

Aetiological pattern of genital ulcer disease (GUD) in Malawi and associations between herpes simplex virus type 2 (HSV-2) and HIV-1: Time for addition of episodic treatment for genital herpes?

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Abstract

Background: Current syndromic management of genital ulcer disease (GUD) in Malawi covers treatment for syphilis and chancroid, but does not include treatment for genital herpes. A randomised placebo-controlled trial evaluating the impact of additional acyclovir as episodic treatment for HSV-2 on ulcer healing and HIV-1 genital shedding is underway in Lilongwe, Malawi.

Methods: Patients are interviewed, examined and samples collected prior to randomisation and at follow-up visits on days 2 or 4, 7, 14 and 28. GUD aetiology is determined by real-time multiplex PCR of lesional swabs. Blood is tested for HIV-1, syphilis, and HSV-2 serologies. CD4 count and plasma HIV-1 RNA are measured among HIV-1 sero-positive patients.

Results: By Nov 2005, 250 patients (204 men, 46 women) were enrolled and randomised. 60% were HIV-1 sero-positive, 74% were HSV-2 sero-positive and 4% had a positive syphilis serology. Ulcer aetiology among 177 patients showed: HSV-2 58%, *H. ducreyi* 19%, LGV 7%, *T. pallidum* 5% and no aetiology 11%. Patients who were HSV-2 sero-positive were more likely to be HIV sero-positive (69% vs. 35%, $p < 0.0001$), as were patients with lesional HSV-2 compared to patients with other aetiologies (67% vs. 51%, $p = 0.03$). Among HIV+ patients with CD4 count < 200 , 72% of ulcers were due to HSV-2.

Conclusions: HIV-1 and HSV-2 are highly prevalent infections in patients with GUD in Lilongwe and are closely associated. HSV dominates GUD aetiologies in this population, while bacterial aetiologies covered by the current management algorithm persist. There is growing evidence to revise GUD guidelines to add acyclovir episodic treatment for genital herpes in Malawi.

Background

Current syndromic management of genital ulcer disease (GUD) in Malawi covers treatment for syphilis and chancroid, but does not include treatment for genital herpes. Predominantly *Haemophilus ducreyi*, *Treponema pallidum*, or *Klebsiella granulomatis* were main causes of GUD in developing countries whilst HSV-2 was the cause of GUD in western countries. There is evidence that a shift in GUD aetiologies has occurred in the last decade showing HSV-2 as a common cause of GUD in most developing countries. HIV-1 has been shown to impact on natural history of HSV-2 while HSV-2 may increase efficiency of HIV-1 acquisition and transmission.

A trial is under way in Lilongwe, Malawi to determine the impact of addition of acyclovir episodic treatment for genital herpes on genital ulcer healing and HIV-1 lesional and genital shedding. This poster describes the aetiology of GUD in the cohort and the association of HSV-2 and HIV-1.

Methods

Study Setting: Kamuzu Central Hospital (KCH) Sexually Transmitted Infection (STI) clinic attending to 800 STI patients per month.

Population: Men and women presenting with GUD at Lilongwe STI clinic in Malawi.

Design: Randomized double - blind placebo - controlled clinical trial. Patients are interviewed, examined and samples are collected at baseline and follow up visits on days 2 or 4, 7, 14 and 28. GUD aetiology is determined by real - time multiplex - PCR of lesional swabs. Blood is tested for HIV-1, syphilis, and HSV-2 serologies. CD4+ count and plasma HIV-1 RNA are measured among HIV-1 sero-positive patients.. Patients are treated with single injection of benzathine penicillin 2.4 MU intramuscularly and single dose - ciprofloxacin 500mg orally before receiving either 20 tablets of 400mg acyclovir or matching placebo to be taken 2 tablets twice a day for 5 days.

Results

By Nov 2005, 250 patients (204 men, 46 women) were enrolled, of whom 150 (60%) were HIV-1 sero-positive and 175/236 (74%) were HSV-2 sero-positive.

Table 1: Ulcer aetiology

	Male	Female	All
Enrolled in Study	N=204	N=46	N=250
Ulcer aetiology Day 0	(n=154)	(n=22)	(n=176)
HSV-2	83 (54%)	19 (86%)	102 (58%)
<i>H. ducreyi</i>	27 (18%)	7 (32)	34 (19%)
<i>T. pallidum</i>	9 (6%)	1 (5%)	8 (5%)
LGV	-	-	11 (7%)
Unknown aetiology	-	-	21 (11%)
Among HSV2 sero+	(n=107)	(n=20)	N=127
HSV-2	59 (55%)	17 (85)	76 (60%)
<i>H ducreyi</i>	20 (19%)	7 (35)	27 (21%)
<i>T pallidum</i>	8 (7%)	1 (5%)	9 (7%)
Among HIV sero+	(n=87)	(n=18)	(n=105)
HSV-2	53 (61%)	15 (83%)	68 (65%)
<i>H ducreyi</i>	10 (11%)	6 (33%)	16 (15%)
<i>T pallidum</i>	5 (6%)	1 (5%)	6 (6%)

▪ Data for ulcer aetiology was available for 176 patients.

▪ Ulcer aetiology was dominated by HSV-2 (58%).

▪ 25% of these had no detectable HSV-2 antibodies (Primary Genital Herpes [PGH] cases), suggesting that these patients might have primary HSV-2 infections

▪ However bacterial aetiologies still persist.

▪ Patients who were HSV-2 sero-positive were more likely to be HIV-1 sero-positive (69% vs. 35%, $p < 0.0001$), as were patients with lesional HSV compared to patients with other aetiologies (67% vs 51%, $p = 0.03$).

▪ Among HIV-1 sero-positive patients with CD4+ count < 200 , 72% of ulcers were due to HSV-2

Discussion and Conclusions

- HIV-1 and HSV-2 are highly prevalent infections in patients with GUD in Lilongwe Malawi.
- HSV-2 dominates GUD aetiologies in this population, while bacterial aetiologies covered by the current syndromic management algorithm persist.
- There is growing evidence to revise GUD guidelines to incorporate acyclovir episodic treatment for genital herpes in Malawi.

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