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Episodic Acyclovir Therapy as Part of Syndromic Management Among Men Presenting With Genital Ulcer Disease: Is There Benefit?

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Introduction

Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcer disease (GUD) throughout the world [1]. This often asymptomatic infection is present in about 1 in 5 Americans (17.0%; 95% CI, 15.8%–18.3% in 1999–2004) [2] and prevalence may exceed 80% in individuals residing in developing countries [1]. Despite the often asymptomatic nature of genital herpes, several studies document the role of HSV-2 infection in increasing genital and plasma HIV-1 viral load, which may, in turn, increase HIV transmission [3]. Episodic acyclovir therapy may result in decreased genital HIV-1 shedding and enhance ulcer healing in individuals receiving syndromic therapy for GUD but no study has specifically addressed this issue in men.

Aims

To determine the impact of episodic acyclovir therapy as part of the syndromic management of GUD on herpetic genital ulcer duration and HIV-1 RNA lesional shedding.

Methods

A total of 615 men ranging in age from 18 to 60 years were included in this double-blind, placebo-controlled trial conducted in three clinics in South Africa from March 2005 through December 2006. Participants were randomly assigned to either acyclovir, 400 mg three times a day for 5 days or placebo, added to the routine syndromic therapy of GUD. All study participants received benzathine penicillin, 2.4 MU intramuscularly and ciprofloxacin, 500 mg orally as part of standard GUD syndromic management. Participants underwent an interview, genital examination, and collection of blood for HIV, HSV-2 and syphilis serologies, plasma HIV-1 viral load, and CD4 cell testing. Genital ulcers were tested for *Treponema pallidum*, *Haemophilus ducreyi*, HSV, *Chlamydia trachomatis* L1-L3, and for the quantity of HIV-1 RNA and HSV-2 DNA shedding. Ulcer healing was defined as either a reduction of 90% or more of ulcer area or complete reepithelialization. Patient reports of ulcer healing were also used to determine median ulcer duration. HIV-positive individuals

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Rating

•Of importance.

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were assessed on days 2 or 4, 7, 14, and 28 and HIV-negative participants returned for periodic follow-up visits through day 28.

Results

A total of 1,559 men were screened, 635 were eligible and 615 were randomly assigned (309 to acyclovir and 306 to placebo) with 28 individuals lost to follow-up in each arm. There were no differences by treatment arm and baseline characteristics between individuals lost to follow-up and those who remained in the study. Among the enrollees, 387 (63.0%) were HIV seropositive and 434 (70.6%) were HSV-2 seropositive; 73.6% of the genital ulcers were herpetic. The ulcer had been present a median of 5.0 days before presentation in the acyclovir group vs 6.0 days in the placebo group ($P=0.08$). Treatment arms were balanced among all participants and HIV-positive participants with a herpetic ulcer. Adherence was >85% in both arms by self-report and by pill count.

Ulcers healed faster in participants receiving acyclovir (64.4% in the acyclovir group were healed at day 7 vs 49.6% in the placebo group; aRR 1.3 [95% CI, 1.1–1.5]), a finding driven primarily by the effect of acyclovir therapy in accelerating ulcer healing among HIV-positive participants at day 7 (aRR 1.4 [95% CI, 1.1–1.8]) and day 14 (aRR 1.1 [95% CI, 1.0–1.2]). Subanalyses found a greater impact of acyclovir therapy for individuals presenting with initial herpes (64.6% healed at day 7 for acyclovir versus 46.6% placebo; aRR 1.5 [95% CI, 1.1–2.1]), for men who presented early (≤ 5 days after ulcer onset) for therapy (70.6% healed at day 7 for acyclovir vs 47.1% placebo; aRR 1.5 [95% CI, 1.1–2.0]) and for HIV-positive individuals with CD4 cell count > 200 cells/ μ L (aRR 1.5 [95% CI, 1.2–2.0]). Among HIV-positive individuals, acyclovir therapy resulted in fewer men with detectable HIV-1 RNA on days 7 (23.9% vs 37.1%; aRR 0.7 [95% CI, 0.4–1.0]) and 14 (14.7% vs 37.5%; aRR 0.4 [95% CI, 0.2–0.9]), as well as a reduction in mean lesional HIV-1 RNA level on day 7 with the greatest impact realized in HIV-positive men with CD4 cell count > 200 cells/ μ L (aRR 0.4 [95% CI, 0.2–0.9]). Acyclovir significantly reduced HSV-2 shedding at every visit among HIV-positive men with an ulcer when compared to placebo and on day 7, the mean quantity of plasma HIV-1 RNA in the acyclovir group was significantly lower than that in the placebo group among all HIV-positive participants ($-0.19 \log_{10}$ copies/mL [95% CI, -0.37 to $-0.02 \log_{10}$ copies/mL]; $P=0.03$).

Discussion

Episodic therapy with acyclovir in this clinical setting improved ulcer healing by a median of 3 days for HIV-positive men with a herpetic ulcer and reduced HIV-1 and HSV-2 shedding from ulcers. There was no significant effect of therapy among HIV-negative men in this study. Although the addition of acyclovir to current antibacterial therapy for the syndromic management of GUD resulted in symptom relief and a reduction of genital HSV-2, the effect of episodic therapy on HIV-1 genital shedding is not likely to have a significant impact on HIV-1 transmission at the population level and more effective interventions are needed.

Comments

This placebo-controlled study demonstrated a significant clinical benefit conferred by episodic acyclovir therapy in a setting in which individuals presented relatively late following genital ulcer onset (median of 5-6 days). The timing of episodic therapy initiation in this study contrasts sharply with current domestic recommendations for optimal HSV episodic therapy initiation (ie, within 1 day of lesion onset or during the prodrome) [4]. Although the benefit in this study was primarily realized by HIV-infected individuals, the

reality is that HIV serostatus is often unknown at the time of the initial clinical encounter in the majority of settings in which syndromic management is practiced. Therefore, these findings support the inclusion of antiherpes medication as part of GUD syndromic therapy as currently recommended by the World Health Organization [5]. Although unable to comment on the effect of acyclovir therapy on overall HIV-1 genital shedding, the investigators found a statistically significant (albeit small) decrease in HIV-1 lesional shedding in the treatment group.

The current study contrasts with another recent study of similar design conducted by Mayaud et al. among HIV-positive African females, which found that at day 7, episodic acyclovir therapy failed to significantly hasten herpetic ulcer healing (median 1-day difference between treatment and placebo arms) and did not significantly decrease genital and plasma levels of HIV-1. Lesional shedding of HIV-1 was slightly less likely in women receiving acyclovir though this finding did not reach statistical significance (RR, 0.70; 95% CI, 0.4–1.2). Although adherence was high, participants in the Mayaud study were relatively immunosuppressed (median CD4=190) and presented a median of 7 days following ulcer onset, slightly later than participants in the Paz-Bailey study [6]. Both issues may have had some impact on the different results reported from the two studies. Therefore, the Paz-Bailey study represents a significant contribution to the literature regarding the impact of episodic HSV management on ulcer healing and, while the authors acknowledge that the decrease in HIV-1 lesional shedding noted in the study was not likely to contribute significantly to HIV transmission on a population basis, the findings remain important.

The issues surrounding the effect of HSV-2 infection on HIV transmission and acquisition are far from straightforward. Unfortunately, two recent randomized, placebo-controlled trials designed to determine whether acyclovir suppression of HSV-2 infection in HIV-1 negative study participants would decrease their risk of HIV acquisition failed to demonstrate a significant benefit [7,8]. Similarly, investigators of a large study designed to determine if suppression of HSV-2 among HIV-1 coinfecting individuals would reduce HIV transmission to their HIV-negative sexual partner recently reported null results [9]. Interestingly, a recent study by Zhu et al. [10] based on skin biopsies performed at healed HSV-2 reactivation sites found that CD4⁺ and CD8⁺ T cells and a mixed population of plasmacytoid and dendritic cells persist at the sites for months after healing, even in the setting of daily HSV suppressive therapy. The persistent CD4⁺ cells reacted to HSV-2 antigen, were enriched for expression of the HIV chemokine receptor, CCR5 and incorporated greater concentrations of CCR5-tropic HIV-1 compared with cells from control skin biopsies. These persistent HSV-2 induced changes may help explain the inability of anti-HSV therapy to reduce HIV acquisition [10]. Therefore, though the recent clinical trial results have been disappointing, I am confident that many important lessons are yet to be learned as investigators continue to unravel the mystery of the HSV/HIV interaction.

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