



Episodic therapy for genital herpes in sub-Saharan Africa: A pooled analysis from three randomised controlled trials

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Background

- HSV2 is the leading cause of genital ulcer disease (GUD)
- Biological and observational evidence that HSV2 facilitates HIV acquisition & transmission
- Aciclovir is not commonly used to treat GUD in developing countries
 - perceived to be expensive
 - has to be started early to be effective
 - generally reduces healing by only 1-2 days
 - **little data among HIV positive individuals and in Africa**

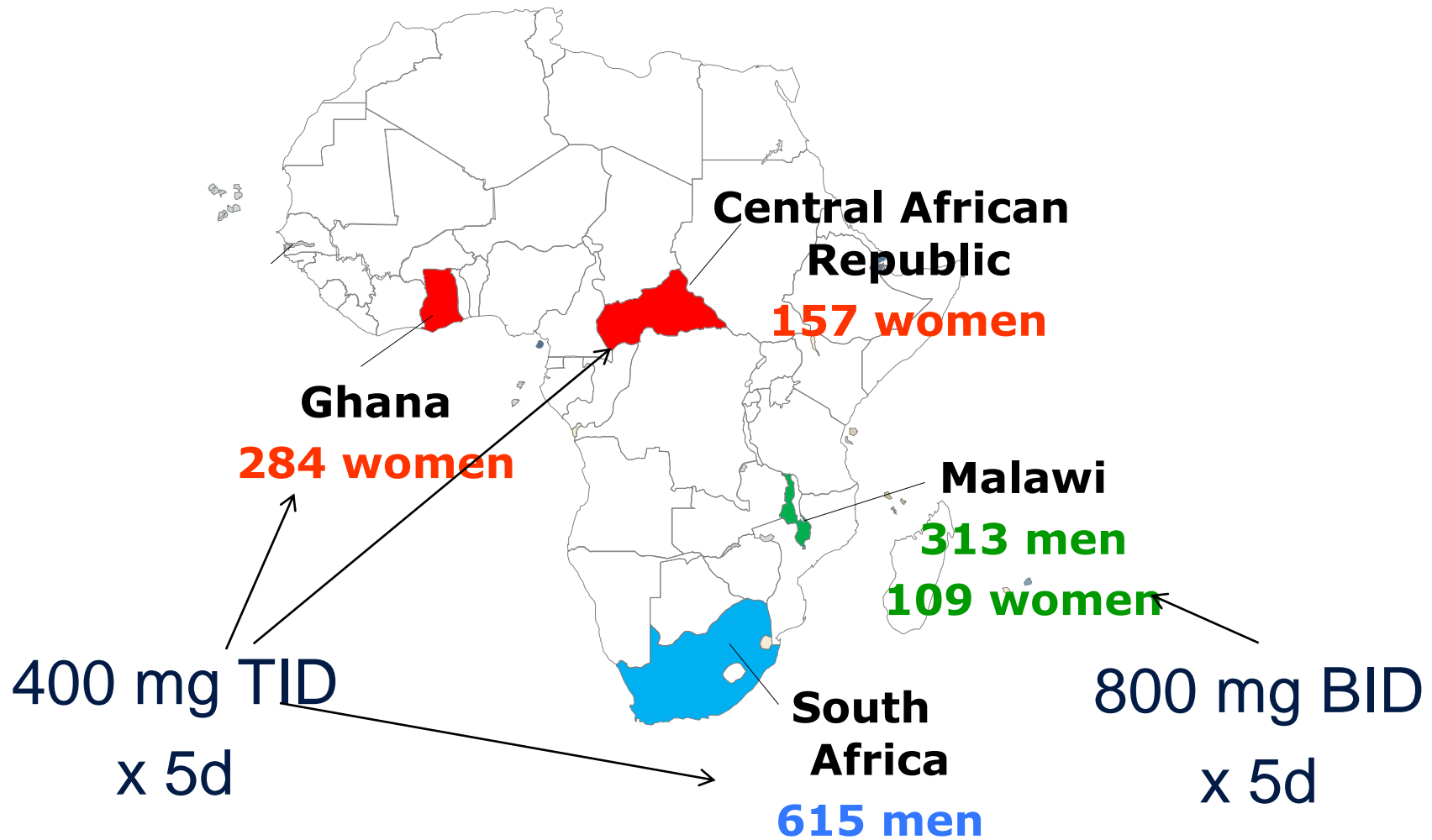
Aims

- **To describe clinical characteristics of the 1,478 GUD cases in 4 African countries**

- **To estimate impact of aciclovir on ulcer healing among:**
 - All patients
 - Subgroups by: HIV serostatus, type of ulcer, time to presentation, size of ulcer

- **To estimate impact of aciclovir on lesional and genital HIV shedding**

Trial settings



Study Design

Genital ulcer disease patients

In Malawi & South Africa

Refused HIV test

In South Africa:

Partially healed ulcer (18%)

Blisters only (10%)

In all trials:

Ulcer >500 mm²

Ulcer duration >30 days

Anal/perianal ulcer only

Non-resident

Pregnancy

Randomisation

D0

**Syndromic Mx
+ Placebo**

**Syndromic Mx
+ Aciclovir**

D2 → D4 → D7 → D10 → D14 → D28

Primary outcomes

Ulcer healing

Lesional and/or genital HIV-1 RNA

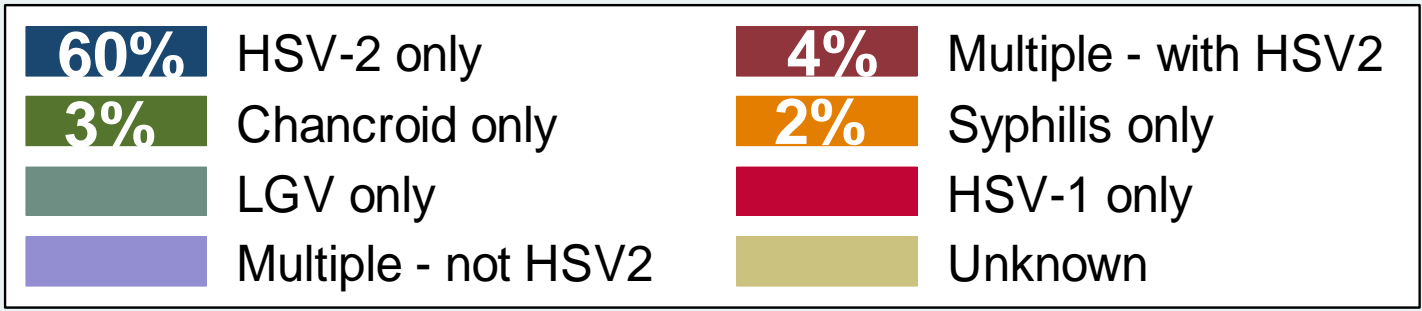
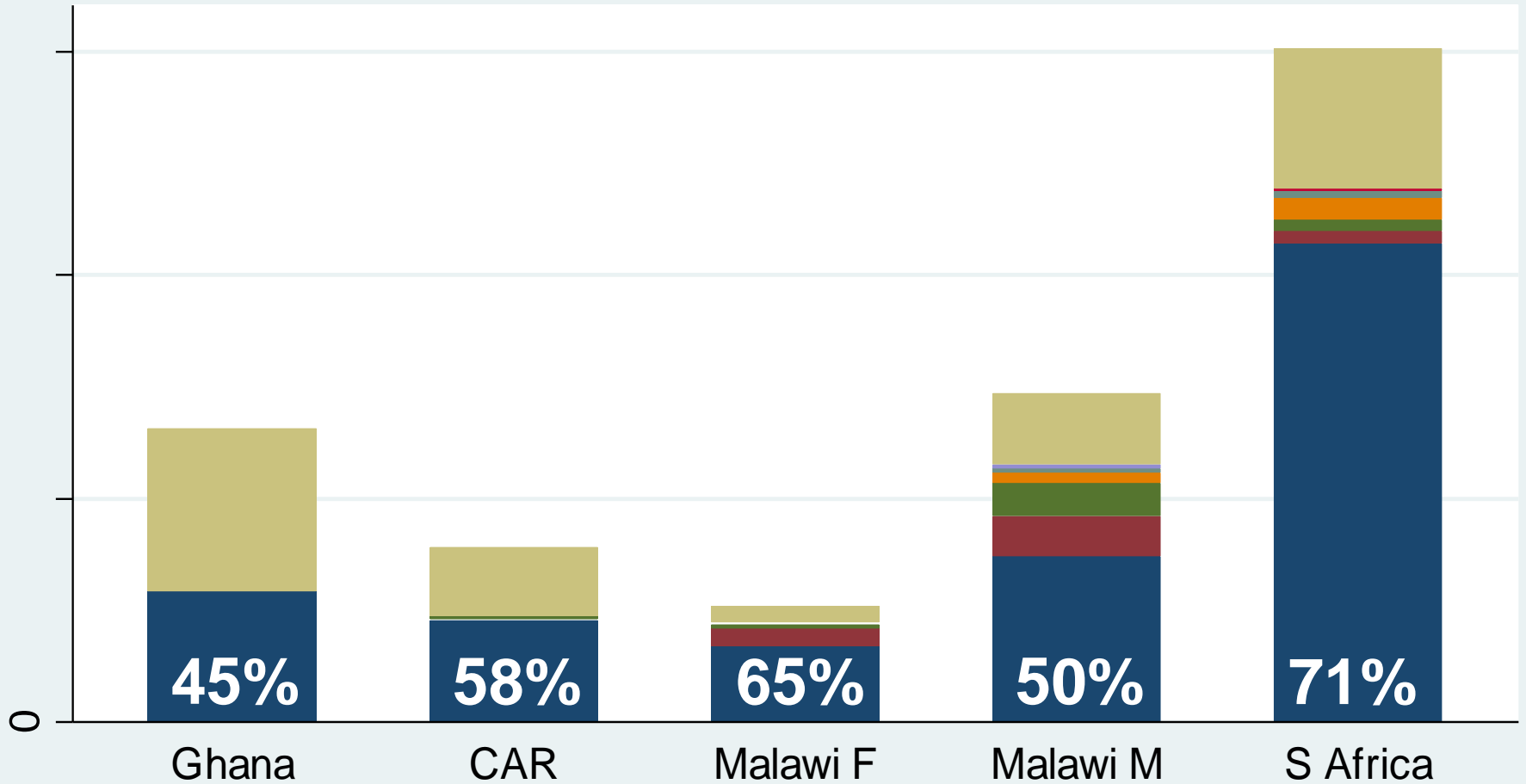
Lab methods & definitions

	Ghana & CAR	Malawi	South Africa
Ulcer aetiology	PCR for HSV, TP, HD and LGV		
Healed ulcer	≥90% reduction in ulcer size		
HSV2 serology	HerpeSelect IgG2 ELISA	HerpeSelect IgG2 ELISA	Kalon IgG2 ELISA
HIV serology	2 complementary ELISAs	2 rapid tests, discordants resolved with ELISAs at ref lab	
HIV infected	Detection of HIV either serologically or in genital/lesional samples (real-time PCR)		
Threshold for genital HIV	250 copies/mL	250 copies/mL	50 copies/mL
1st episode genital HSV2	HSV2 seronegative with detectable lesional HSV2		

Baseline characteristics

	Ghana F	CAR F	Malawi F	Malawi M	South Africa M
Number enrolled	284	157	109	313	615
Median age (yrs)	27	29	28	28	29
Median duration of ulcer (days)	5	7	7	6	5
Median size (mm²)	147	130	21	28	35
HSV2 seropositive	70%	95%	81%	69%	71%
HIV seropositive	34%	69%	77%	55%	63%

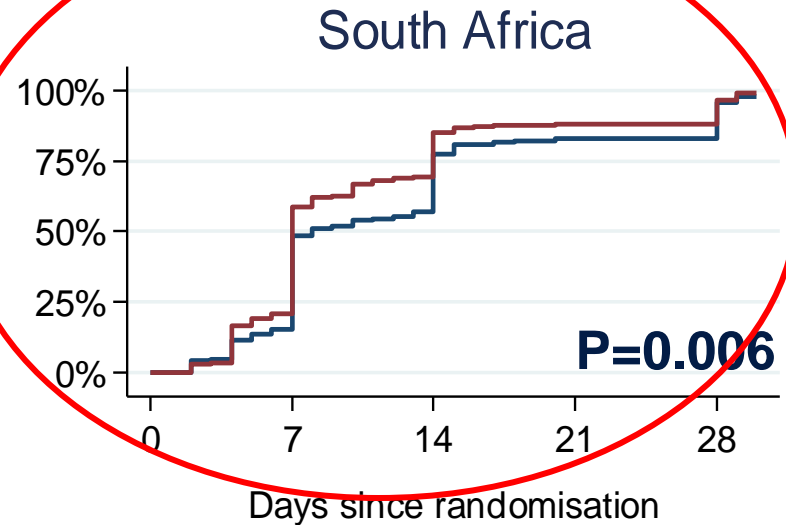
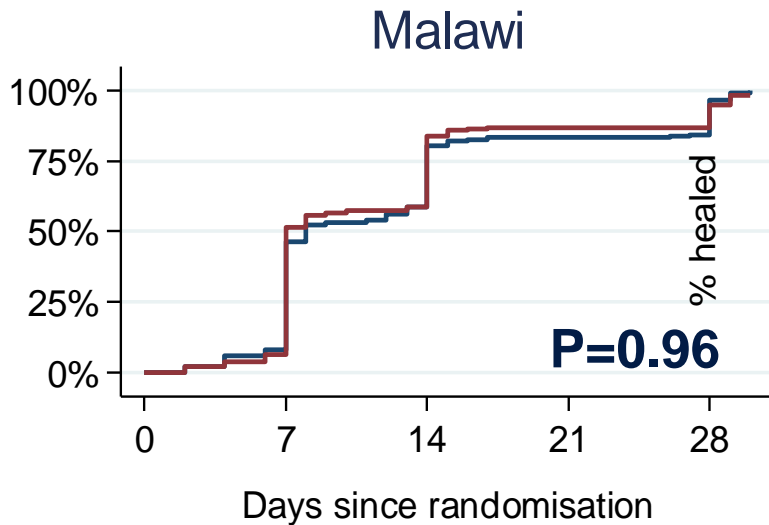
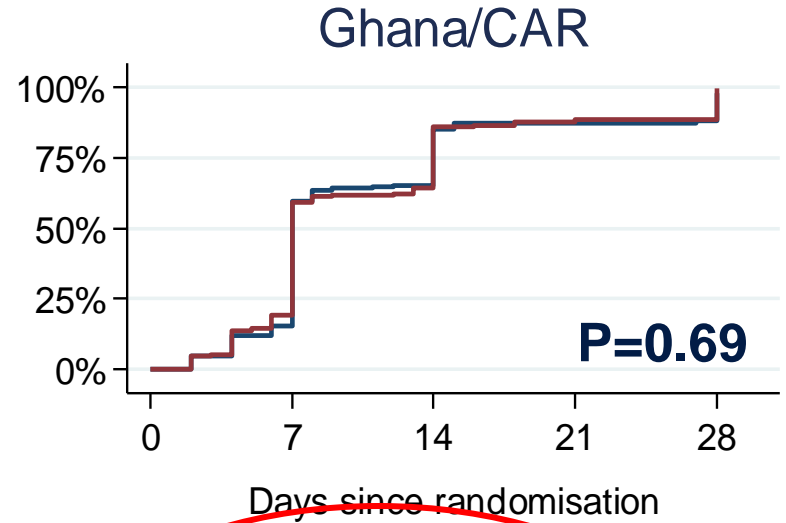
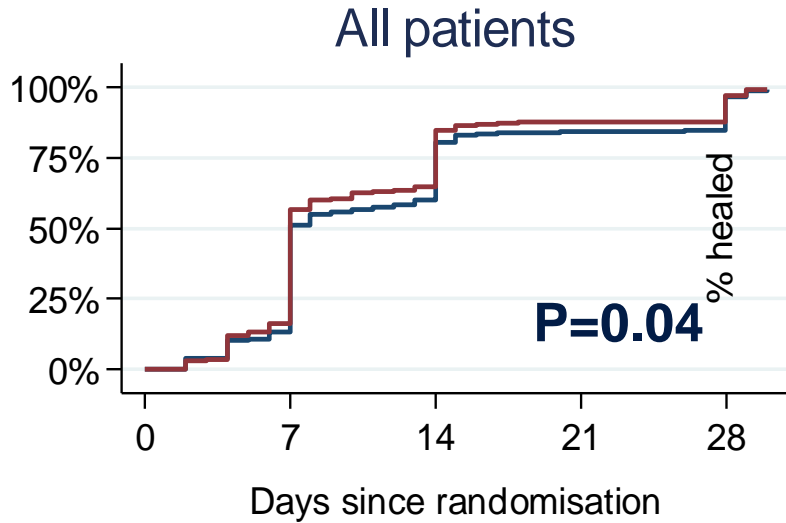
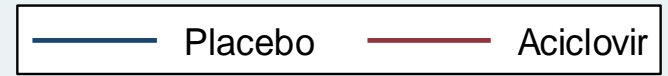
Ulcer aetiology



Impact of aciclovir on ulcer healing at Day 7 (85% follow-up, 1254 ulcers)

	Placebo	Aciclovir	Risk ratio (CI)
	% healed at day 7		
All patients	57%	63%	1.10 (1.0-1.2)
			P-int=0.13
Ghana F	81%	80%	0.99 (0.9-1.1)
CAR F	34%	35%	1.02 (0.6-1.6)
Malawi F	69%	70%	1.01 (0.8-1.3)
Malawi M	53%	54%	1.02 (0.8-1.3)
South Africa M	52%	65%	1.24 (1.1-1.4)
			P-int=0.14
HIV positive	49%	57%	1.17 (1.0-1.3)
HIV negative	68%	70%	1.02 (0.9-1.1)

Ulcer healing By site



Impact of aciclovir on ulcer healing at Day 7, stratified by ulcer characteristics

	% healed at Day 7		Risk ratio (CI)
	Placebo	Aciclovir	
Non HSV2 ulcer	62%	61%	0.98 (0.8-1.1)
HSV2 ulcer	53%	63%	1.19 (1.1-1.3)
First episode	56%	70%	1.24 (1.0-1.6)
Recurrent HSV2	52%	62%	1.18 (1.0-1.4)
			P-int=0.002
Ulcer <50 mm²	60%	74%	1.23 (1.1-1.4)
Ulcer ≥50 mm²	53%	45%	0.92 (0.8-1.1)

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First episode	56%	70%	1.24 (1.0-1.6)
Recurrent HSV2	52%	62%	1.18 (1.0-1.4)
			P-int=0.002
Ulcer <50 mm ²	60%	74%	1.23 (1.1-1.4)
Ulcer ≥50 mm ²	53%	45%	0.92 (0.8-1.1)
			P-int=0.51
Duration <5 days	67%	77%	1.15 (1.0-1.3)
Duration ≥5 days	54%	58%	1.08(1.0-1.3)

Impact of aciclovir on ulcer healing at D7 among HIV seropositive patients

	Risk ratio (CI)	
	Among HIV+ (n=726)	
All	1.17 (1.0-1.3)	
	P-int=0.33	
Ghana F	0.99 (0.8-1.2)	
CAR F	1.17 (0.6-2.2)	
Malawi F	0.93 (0.7-1.3)	
Malawi M	1.08 (0.8-1.5)	
South Africa M	1.31 (1.1-1.6)	
	P-int=0.31	
HSV2 ulcers	1.22 (1.0-1.4)	
Non HSV2	1.05 (0.8-1.3)	

Impact of aciclovir on ulcer healing at D7 among HIV seropositive patients

	Risk ratio (CI)	
	Among HIV+ (n=726)	Among HIV+ with HSV2 ulcers (n=506)
All	1.17 (1.0-1.3)	1.22 (1.0-1.4)
	P-int=0.33	P-int=0.09
Ghana F	0.99 (0.8-1.2)	0.91 (0.7-1.2)
CAR F	1.17 (0.6-2.2)	2.10 (0.9-5.2)
Malawi F	0.93 (0.7-1.3)	0.89 (0.6-1.2)
Malawi M	1.08 (0.8-1.5)	1.10 (0.7-1.7)
South Africa M	1.31 (1.1-1.6)	1.37 (1.1-1.8)
	P-int=0.31	
HSV2 ulcers	1.22 (1.0-1.4)	
Non HSV2	1.05 (0.8-1.3)	

Impact on lesional HIV-1 RNA at Day 7 among HIV infected with HSV-2 ulcers

	% with lesional HIV		Risk ratio (95% CI)
	Placebo	Aciclovir	
All patients	29%	19%	0.66 (0.5-0.9)
Ghana F	0%	6%	0
CAR F	55%	44%	0.71 (0.4-1.2)
Malawi F	9%	4%	0.35 (0.1-3.2)
Malawi M	26%	23%	0.89 (0.4-1.9)
South Africa M	32%	18%	0.57 (0.4-0.9)

Impact on lesional HIV-1 RNA at Day 7 among HIV infected patients with HSV2 ulcers

	% with lesional HIV		Risk ratio (95% CI)
	Placebo	Aciclovir	
			P-int=0.31
First episode	28%	6%	0.30 (0.1-1.5)
Recurrent HSV-2	29%	21%	0.70 (0.5-0.9)
			P-int=0.69
Ulcer <50 mm ²	19%	10%	0.53 (0.3-1.0)
Ulcer ≥50 mm ²	44%	31%	0.71 (0.5-1.0)
			P-int=0.08
Duration <5 days	18%	10%	0.53 (0.2-1.3)
Duration ≥5 days	28%	21%	0.74 (0.5-1.0)

Summary: clinical characteristics


- 1,478 genital ulcer patients seen
- 928 male patients; 550 female patients

- 64% HSV2 ulcers; 29% unknown
- 16% have first episode genital HSV2
- 3% chancroid; 2% syphilis
- Average duration before presentation: 6 days

- 58% HIV seropositive
- 37% with AIDS defining condition

Summary

- Significant impact of aciclovir on ulcer healing by Day 7 among
 - All patients
 - Patients with smaller ulcers
 - HIV patients with HSV2 ulcers
 - Men in South Africa
- Some effect on genital and lesional HIV at Day 7 among men, but not among women

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- The greater impact in South Africa is not explained by HIV serostatus, ulcer aetiology, size and duration of ulcer at baseline
 - May be partly due to different eligibility criteria (exclusion of partially healed ulcers which may be less susceptible to aciclovir)

Conclusions

- Aciclovir can improve ulcer healing in Africa
- Greatest impact on HIV positive patients, those with HSV2 ulcers (esp. primary genital herpes) and small ulcers
- GUD patients provide an entry point for provider-initiated HIV testing, and possibly HSV suppressive therapy

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Extra slides

Characteristics of HIV positive patients

	Ghana F	CAR F	Malawi F	Malawi M	South Africa M
Mean PVL (log ₁₀ copies/ml)	4.26	4.95	4.74	4.90	4.80
Median CD4 (cells/mm ³)	361	193	173	263	282
% CD4 <200 (cells/mm ³)	36%	52%	56%	34%	34%
% on ARV	7%	11%	8%	3%	2%
% with an AIDS defining condition	32%	86%	75%	63%	32%

Impact of aciclovir on ulcer healing at D7 among HIV seropositive patients, by CD4 count

	Among HIV positives	Among HIV positives with HSV2 ulcers
	% healed at day 7	
	P-int=0.88	P-int=0.65
CD4>200	1.19 (1.0-1.4)	1.19 (1.0-1.5)
CD4≤200	1.16 (0.9-1.6)	1.10 (0.8-1.5)

Characteristics of HSV2 ulcers

	First episode (n=229)	Recurrent (n=701)	P-value for difference
Median age, years	26	30	<0.001
New partner in last 3 months	54%	28%	<0.001
HIV seropositive	37%	72%	<0.001
Median duration of ulcer, days (IQR)	5 (3-7)	6 (4-11)	<0.001
Median size, mm² (IQR)	30 (14-77)	40 (15-104)	0.07
Mixed ulcer aetiology	4%	6%	0.22