HPTN 039:

A phase III, randomized, double-blind, placebo-controlled trial of acyclovir for the reduction of HIV acquisition among high-risk HSV-2 seropositive, HIV seronegative persons

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Acknowledgments

- Anna Wald, co-chair
- Larry Corey, co-investigator
- Jim Hughes, Statistician
- Site PIs:
  - Jorge Sanchez, Abner Ortiz, Martin Casapia (Peru)
  - Stewart Reid, Sinead Delaney-Moretlwe, Frances Cowan (Africa)
  - Susan Buchbinder, Jon Fuchs, Beryl Koblin (US)
- Site Staff
- Protocol support: Scott Rose, Sam Griffith, FHI
- Data management: Jing Wang, Marla Husnik, Carol Antone, Karen Patterson, Alicia Young, Tom Perdue, SCHARP
- Central Laboratory: Estelle Piowar-Manning (Hopkins); Anne Cent, Rhoda Morrow, Meei-li Huang, & Bob Coombs (UW)

- DSMB, IRBs, CABs
- Sponsor: Division of AIDS, NIAID, NIH
- Study Participants

HSV-2 increases HIV susceptibility

- **Epidemiologic Data**
  - Longitudinal studies which adjusted for age & sexual behavior (n=18)
  - Prevalent HSV-2 infection and HIV acquisition
    - Men RR 2.7 95% CI 1.9-3.9
    - Women RR 3.1 95% 1.7-5.6
    - MSM RR 1.7 95% CI 1.2-2.4
  - 38-69% of new HIV infections in ♀ & 8-49% in ♂ due to prevalent HSV-2 (Freeman AIDS 2006)

- **Biologic Plausibility**
  - HSV-2 causes macro- & microscopic ulcerations
  - HSV-2 reactivation is frequent: 20% of days HSV PCR+ in HIV-negative persons (Mark ISSTDR 2007)
  - ⇑ cervical CD4 T cells & immature dendritic cells in HSV-2 seropositive women (Rebbapragada AIDS 2007)

HPTN 039: HSV-2 suppressive therapy to prevent HIV acquisition

HIV- HSV-2+
heterosexual women

Harare, Zimbabwe
Lusaka, Zambia
Johannesburg, So Africa

and

HIV- HSV-2+ MSM

Lima, Iquitos, Pucallpa: Peru
Seattle, San Francisco, NYC

Randomize

Acyclovir 400 mg bid

Matching Placebo bid

Both arms received episodic ACV for GUD & risk reduction counseling

1° endpoint: HIV infection

Assumptions and Analyses

- Sample size assumptions:
  - 50% effect size
  - 90% power
  - 3.5% HIV incidence in placebo arm
- Primary analysis: Intent-to-treat
- Risk estimates adjust for gender, age, GUD at enrollment & # of sex partner in last 12 months at entry
- Additional analyses adjust for sexual behavior during the study as time-dependent covariates
- Adherence measured by monthly pill count & self report

Entry criteria

- Age of informed consent (≥18 yrs)
- HIV negative
- HSV-2 seropositive
  - Focus EIA index value > 3.4; confirmed with UW HSV Western blot
- Behavioral criteria
  - Women from southern Africa:
    - ≥1 episode of unprotected vaginal sex in past 6 months
  - MSM from U.S. and Peru:
    - ≥ 1 episode of anal intercourse in past 6 months & not mutually monogamous with HIV- man

Monthly visit procedures

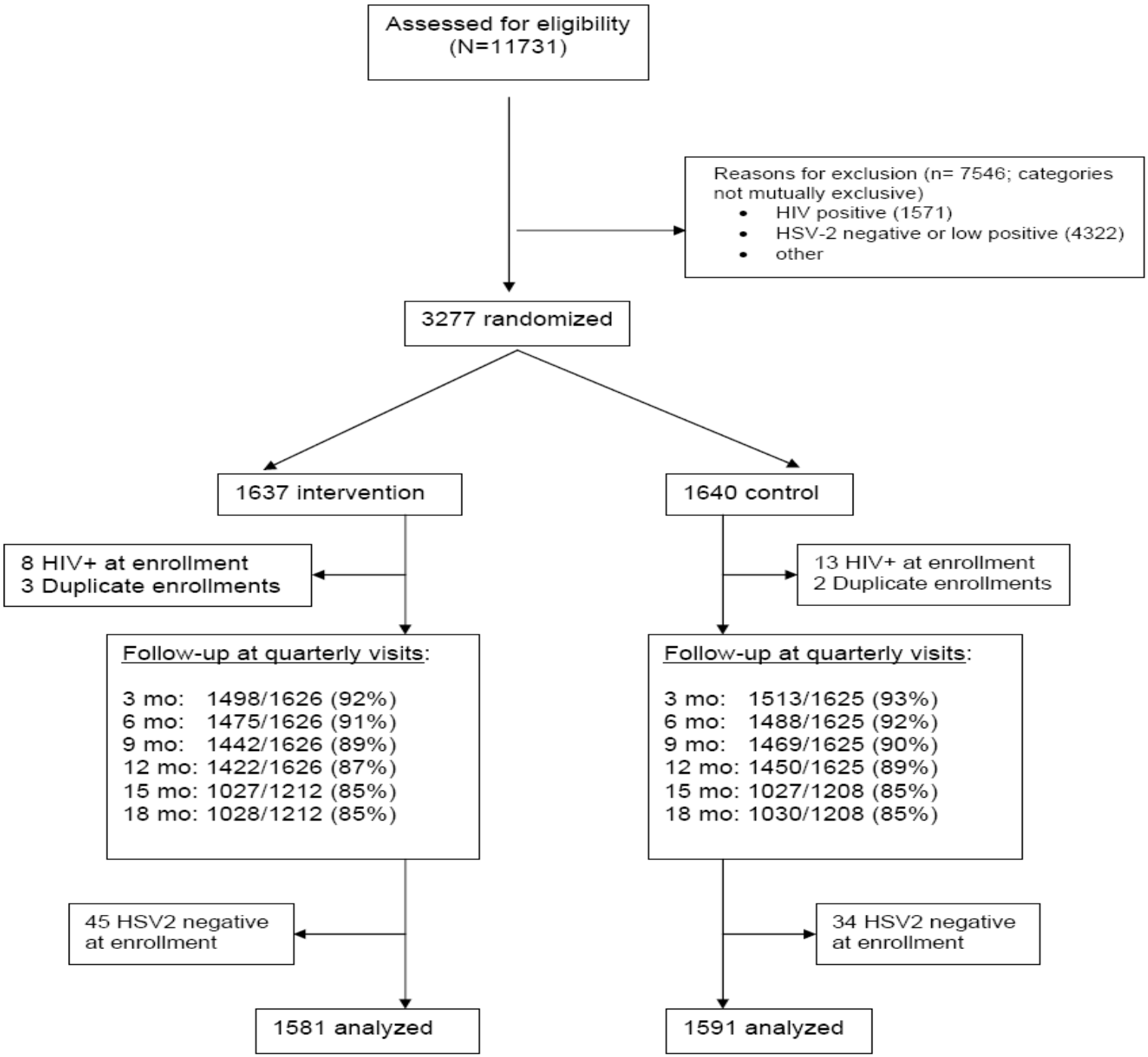
- Ascertain adherence by pill count & self report
- Counsel about adherence
- Dispense study drug
- Questionnaire about GU history, STD symptoms and sexual behavior
- Genital exam & syndromic therapy (if symptomatic)
- Safer sex counseling & condom provision

Additional study procedures

- Quarterly visits
  - Blood draw for HIV antibody
  - Genital exam
  - Swabs for HSV if ulcers present
- Episodic acyclovir offered for genital herpes recurrences
- Pregnant women taken off study drug, given limited experience with ACV in pregnancy in Africa
  - Continued in study & drug restarted after pregnancy

Follow up

- Initially for 1 year
- Extended to 18 months, due to accrual rate
- Primary analysis included all appropriately enrolled participants
- To avoid potential bias, excluded data for 12-18 months from primary analyses from 2 sites that did not achieve >94% re-consent rate


Assessed for eligibility (N=11731)
Reasons for exclusion (n= 7546; categories not mutually exclusive)
HIV positive (1571)
HSV-2 negative or low positive (4322)
other
3277 randomized
1637 intervention
1640 control
8 HIV+ at enrollment
3 Duplicate enrollments
13 HIV+ at enrollment
2 Duplicate enrollments
Follow-up at quarterly visits:
3 mo: 1498/1626 (92%)
6 mo: 1475/1626 (91%)
9 mo: 1442/1626 (89%)
12 mo: 1422/1626 (87%)
15 mo: 1027/1212 (85%)
18 mo: 1028/1212 (85%)
Follow-up at quarterly visits:
3 mo: 1513/1625 (93%)
6 mo: 1488/1625 (92%)
9 mo: 1469/1625 (90%)
12 mo: 1450/1625 (89%)
15 mo: 1027/1208 (85%)
18 mo: 1030/1208 (85%)
45 HSV2 negative at enrollment
34 HSV2 negative at enrollment
1581 analyzed
1591 analyzed

Study population

- Total enrolled: 3277
- Inappropriately enrolled: 105
  - HIV PCR+ at enrollment, duplicate enrollment, HSV-2 neg by Western blot
- Appropriately enrolled: 3172
  - MSM, Peru sites: 1355
  - MSM, U.S. sites: 459
  - Women, Africa sites: 1358
- Retention at 18 months: 85% in both arms

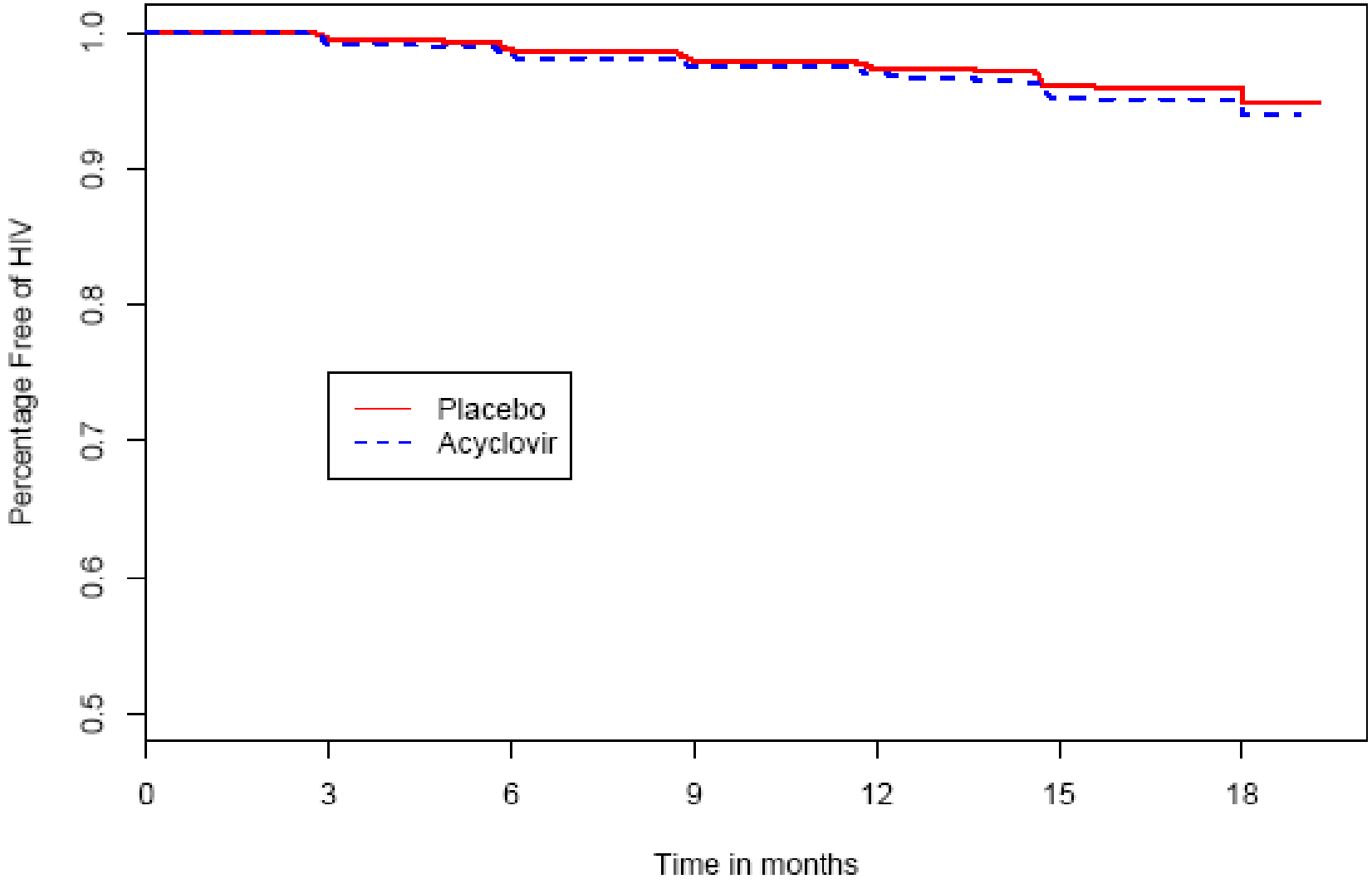
Demographic & behavioral characteristics at enrollment

	Women N =1358	Peru MSM N =1355	U.S. MSM N = 459
Age (median)	31	28	40
<secondary education	96%	61%	16%
# SP, past year (median)	1	10	6
# SP, past month (median)	1	2	1
# sex acts past 3 months	24	6	6
Any unprotected vaginal sex, past 3 months	90%	-	-
Any unprotected receptive anal sex, past 3 months	-	56%	33%
Any unprotected insertive anal sex, past 3 months	-	21%	40%

HPTN 039:
Clinical characteristics of participants

	Women (n=1380)	Peru MSM (n=1355)	U.S. MSM (n=459)
History of anogenital herpes in past 3 months, at enrollment	26%	8%	22%
Laboratory confirmed STIs, enrollment			
Syphilis seropositivity	4%	31%	4%
median titer	1:8	1:4	1:2
Gonorrhea (cervical /rectal)	0.8%	0.3%	0.8%
Chlamydia (cervical)	6.0%	--	--
Trichomoniasis	8.0%	--	--
Pregnancy incidence during study	14%	--	--
Male circumcision	--	6%	82%

Time to HIV by study arm



P = 0.39

HIV acquisition events & rate per 100 person-years by gender

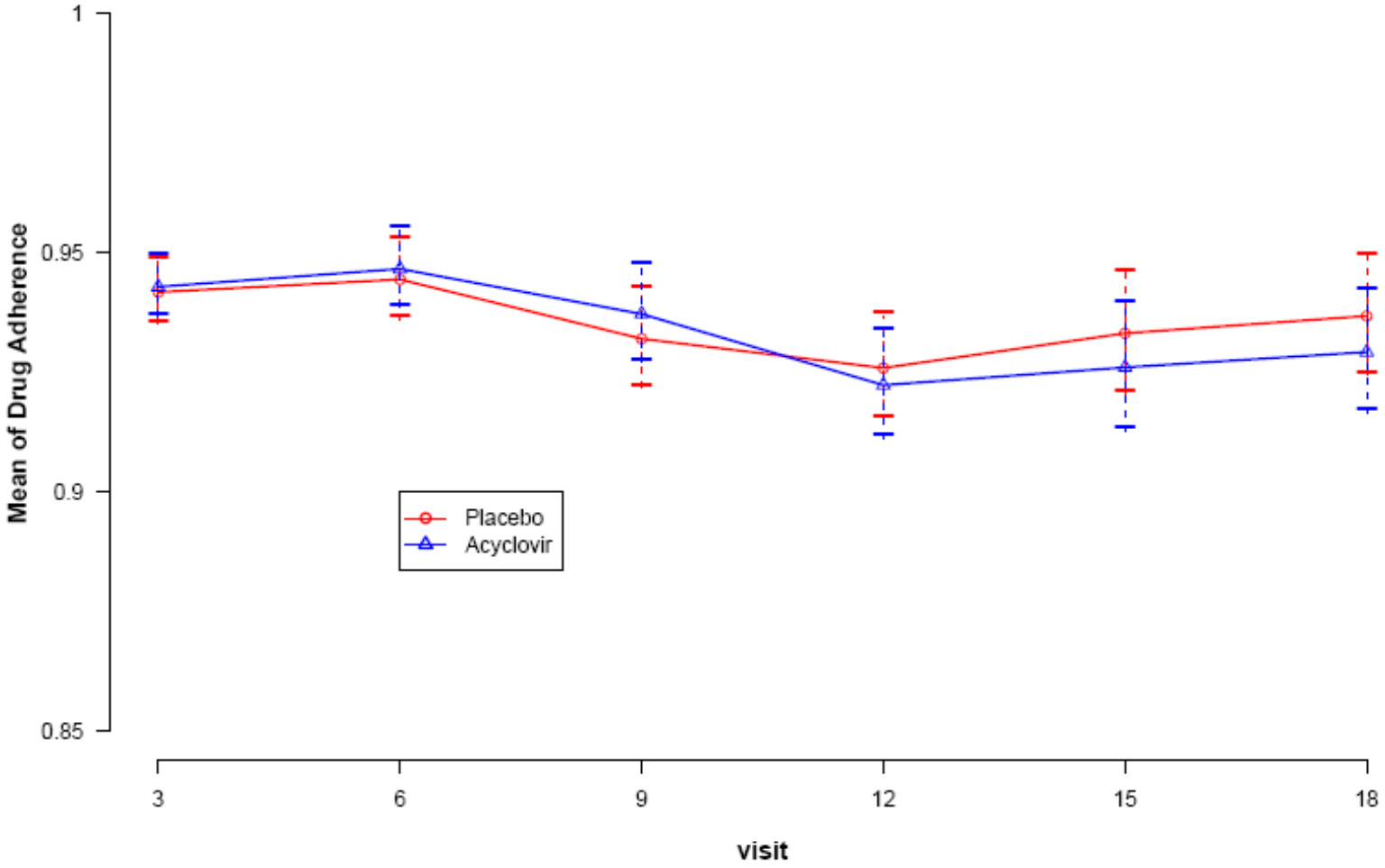
	Acyclovir		Placebo		Total	
	N	Rate/ 100 py	N	Rate/ 100 py	N	Rate/ 100 py
Men	31	3.0	36	3.4	67	3.2
Women*	44	4.9	28	3.1	72	4.0
Total	75	3.9	64	3.3	139	3.6

Overall HR 1.16 (95% CI 0.83-1.62)

*Excluding time off study drug due to pregnancy; HIV incidence in women was 3.8/100 p-yrs (acyclovir) & 3.3/100 p-yrs (placebo)

- Overall HR 1.13 (95% CI 0.81-1.59)

Mean quarterly adherence by pill count & self-report by treatment arm



Consecutive missed doses (≥6) reported at <4% of visits

HIV incidence by level of adherence to the study drug

Adherence	Arm	Events	Person-years	Rate per 100 p-yrs	RR (95% CI)
<90%	Placebo Acyclovir	14 22	401 402	3.5 5.5	1.6 (0.8, 3.1)
≥90%	Placebo Acyclovir	44 45	1364 1328	3.2 3.4	1.0 (0.7, 1.6)

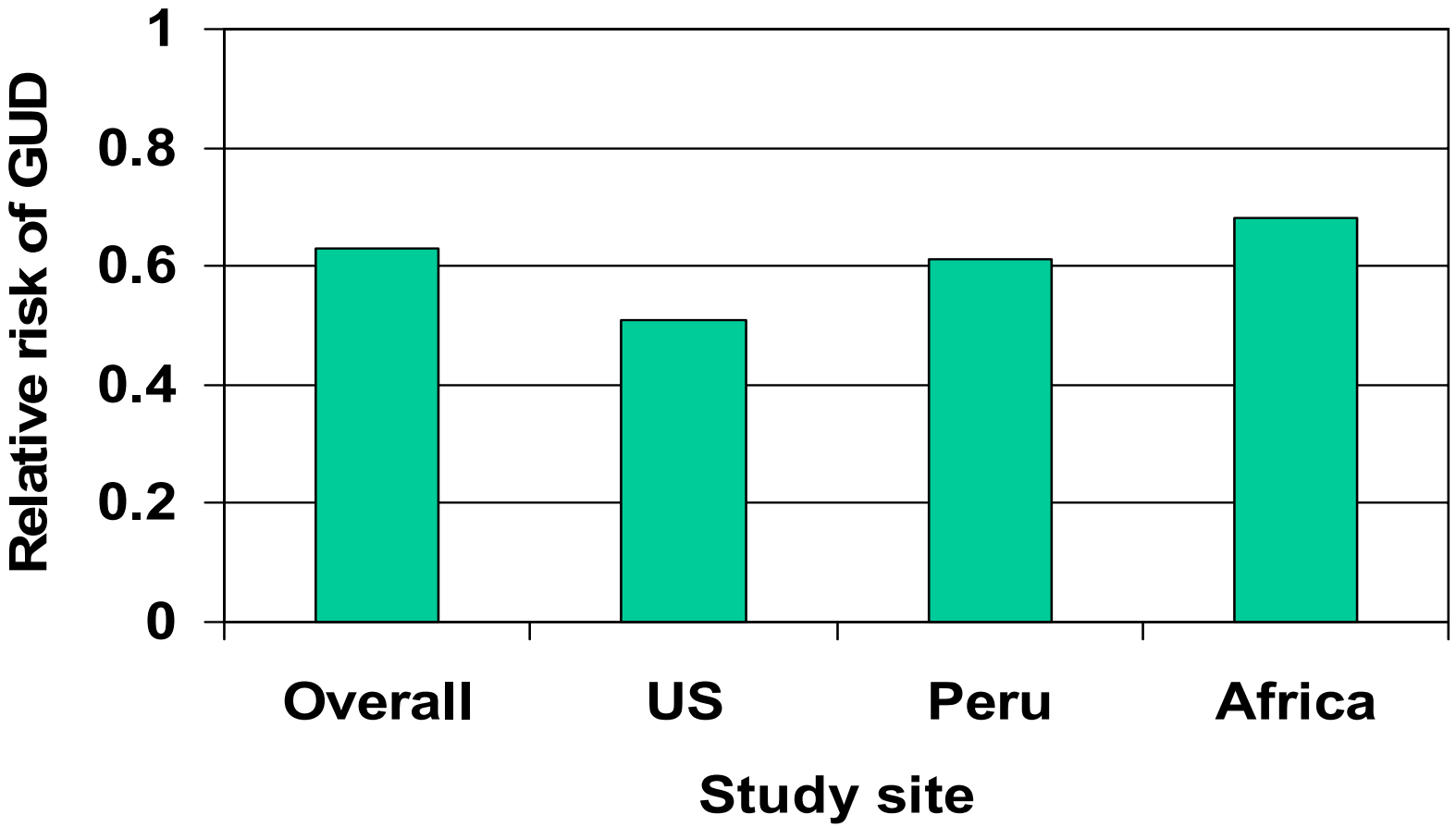
- For those with >105% adherence or missing data, RR 1.8 (0.4, 7.3)
- Based on Cox model, stratified by site & adjusted for age, GUD at enrollment, & # of SP in past 12 months

Safety of acyclovir – SAE's

- 63 (4%) in the placebo group
  - All considered to be unrelated
  - 2 deaths
  - Infections (n=21), trauma (n=12)

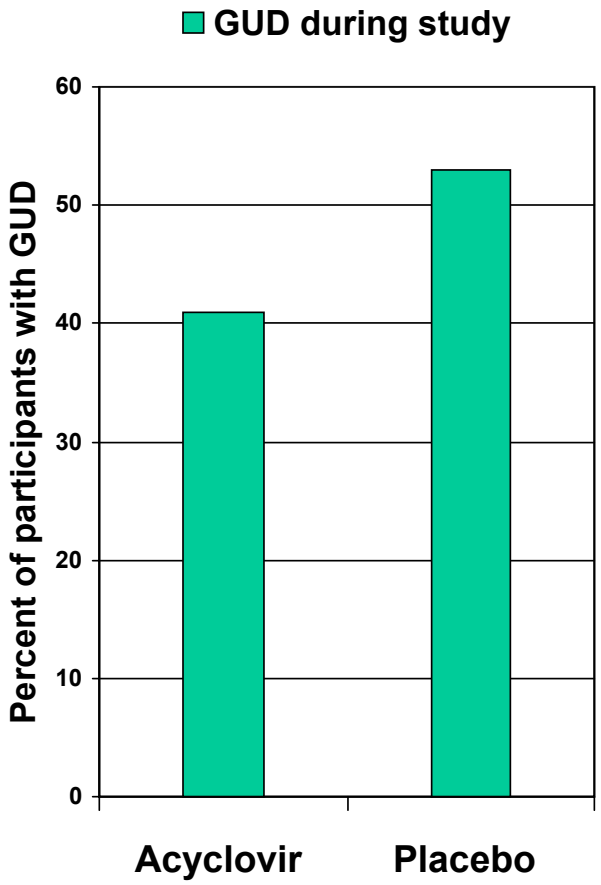
- 75 (5%) in the acyclovir group
  - All considered to be unrelated
  - 6 deaths (inc. 3 traumatic)
  - Infections (n=22), trauma (n=10)

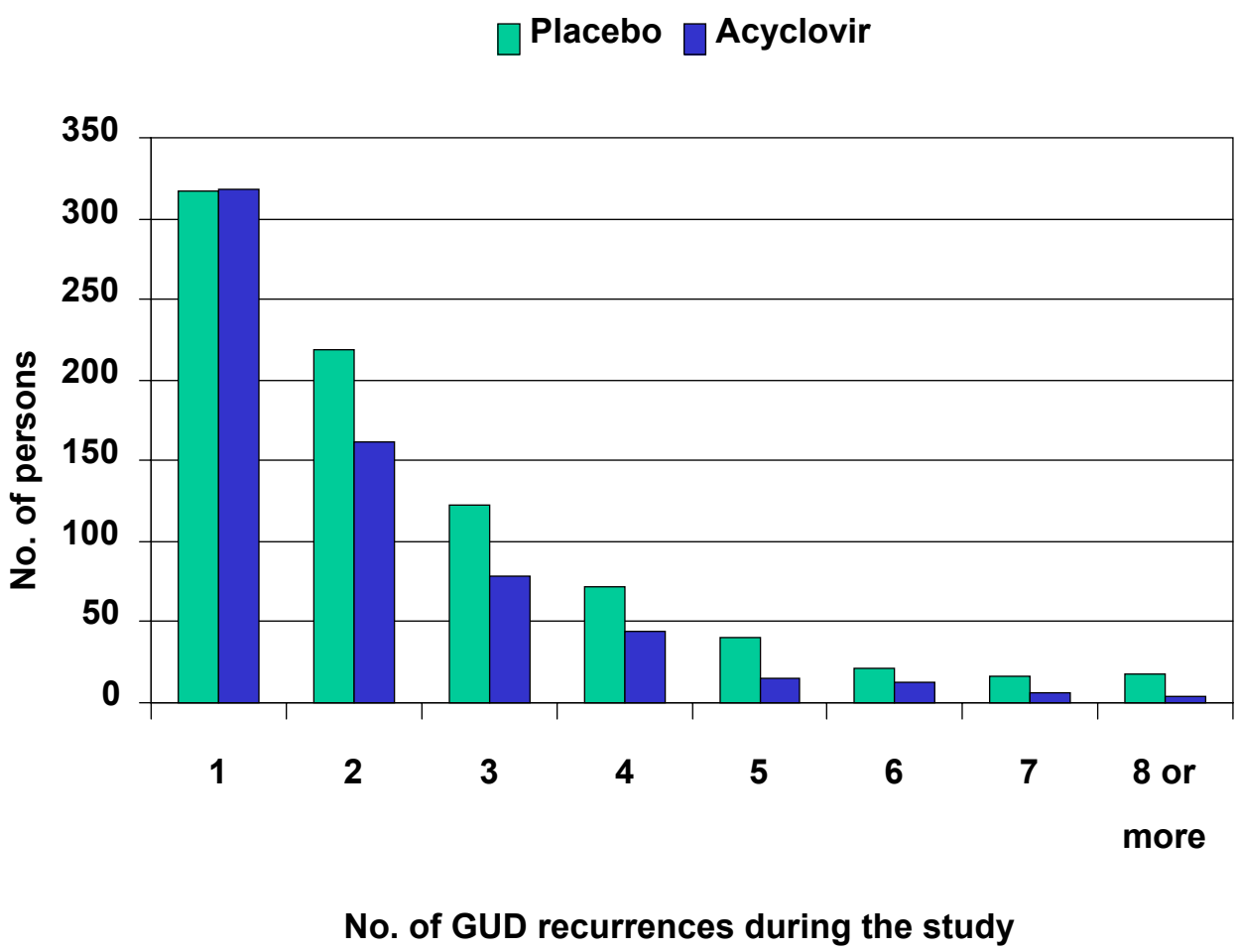
Relative risk of GUD, acyclovir vs. placebo arm, p<0.001 for all sites



- Overall, 37% reduction in incidence of GUD in acyclovir arm
- Significant differences in reduction in GUD by region (p=0.01)

GUD episodes by study arm





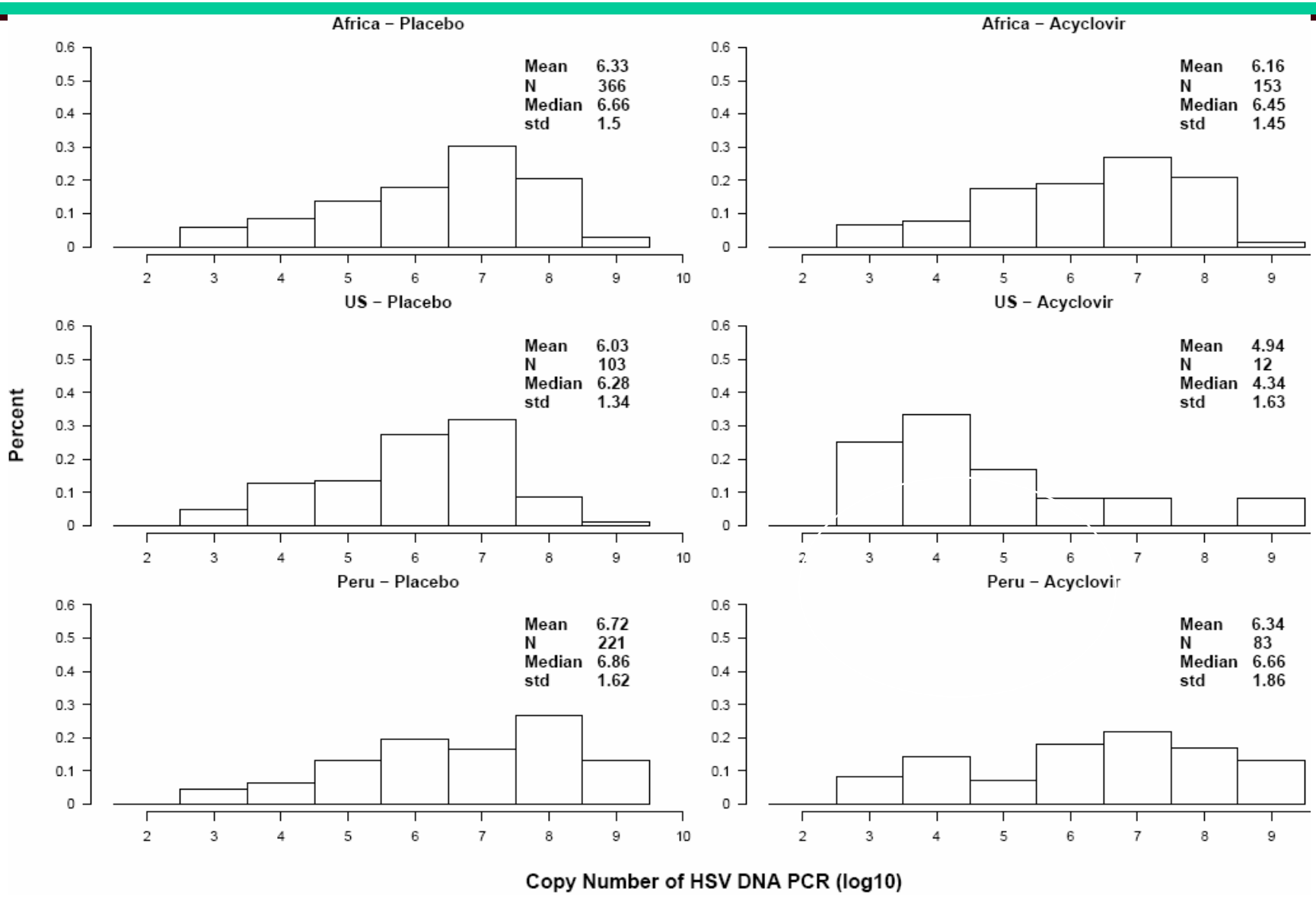
Frequency of HSV detection from genital ulcers during the study

	Acyclovir N = 729 swabs	Placebo N = 1258 swabs
HSV-2* PCR +	246 (33.7%)	688 (54.7%)**
Negative	473 (64.9%)	552 (43.9%)
Inhibited	8 (1.1%)	16 (1.2%)

* Only 2 samples positive for HSV-1 DNA

** p <0.001

Quantity of HSV DNA detected (log10) among HSV positive episodes of genital ulcers, by region



Conclusions

- Acyclovir 400 mg bid did not reduce the risk of HIV acquisition among high-risk HSV-2 seropositive MSM and women
- Adherence to study drug was excellent
- Acyclovir 400 mg bid was safe and well-tolerated; largest trial ever of HSV-2 suppression
- Suppressive acyclovir led to a significant reduction in incidence of genital ulcers
- Quantity of HSV-2 detected in ulcers was not reduced in Peru and in Africa

Summary

- Our study is consistent with the Mwanza trial that showed no reduction in HIV acquisition among high risk women treated with acyclovir 400 mg bid
- Surprising, disappointing, and important result for HIV prevention
- Question is whether the lack of efficacy is related to the concept or the intervention

Possible Interpretations

- HSV-2 is not a risk factor for HIV
  - Unlikely to be only confounding, given plethora of epidemiologic data
- HSV in Africa responds less well to acyclovir
  - Less decrease in GUD & HSV quantity in GUD than in prior trials
  - Are acyclovir pharmacokinetics or susceptibility a factor?
  - Was adherence overestimated by pill count & self-report?
  - Other etiologies of genital ulcers also important?
- We have underestimated HSV-2 in terms of frequency of reactivation & genital immune response
  - Need higher doses, new HSV drugs or combination therapy?
  - Need interventions to effectively shut down genital immune response to HSV?

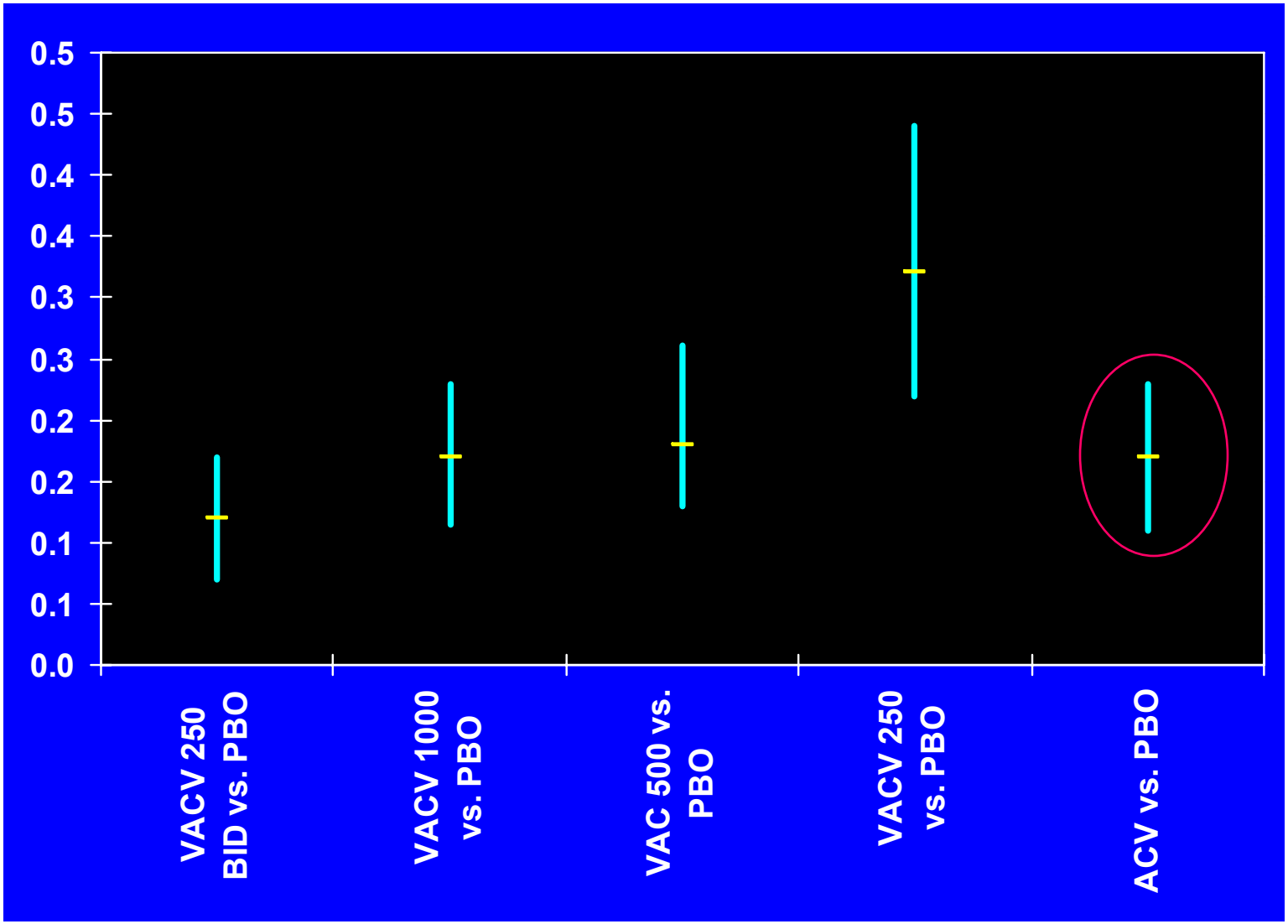
Research Priorities

- HSV-2 interacts with HIV through different mechanisms; should complete studies that are testing different hypotheses
  - HIV transmission (Partners in Prevention)
  - HIV ‘set-point’ (seroconverters in HPTN 039)
  - HIV disease progression (Partners in Prevention, Rakai)
- Biology of HSV-2 in HIV-negative & HIV-positive persons
  - Genital immune activation & persistence
  - Significance of short bursts of HSV shedding
- HSV drugs: new targets, longer duration of activity
- HSV vaccines

Many Thanks to All the Study Participants

Lusaka 039 Participant Support Group

Acyclovir and Valacyclovir Suppression: Similar Effect on GUD Incidence



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