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Can we reduce the spread of HIV infection by suppressing herpes simplex virus type 2 infection?

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Abstract

Overwhelming evidence from observational epidemiological studies indicates that herpes simplex virus type 2 (HSV-2) infection enhances the risk of acquiring HIV infection. Studies of genital shedding of HIV have suggested that HSV-2 infection also increases the onward transmission of HIV-1 by HIV/HSV-2 co-infected patients. Several randomized controlled trials were initiated to assess the impact of HSV-2 suppressive therapy on the acquisition of HIV infection by HSV-2 infected men and women, and on the onward transmission of HIV by HSV-2/HIV co-infected men and women. In the past 2 years the results of these trials have been published. HSV-2 suppressive therapy was not found to have any effect on HIV acquisition nor on onward transmission of HIV. However, suppressive therapy with acyclovir was found to slow down disease progression in HIV/HSV-2 co-infected patients. The effect was rather modest and cost-effectiveness studies are needed to assess whether HSV-2 suppressive therapy has a place in the management of HIV-1 infected patients, especially in low and middle income countries.

Introduction and context

The World Health Organization and The United Nations Joint Programme on HIV/AIDS (UNAIDS) estimated that in 2008, 2.7 million people became newly infected with HIV, of whom 1.9 million were living in sub-Saharan Africa [1]. Since the beginning of this century, considerable progress has been made in the scaling up of antiretroviral treatment in low and middle income countries. However, coverage remains suboptimal and new HIV infections continue to outnumber patients who are put on antiretroviral treatment [2]. It is clear that HIV treatment programs are not sustainable unless the tide of new HIV infections is stemmed.

Strategies to reduce the spread of HIV infection can be broadly categorized into behavioural interventions and biomedical interventions. The latter interventions aim to reduce the probability of transmission of HIV during sexual intercourse and one of the most promising interventions in this field was the control of other sexually transmitted infections (STIs) as they have been shown to facilitate the transmission of HIV [3]. Several randomized trials have been conducted to assess the impact of STI control on the incidence of HIV infection, with conflicting results. It appeared that the impact of STI control on the spread of HIV is dependent on the stage of the HIV epidemic, with a larger impact in earlier stages of the epidemic [4]. Moreover, it became clear that infection with herpes simplex virus type 2 (HSV-2) a viral STI that cannot be controlled by early detection and treatment of infected persons, plays an overwhelming role in the spread of HIV, especially in sub-Saharan Africa, where the prevalence of HSV-2 infection in adults in the general population ranges from 30% to 80% in women and from 10% to 50% in men [5]. A meta-analysis of longitudinal studies found that men and women who are infected with HSV-2 have a three-fold increased risk of acquiring HIV infection [6]. Using this relative risk and data on prevalence of HSV-2 infection, it has been estimated that in sub-Saharan Africa, 38-60% of new HIV

infections in women and 8-49% of new infections in men may be attributable to HSV-2 infection [6]. In addition, studies on shedding of HIV and HSV-2 in the genital tract have shown that reactivation of HSV-2 infection is associated with increased shedding of HIV, suggesting that HSV-2 infection increases the infectivity of HIV/HSV-2 co-infected men and women [7-10].

A reduction in incidence and prevalence of HSV-2 infection could thus have a considerable impact on the incidence of HIV infection. However, apart from behaviour change interventions and condom use, there are very few options to control HSV-2 infection with biomedical interventions. The only vaccine with some proven efficacy prevents HSV-2 acquisition in women who are not infected with HSV-1, but does not prevent acquisition in men, or in women who are infected with HSV-1 [11]. This vaccine is thus of very limited use in low and middle income countries where the prevalence of HSV-1 among young people and adults is still very high. To date the only alternative strategy is suppressive therapy with acyclovir or valacyclovir, which has been shown to decrease episodes of reactivation of HSV-2 infection and transmission of HSV-2 [12,13]. Several randomized controlled trials were initiated to assess the impact of HSV-2 suppressive therapy on the acquisition of HIV infection by HSV-2 infected men and women, and on the onward transmission of HIV by HSV-2/HIV co-infected men and women. In the past 2 years the results of these trials have been published, and it is time now to take stock.

Recent advances

Does suppressive therapy reduce the risk of HIV infection in HSV-2 infected men and women?

Two trials have assessed the effect of HSV-2 suppressive treatment with acyclovir 400 mg twice daily on HIV acquisition [14,15]. Study populations included women in Tanzania at high risk of HIV infection; women at lower risk of HIV infection in South Africa, Zimbabwe and Zambia; and men who have sex with men in Peru and in the USA. Suppressive treatment with acyclovir reduced the incidence of genital ulcerations but did not have any effect on HIV incidence (Table 1).

Whenever the results of a trial are negative, two major questions are raised: (a) was the intervention that was tested the right one; and (b) was there an effect that was not measured? The above trials were powered to detect a 50% protective effect of suppressive therapy with acyclovir and had sufficient endpoints to detect such effect. The two trials might have missed a modest effect of more limited public health significance. Suboptimal adherence to the study drugs could have attenuated any difference in HIV incidence between the two study arms. In both trials very high adherence levels were achieved. In the Tanzanian trial there was an effect in those women who took more than 90% of the prescribed medication, but it was not statistically significant (rate ratio 0.58, 95% confidence interval [CI] 0.25-1.38) and such effect was not found in the trial by Celum *et al*. [15] (hazard ratio [HR] 1.0, 95% CI 0.67-1.50).

The most likely explanation for the lack of effect is that the intervention was not right. The authors of both papers considered the possibility that valacyclovir or higher dose acyclovir might have been a better choice for suppressive therapy. Studies on the effects on herpes recurrences of acyclovir and of valacyclovir, however, suggest that both drugs may have similar effects and that it is unlikely that a larger impact on HIV incidence would have been found with valacyclovir. The most likely explanation is that the concept of the intervention was not right and that suppressing clinical and subclinical reactivation of HSV-2 infection is not enough to reduce the vulnerability to HIV infection associated with HSV-2 infection. Indeed, a study published in 2009 found evidence that HIV receptor-positive inflammatory cells persist in the genitalia for a very long time after healing of reactivation [16].

Table 1. Summary of trials that assessed the impact of suppressive therapy with acyclovir on HIV acquisition

			Incidence of HIV per 100 pyr			
Study population	Site	Total (n) enrolled	Treatment group	Placebo group	Rate ratio/HR (95% CI)	Reference
Women at higher risk of HIV	Tanzania	821	4.44	4.12	1.08 (0.64-1.83)	[7]
Women at lower risk of HIV	South Africa, Zimbabwe, Zambia	1358	4.9	3.1	1.53 (0.95-2.46)	[8]
MSM	Peru	1355	3.2	3.8	0.82 (0.48-1.41)	[8]
	USA	459	2.5	2.2	1.09 (0.36-3.24)	

CI, confidence interval; HR, hazard ration; MSM, men who have sex with men; pyr, person-years.

Does suppressive therapy reduce onward transmission of HIV infection by HSV-2/HIV co-infected men and women?

Several randomized trials published in recent years found that suppressive therapy with acyclovir or valacyclovir reduced plasma HIV viral load and genital shedding of HIV-1 RNA in HIV-infected women and men who were co-infected with HSV-2 [17-21]. This suggests that suppressive therapy of HSV-2 infection could reduce the infectivity of HIV/HSV-2 co-infected persons. However, the proof of the pudding is in the eating. The Partners in Prevention HSV/HIV Transmission Study directly assessed the effects of suppressive therapy with acyclovir on onward transmission of HIV from an HIV/HSV-2 co-infected person to his/her HIV uninfected stable partner [22]. Study participants taking 400 mg acyclovir twice daily had significantly less episodes of genital ulcers than study participants in the placebo group. They also had a significantly lower plasma HIV viral load. Yet, there was no difference in HIV transmission: in the intention-to-treat analysis the incidence of HIV infection was the same in the intervention group and the placebo group, 2.7 per 100 person-years (HR 0.99, 95% CI 0.71-1.40).

The study was powered to detect a 50% reduction in HIV transmission, so a modest effect might have been missed that would have been of limited public health significance. The most likely explanation for the disappointing result is that the reduction in plasma HIV viral load was just not enough to reduce infectivity. During the follow-up period the mean plasma viral load was 0.25 log lower in the acyclovir group compared to the placebo group [22]. An observational study of HIV discordant couples in Uganda suggests that larger reductions in plasma viral load are needed to have a substantial effect on onward transmission of HIV. In this study the mean plasma viral load was 4.48 log in HIV-1 infected subjects whose partner seroconverted and 3.89 log in HIV-1 infected subjects whose partner did not seroconvert [23].

The Partners in Prevention HSV/HIV Transmission Study was also the first study that directly assessed the long-term effects of HSV-2 suppressive therapy on disease progression [24]. In the patients who took acyclovir, the decline in CD4 cell count was slower, initiation of antiretroviral treatment was delayed, and mortality was reduced compared with patients in the control group.

Implications for clinical practice

The trials with HSV-2 suppressive therapy have not found any effect on HIV acquisition nor on HIV transmission. Consequently, suppressive therapy with acyclovir and valacyclovir does not have any place in HIV prevention. This does not imply, however, that there is no interaction between HSV-2 infection and HIV-1 infection. The evidence – though observational – that HSV-2 enhances the transmission of HIV is overwhelming. The problem lies in the lack of biomedical interventions that can substantially reduce the incidence and prevalence of HSV-2 infection. Meanwhile, valuable lessons have been learned from these trials and we have made progress in our understanding of the mechanisms underlying the increased vulnerability to HIV-1 infection associated with HSV-2 infection.

Suppressive therapy with acyclovir had a beneficial effect on disease progression in HIV/HSV-2 co-infected subjects. However, this benefit was rather modest and cost-effectiveness analyses will have to be done to assess whether acyclovir can have a place in the management of HIV-infected patients in low- and middle-income countries [25].

Abbreviations

CI, confidence interval; HR, hazard ratio; HSV, herpes simplex virus; STI, sexually transmitted infection.

Competing interests

The author declares that she has no competing interests.

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