcer disease (GUD) in Africa, in terms of its safety, tolerance and adherence profile. Moreover, the intervention showed benefit to patients with a reduction in HSV-2 shedding and improved lesional healing in the

treatment arm. The study also highlighted the importance of offering HIV voluntary counselling and testing (VCT) in STI clinics, since over 50% of women attending these clinics were found to be infected, many at advanced disease stages, were not aware of their status and thus not yet taking HAART.

Additional data from a trial conducted among 300 HIV-positive women by our partners in South Africa (Reproductive Health Research Unit, RHRU) with support of the Wellcome Trust (WT), and smaller trials in women in Thailand (CDC) and men who have sex with men in Peru (University of Washington, UOW), were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in Los Angeles (February 2007). They support the ANRS 1285 findings in terms of impact of aciclovir on HIV-1 genital and plasma levels. (Further longer term follow-up data are awaited from a WT/MRC-funded trial in Mwanza where women are being followed up to 30 months.) Although such results are encouraging, their translation in terms of HIV-1 transmission is still unknown. The multicentre 'Partners in Prevention' trial of HIV-1 serodiscordant couples (Table 1), conducted by Dr Connie Celum and investigators at UOW (which include RHRU as a partner), will be able to directly assess the impact of suppressive therapy on HIV transmission. Results are expected in 2008.

The role of herpes treatment in HIV prevention and management

The suppressive treatment trials strongly support the hypothesis of a causal relationship between HSV-2 reactivations and HIV-1 replication, and the episodic treatment study underscores the need to prevent reactivations if any effect is to be seen. This opens a new avenue for the control of HIV.

Interesting additional findings from the ANRS 1285 and WT South African trials include the impact on HIV-1 plasma viral loads. It can be hypothesized that sustained reductions in plasma viral load may provide an individual benefit to patients with HIV-1, if this virological effect was accompanied by a slower CD4 decline. This could potentially help delay the need for HAART in many patients, with attendant cost saving, reductions in side effects, and improvement in quality of life. Further studies are required to address these important questions.

Research published recently reinforced the hypothesis that HSV-2 facilitates HIV-1 acquisition: in a cohort study of sex workers in Nairobi, Kenya, the investigators showed that HSV-2 seropositive women had a 10-fold increased number of dendritic DC-SIGN positive cells, which have been implicated in HIV-1 transportation from mucosal sites to lymphatic tissues during the initial process of HIV-1 infection[12]. In addition to the Partners in Prevention trial of the impact of suppressive therapy on HIV transmission, two major trials are in progress to demonstrate that HSV-2 suppressive therapy can help decrease HIV-1 acquisition. A WT/MRC-funded study among high-risk women in Tanzania, conducted in collaboration with partners from the National Institute for Medical Research (NIMR) in Mwanza, AMREF and LSHTM, has been completed and results will be presented at the IAS Conference, Sydney, and the ISSTDR conference, Seattle, in July and August 2007.

If we anticipate positive results from these proof-of-concept trials, what would the likely impact at population level be, if these treatment strategies (or a vaccine with similar efficacy) were used on a large scale in sub-Saharan Africa and elsewhere? Several modelling exercises have been conducted by staff at LSHTM[4], using different levels of HSV-2 treatment or vaccine efficacy on HIV-1 transmission. A minimalist approach using suppressive treatment targeting sex workers and their clients would reduce HIV-1 incidence by 14–17% in sub-Saharan Africa after 10 years (IAC 2006: abstract TUPE0403). In all situations, suppressive therapy is likely to yield a greater population impact than episodic therapy, but may be less likely to be adopted widely. If a prophylactic HSV-2 vaccine with 80% hypothetical efficacy were to be available, it could reduce (with 80% coverage) HIV incidence from 18% to 25% (IAC 2006 abstract: TUPE0414). Further modelling work and meta-analyses are in progress to determine the population-level impact of herpes treatment strategies using empirical data from our trials, and to model the joint effects of herpes treatment with other HIV prevention strategies, such as expansion of male circumcision services or effective microbicides with anti-HIV/HSV-2 activity.

It should be noted that treatment with aciclovir (or valaciclovir) has been shown to be very safe and does not require any clinical or biological monitoring. Resistance emergence, particularly among HIV-positive individuals, has been shown to be limited and stable over time (under 5% in developed country settings), is manageable, and should not hinder a wider use of the drug, should it prove to be beneficial for HIV-1 transmission and for HIV-1 disease progression. Data on HSV-2 resistance ought to be gathered from some developing countries. The real barriers to wide-scale use of anti-herpes therapy, however, are its cost and scarcity in developing countries, despite aciclovir being available in generic form for many years. For example, the monthly cost of a suppressive therapy in Burkina Faso is currently £7 (although much cheaper alternatives are available from international tenders), but it could be reduced in the future through lobbying activities organised by WHO and other agencies. Research coordinated by UOW colleagues and RPC partners will attempt to determine the barriers to aciclovir in Africa.

The implications of the use of aciclovir and the challenges for wider implementation have been discussed at two WHO Expert Meetings that reviewed evidence and guidelines for STI & HIV Prevention (Geneva, July 2006) and HIV Management (Montreux, June 2006). Recommendations and guidelines will be developed with the aim of sensitising programme managers, physicians and populations, in resource-constrained countries to the problem of genital herpes, and the possibility of getting them prepared to include these interventions in HIV control programmes. However, the field of HSV/HIV control would be considerably simplified if an effective HSV-2 vaccine was available. At present, there are no efforts to develop and test a vaccine that would address the needs of populations in developing countries. This prevention gap should, in the light of accumulating evidence, be filled urgently.

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Table 1 Trials assessing the impact of HSV-2 suppressive therapy (aciclovir 800mg/day) or HSV-2 episodic therapy (aciclovir 1200mg/day for 5 days) on HIV acquisition and transmission

Project	Study Populations	Outcome	Sponsors
Suppressive therapy			
Aim: to reduce HIV-1 acquisition			
University of Washington (UOW), Seattle	HIV-1 negative/HSV-2 positive African women & men who have sex with men (MSM) (USA & Latin America)	HIV incidence	National Institutes of Health (NIH), Division of AIDS
LSHTM & National Institute of Medical Research (NIMR)	HIV-1 negative/HSV-2 positive female sex workers in Tanzania	HIV incidence	Wellcome Trust
Aim: to reduce HIV-1 transmission			
UOW 'Partners in Prevention'	Sero-discordant couples (HIV-1/HSV-2 co-infected partner with CD4 >250/µL receives the intervention)	HIV incidence in partners	Bill & Melinda Gates Foundation
Aim: to reduce genital HIV-1 shedding (transmissibility/infectiousness)			
Centre Muraz, Univ. Montpellier and LSHTM	HIV-1/HSV-2 co-infected women in Burkina Faso in 2 trials: a) not eligible for HAART (CD4 >200/µ); and b) taking HAART	Frequency & quantity of genital HIV-1, plasma HIV-1	ANRS
Reproductive Health & Research Unit (South Africa) & LSHTM	HIV-1/HSV-2 co-infected women with CD4 >250/µL, South Africa	Frequency & quantity of genital HIV-1, plasma HIV-1 and CD4	Wellcome Trust
NIMR & LSHTM	HIV-1/HSV-2 co infected female sex workers in Tanzania	Frequency & quantity of genital HIV-1	Wellcome Trust
UOW	MSM in Peru in cross-over trial	Frequency & quantity of rectal HIV-1, plasma HIV-1	NIH
UOW	Women in Cameroon in cross-over trial	Frequency & quantity of genital HIV-1, plasma HIV-1	NIH
Centers for Disease Control (CDC)	Women in Thailand in cross-over trial	Frequency & quantity of genital HIV-1, plasma HIV-1	CDC
Episodic therapy			
Aim: to reduce genital HIV-1 shedding (transmissibility/infectiousness)			
INSERM France, LSHTM, WAPCAS Ghana, CRNMST Bangui, Univ. Sherbrooke, Canada	Women with GUD in Ghana and Central African Republic	Frequency & quantity of genital HIV-1, plasma HIV-1, ulcer healing	ANRS
CDC & LSHTM	Men with GUD in South Africa	Frequency & quantity of lesional HIV-1	CDC
LSHTM, University of North Carolina, Lighthouse (Malawi)	Men and women with GUD in Malawi	Frequency & quantity of genital or sperm HIV-1, ulcer healing	University of North Carolina