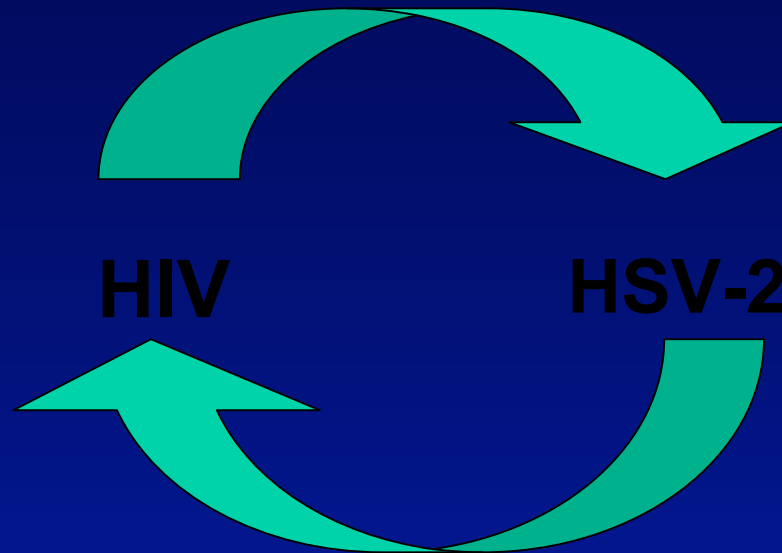


Interactions: HSV-2 and HIV



Effect of HIV on HSV-2

- ~85% of HIV+ are HSV2+
- Alters clinical presentation & frequency of HSV-2 shedding
- Longer duration of lesions (CD4 <200)
- HIV ↑ HSV-2 acquisition & transmission

Effect of HSV-2 on HIV

- ~ 50% are HSV-2
- HSV-2 ↑ HIV acquisition
- HSV-2 ↑ HIV levels in plasma & genital tract
- GUD ↑ HIV transmission

Gray 2001 & 2003, Corey 2004, Wald 2002, Freeman 2004 & 2006

Summary: HSV-2 & HIV Interactions

- HSV-2 is highly prevalent in HIV-infected persons
- Strong epidemiologic & biologic data:
 - HSV-2 increases HIV susceptibility & infectiousness
- Large proof-of-concept study: ↓ HIV in plasma & genital tract
- Complimentary HSV-2 suppression studies:
 - HIV acquisition & HIV transmission
 - Acyclovir & HAART, ACV in GUD management
- HSV-2 provides a needed prevention strategy while developing HIV vaccines, microbicides, new interventions

Proving HSV-HIV synergy: interventions, populations and impact covered by current RCTs

1. Symptomatic HSV-2 increases **HIV transmission***
2. Symptomatic HSV-2 increases **HIV acquisition**
3. HSV-2 infection increases **HIV transmission***
4. HSV-2 infection increases **HIV acquisition**

	HIV positive	HIV negative
Episodic therapy	1	2
Suppressive therapy	3	4

** Includes studies of HIV and HSV genital shedding*

What about episodic treatment of genital ulcers in HIV+ persons?

● Rationale

- Currently not treating major cause of GUD
- ↑ HIV shedding from genital ulcers

● Case Management

- Shorten duration of lesion, symptom relief

● Public Health Impact

- Only 25% of HSV-2 is symptomatic
- Minority seek care ► 'Tip of the iceberg'
- No reduction in HIV shedding
- Unlikely to impact HIV transmission

Acyclovir can treat Herpes.

Herpes is a common STD. Untreated Herpes helps spread HIV. Clinics do not have Acyclovir.

Blisters... sores... STD?

Ask for Acyclovir!

TAC TREATMENT ACTION CAMPAIGN

People with HIV get Herpes more often and more severely.

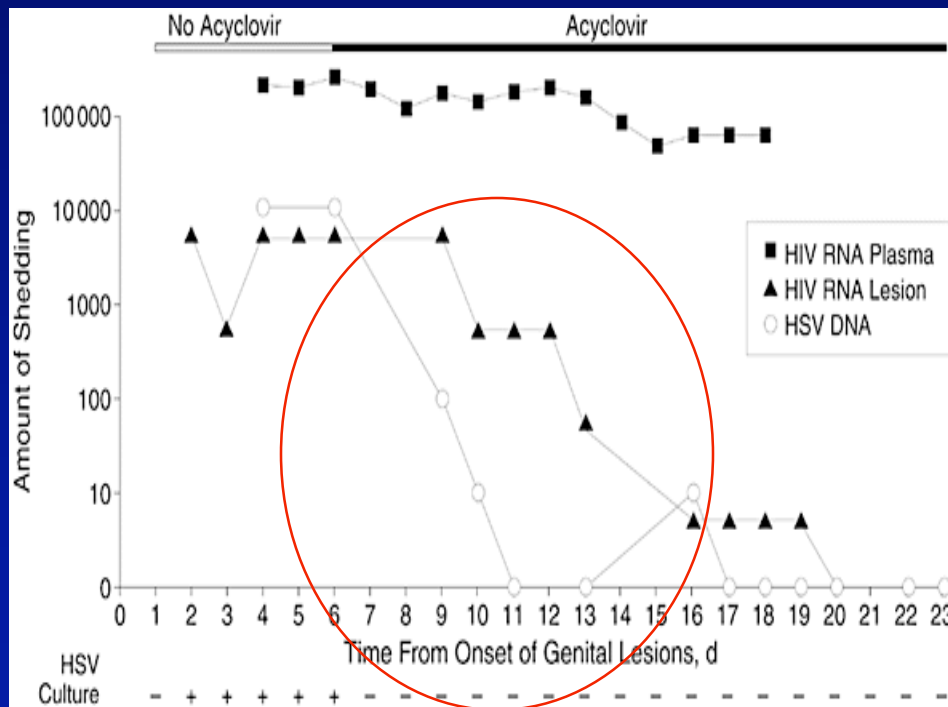
NATIONAL OFFICE: 021-788 3307
DURBAN: 031-204 2672 JOHANNESBURG: 011-453 2293
EAST LONDON: 043-740 0590 CAPE TOWN: 021-354 5499
Website: <http://www.tac.org.za>
Support voluntary HIV counselling and testing. There are direct benefits if you know your HIV status. There are medicines that improve your health. Always practice safer sex and use condoms.

Episodic therapy trials: outline

Place	Primary outcome	Interv'n	N	F-u	Measurement	Progress
Ghana / CAR ANRS1212	HIV shedding	Acy. 400mg TDS x 5 d	441 F	1 mo.	D2/D4, D7, D14, D28	Completed/ results available
Malawi DFID & UNC	Ulcer healing (HIV shedding)	Acy. 800mg BD x 5 d	500 M/F	1 mo.	D2/D4, D7, D14, D21, D28	Completed/ analysis
S Africa CDC	HIV shedding	Acy. 400mg TDS x 5 d	300 M	1 mo.	D7, D14, D21, D28	2007

Episodic HSV-2 Therapy: Reduced HIV Levels in Lesions & Blood Plasma

Lesional HIV shedding



Schacker. *JAMA*. 1998.

Blood plasma HIV

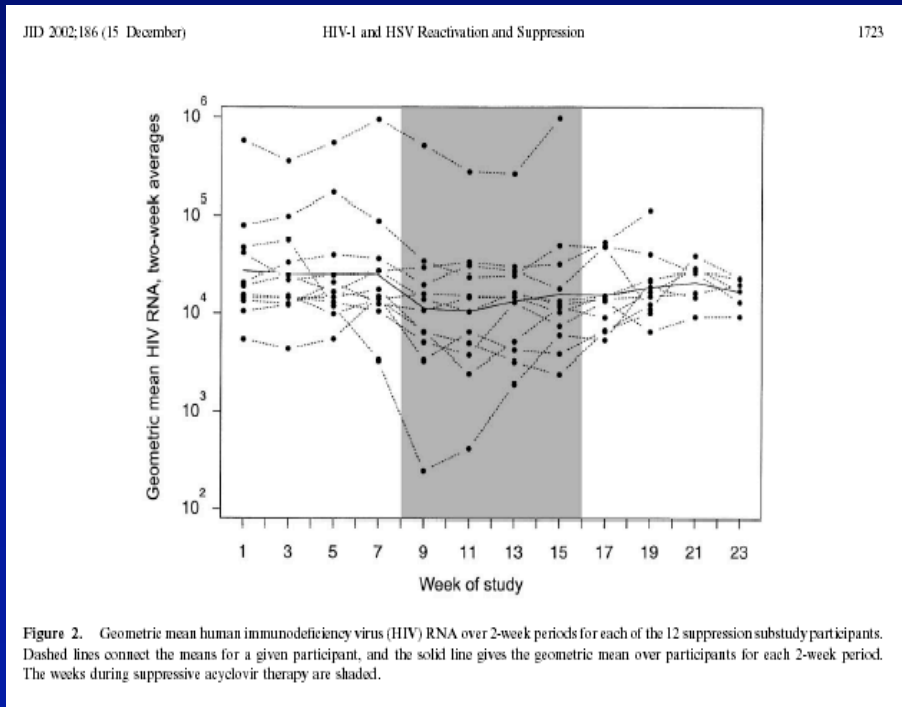


Figure 2. Geometric mean human immunodeficiency virus (HIV) RNA over 2-week periods for each of the 12 suppression substudy participants. Dashed lines connect the means for a given participant, and the solid line gives the geometric mean over participants for each 2-week period. The weeks during suppressive acyclovir therapy are shaded.

Schacker. *J Infect Dis*. 2002.

Suppressive therapy trials: outline (1/2)

Place Funder	Primary outcome	Interv'n	N	F-u	Measurement	Progress
Burkina Faso ANRS1285	HIV shedding	Val. 500mg BD	60 F (ARV) 150 F	3 mo.	Bi-weekly	Completed/ results available
S Africa WT	HIV shedding	Acy. 400mg BD	300 F	3 mo.	Monthly	Completed/ analysis
Zimbabwe NIH	HIV shedding	Acy. 400mg BD	250 F	1 mo.	Weekly	Completed/ analysis
Peru GSK/UW	HIV shedding	Val. 500mg BD	20MSM 20 F	18 wks	3x wk mucosal/ Weekly blood	Completed /results available
Cameroon NIH/UW	HIV shedding	Acy. 400mg BD	40 F?	1mo.?	3/week	Completed

Suppressive therapy trials: outline (2/2)

Place	Primary outcome	Interv' n	N	F-u	Measure ment	Progress
Mwanza, Tanzania WT	HIV shedding	Acy. 400mg BD	500 F	30 mo.	6- monthly	Mid 2007
Mwanza, Tanzania WT	HIV incidence	Acy. 400mg BD	830 F	30 mo.	6- monthly	Mid 2007
Multicenter HPTN 039	HIV incidence	Acy. 400mg BD	3277 MSM & F	18 mo.	3- monthly	Enrollment completed mid 2007
Multicenter Partners in Prevention -BMGF	HIV transmission	Acy. 400mg BD	3000 HIV disc couples	12-24 mo.	3- monthly	~2300 couples Late 2008

Suppressive HSV-2 therapy for HIV Prevention

- Likely bigger impact than episodic ACV
- Higher cost
 - Lowest is \$40 for 1 year with generic ACV
 - Higher pricing in developing countries
- Is it possible to target suppressive HSV-2 therapy?
 - For clinical benefits in HIV+:
 - Based on frequency of HSV-2 reactivations?
 - Based on CD4 (&/or plasma HIV levels)
 - For public health, if reduces HIV transmission:
 - Based on sexual activity

Summary of ongoing research

- **We will know**

- Proof of concept trials
- Impact on HIV acquisition (HPTN, WT)
- Impact on HIV transmission (Partners in Prevention)
- Mechanistic explanation (shedding)
- Different durations, different settings
- VACV vs. ACV (potential difference in adherence)

- **We won't know**

- Exact biological mechanisms (impact through other herpes viruses? Important to know for VACCINE)
- Impact on HIV disease progression (some data on surrogate markers, virological endpoints and CD4)

- **Still required/we will do:**

- Economic analysis
- Impact of various combination of approaches for epidemiological impact (modelling)
- Evaluation of HSV treatment to improve HIV disease in individuals



Looking forward...

- Potential big impact on HIV epidemic if proof-of-concept trials reduce HIV acquisition and/or transmission
 - Population attributable fraction of new HIV infections due to HSV-2 ~50%
- Impact of HSV-2 interventions & who to target?
 - Mathematical modeling of population impacts & targeting HIV- vs HIV+ persons
- How to increase treatment of HSV-2?
 - Costs, availability & prescribing authority for acyclovir in developing countries
- What is role of serologic testing?
 - Particularly for HIV+ persons with 80% coinfection
- What provider Interventions are needed?
 - Training about diagnosis, counseling, and management of genital herpes
 - Little demand: perception from prescribers, patients, governments – still high cost of drug, though generic...
- Acyclovir is not a 'magic' bullet – ultimately need HSV-2 VACCINES+++
 - Will require lobbying!! (role of WHO, BMGF, EU, PEPFAR and others)