NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Genital HSV-2 in HIV-infected patients

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Genital HSV-2 in HIV-infected patients

Clinical Case

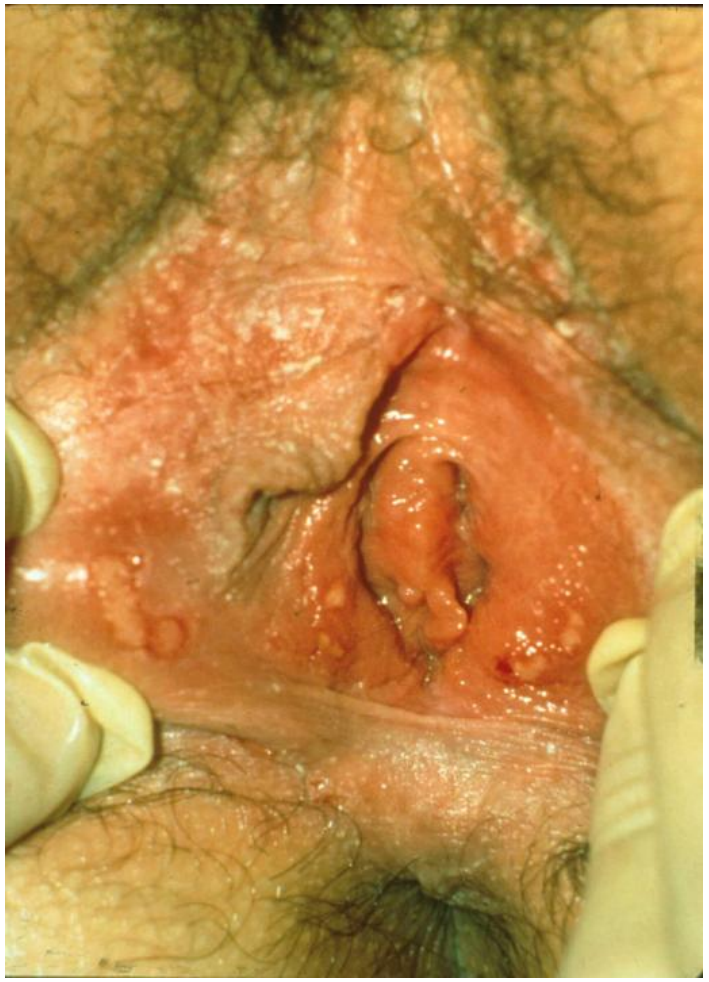
- 35 yo woman with stage 3 HIV
  - Diagnosed 10 years ago
  - Received ART during pregnancy 5 years ago
  - Now off ART for 3 years and out of care
  - Presented with L sided weakness, dysarthria, facial droop
    - Diagnosed with CNS toxo, started on pyrimethamine, sulfadiazine, leucovorin
    - CD4=56 (4%), HIV VL=917,200
    - Started on atazanavir/ritonavir/truvada

Clinical Case

- 3 weeks later, presents with severe pain in the genital region
  - Local ER diagnosed BV
  - On exam, ~10 shallow painful ulcerations on R labia majora, L labia minora
  - HSV-2 culture positive

  - No prior history of genital herpes
  - HSV-1 and HSV-2 seropositive

HSV-2 is one of the most common causes of IRIS



HSV-2 infection is highly prevalent in HIV-infected persons

Age-adjusted HSV-2 prevalence in US population:
- 16%

In HIV-infected persons
- Multiple studies have shown seroprevalence of 50-90%
- Cohorts of MSM in Peru and African FSW:
  - 80-90% HSV-2 seropositive
- SUN study: Prospective cohort in 4 US cities:
  - 60% HSV-2 seropositive

Xu et al, JAMA 2006; 296(8)
Lama et al, JID 2006; 194 (10)
Mbopi-Keou et al, JID 2000; 182(4)
Patel et al STD 2012; 39(2)

HSV-2 is the leading cause of GUD worldwide

City	No. tested by M-PCR	*Haemophilus ducreyi* No. (%)	*Treponema pallidum* No. (%)	HSV No. (%)	*T. pallidum*/HSV No. (%)	Negative No. (%)
Birmingham	50	0	13 (26)	25 (50)	0	12 (24)
Chicago	49[a]	6 (12)	4 (8)	24 (49)	1 (2)	14 (29)
Cincinnati	52	0	1 (2)	41 (79)	0	10 (19)
Dallas	52	0	6 (12)	35 (67)	2 (4)	9 (17)
Houston	51	0	1 (2)	38 (75)	1 (2)	11 (22)
Los Angeles	54	0	0	41 (76)	0	13 (24)
Memphis	50	10 (20)[b]	15 (30)	14 (28)	6 (12)	5 (10)
New York	55	0	1 (2)	36 (65)	1 (2)	17 (31)
Philadelphia	50	0	3 (6)	38 (76)	1 (2)	8 (16)
St. Louis	53	0	7 (13)	28 (53)	1 (2)	17 (32)
Total	516	16 (3)[b]	51 (10)	320 (62)	13 (3)	116 (22)

[a] 50 patients were enrolled; 1 specimen was unsatisfactory and was not tested.

[b] Includes 1 participant with both *H. ducreyi*/herpes simplex virus (HSV) detected and 2 with both *H. ducreyi*/*T. pallidum* detected.

Similar findings in studies from around the world
Tanzania, Botswana, S. Africa, Zambia, Uganda
Thailand, Australia

Mertz, JID 1998, Nielsen Act Ven 2007, Paz-Bailey CID 2005, O'Farrell STD 2008, Makasa STD 2012. Brankin Int J STD AIDS 2009, Beyrer JID 1998, Wilkey Sex Health 2006

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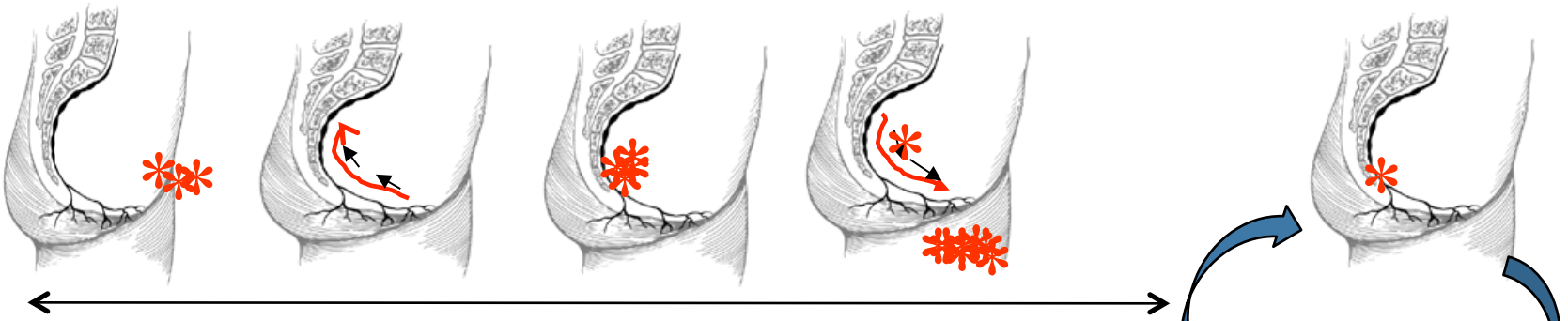
HSV pathogenesis



- **Primary infection:**
  - Inoculation/epithelial replication
  - Retrograde transport to sensory ganglia
  - Ganglionic replication, inter-neuronal spread
  - Acute anterograde transport to periphery
  - Immune control
- **Latency in sensory neurons**
  - Establishment, maintenance, **reactivation**
  - Immune control
- **Lytic replication, axon, across "gap" to keratinocyte**
  - Immune control
- **Epithelial replication, shedding, ± lesions, ± transmission**
  - Immune control

HSV-2 in HIV-infected persons

Increased number of recurrences

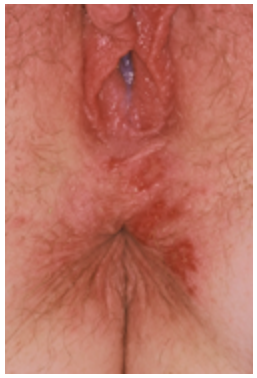
More severe and longer lasting recurrences

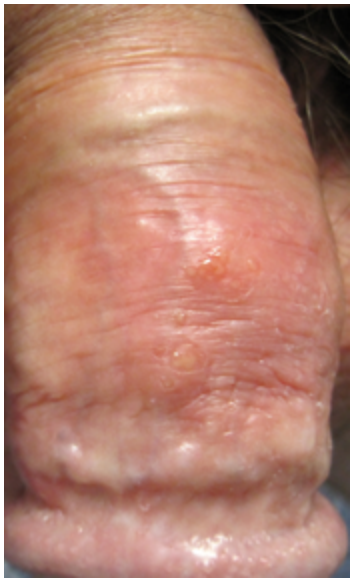
Atypical disease presentations

Increased risk of genital shedding

Increased risk of ACV-resistant herpes

Risk of IRIS in persons starting ART

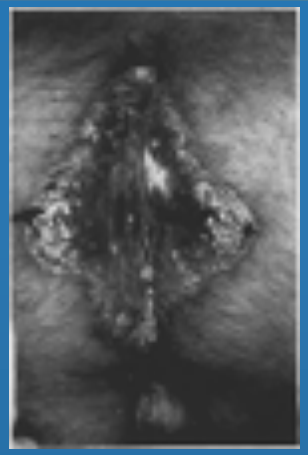




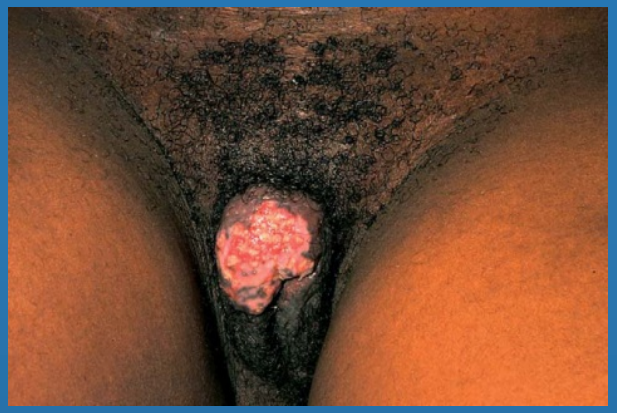
Likely due to CD4+

T cell/immunologic defect

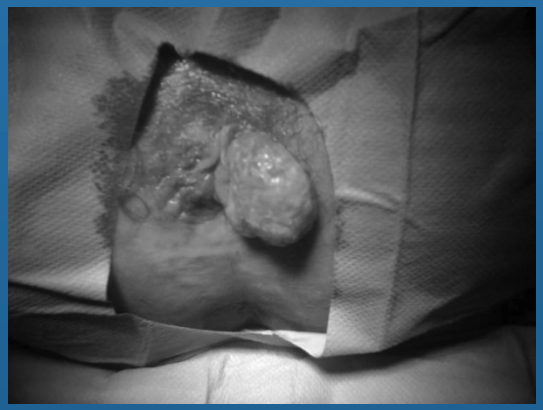
Atypical clinical presentation



Siegal et al, NEJM 1981

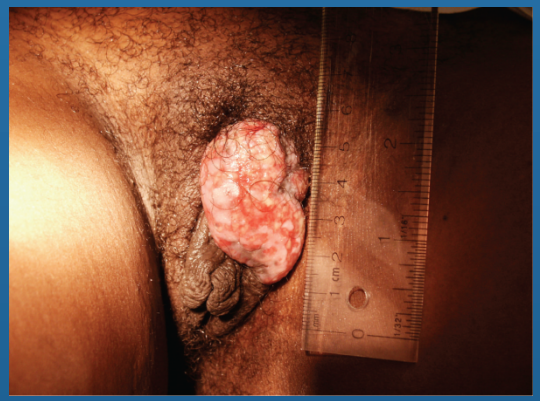


Boothy & Radcliffe, Int J STD AIDS 2007



Cury, STD 2010

Maharaj , J Clin Virol 2009



Yudin & Kaul ID OB Gyn 2008

Diagnosis

If lesion is not present:

- Type specific gG serology (ELISA or Western Blot)
- No firm guidelines about whether to screen HIV positive
  - Per CDC guidelines: screening “can be offered” for HIV positives during initial visit
  - Personal opinion: Screen – for counseling, diagnostic, IRIS purposes

Serology + Culture or PCR if lesion is present

- PCR is 4-fold more sensitive, may become more widely available
  - Type specific NAAT test from BD is FDA approved and available
- Culture highly specific, but sensitivity as low as 23% compared to PCR
- Both are type specific

Treatment of Genital Herpes

Antiviral is safe, well-tolerated, and does not interact with ART

Clinical Setting	Acyclovir	Valacyclovir	Famciclovir
First Episode	400 mg TID x 7-10 days*	1 gm BID x 7-10 days*	250 mg TID x 7-10 days**
Episodic	400 mg TID x 5-10 days*	1 gm BID x 5-10 days*	500 BID x 7-10 days**
Suppression	400 mg-800 mg BID-TID	Valacyclovir 500 mg BID	Famciclovir 500 mg BID

Lesions should be treated until completely healed
Strongly consider suppressive therapy for frequent recurrences

Benefits of Suppressive Therapy

Significant decrease in time to first recurrence on placebo vs valacyclovir 500 BID (median 59 vs >180 days)

70-80% reduction in genital shedding

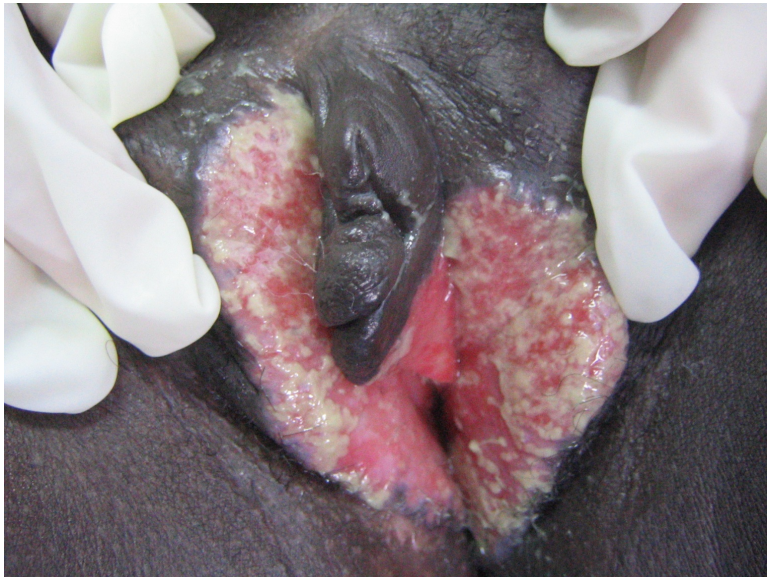
In HIV negative persons, valacyclovir 500 mg daily is associated with ~50% reduced risk of HSV-2 transmission in HSV-2 discordant couples – we do not have data in HIV positives

Suppressive therapy will not decrease risk of HIV acquisition (in HIV negatives) or HIV transmission (in HIV positives)

Clinical Case

A patient with a CD4 count of 130 not on ART presents with one month history of non-healing genital ulcers despite use valacyclovir 1 gm BID. Culture from the lesion grows HSV-2. What should you do next?

1. Send phenotypic resistance testing and initiate foscarnet while awaiting results
2. Continue valacyclovir at current dose
3. Start imiquimod in addition to valacyclovir
4. Switch to famciclovir 500 mg BID
5. Stop valacyclovir and start topical cidofovir



ACV Resistance: Epi and risk factors

HSV isolates studied in United States STD clinics

- ACV-Resistance
  - Prevalence of 5.3 percent in HIV-positive patients
  - Prevalence of 0.18 percent in HIV-negatives
- Similar findings in European surveillance studies
- In vitro resistance does not predict in vivo resistance

Risk Factors:

- History of recurrent HSV infection
- Prior acyclovir/antiviral exposure (especially with suboptimal dose)
- Low CD4 count (<50 c/mm3)
- History of non-healing lesion

Reyes Arch Intern Med 2003; 163(1), Stranska et al J Clin Virol 2005; 32, Danve-Szatanek J Clin Micro 2004;42(1), Lalezari et al JID 1997; 176(4), Safrin NEJM 1991; 325; (8)

ACV Resistance: Diagnosis & Management

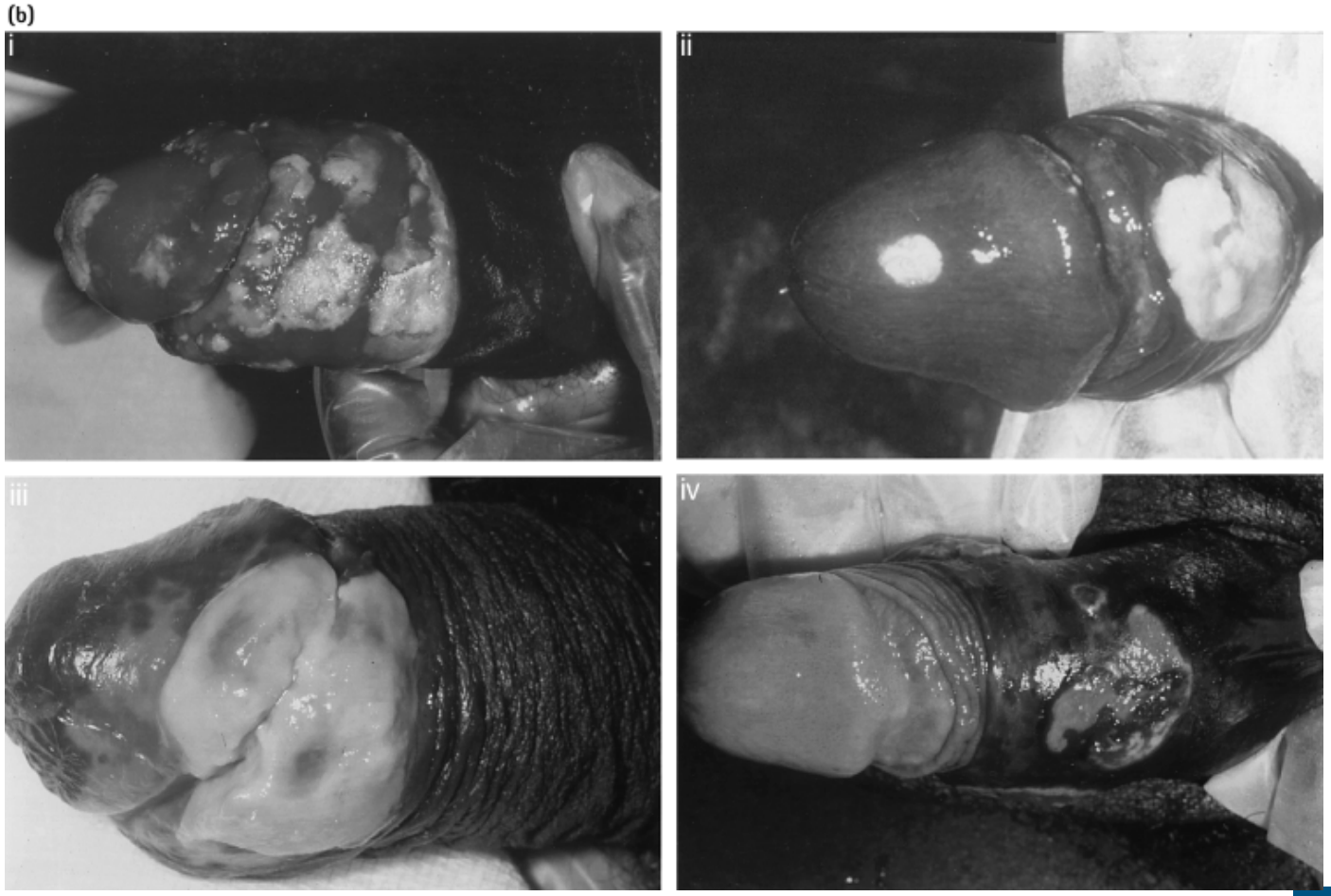
Diagnosis:

- Lesion culture
  - Send for phenotypic testing: in vitro acyclovir susceptibility testing
    - ViroMed lab; IC50≥2 mcg/mL
    - Slow
      - Molecular testing may be available someday

Foscarnet is treatment of choice (Safrin NEJM 1991)

- Limited by nephrotoxicity, only IV option available, and need for intensive monitoring of electrolytes/renal function
- Case reports describe success with topical imiquimod, cidofovir
- Case reports describe success with intralesional cidofovir

HSV in the setting of recent HAART



Fox HIV Medicine 1999

HSV-2 IRIS

Defined as increased severity of ulcerative disease

Increased frequency of recurrences

GUD increases 2-fold in first month after HAART initiation

- Risk factors CD4<100, history of GUD
  - Incidence of HSV-associated GUD IRIS:
    - Most common cause of IRIS in one cohort of 199 persons starting ART
    - 50% of patients with IRIS had anogenital HSV-2

2-fold increased risk of GUD and increased risk of shedding in 3-6 month period after starting ART

- Decreased risk of GUD and HSV-2 shedding in persons on ACV compared to placebo in RCT in Uganda

Graham, JAIDS 2009, Ratnam CID 2006, Tobian, JID 2013

HSV-1 and Genital Herpes

In MSM <28 yrs of age in Australia, 76% of cases of first episode anogenital herpes in 2004-2006 were due to HSV-1 (up from 17% in 1992-94)

In Paris, MSM were at 8.6 increased odds of HSV-1 as etiology of genital herpes; receptive anilingus was associated with 6 fold increased odds.

University setting; 78% of cases first episode genital herpes due to HSV-1

Whether genital HSV-1 is associated with same increased risk of HIV acquisition as HSV-2 is unknown

Ryder et al STI 2009; 85 (416), Janier et al Int J STD AIDS 2006; 17, Roberts et al STD 2003; 30 (10)

Summary

HSV-2 is highly prevalent in HIV positive populations.

Clinical manifestations of HSV-2 may be atypical in HIV population

ACV resistance may occur in HIV positive persons.

HSV-2 IRIS may occur upon starting ART, especially among those with low CD4 count, even among previously asymptomatic persons.

HSV-1 is emerging as a prominent cause of genital herpes in young adults (both MSM and women).